

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203341Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 4, 2012

To: Dianne Hanner – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Division of Direct to Consumer Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft Bolsulif (bosutinib) tablets, for oral use
Patient Information (PPI)

This consult is in response to DHP's January 6, 2012 request for OPDP review of the draft Bolsulif Patient Information. DCDP comments are based on the proposed draft marked-up labeling submitted by Pfizer on August 31, 2012.

We have made no comments at this time.

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

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

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/s/

RICHARD A LYGHT
09/04/2012

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

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

Memorandum

Date: 9/4/2012

To: Diane Hanner, Senior Program Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Drug Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 203341, Bosulif (bosutinib) tablets

In response to your labeling consult request on January 6, 2012, we have reviewed the draft Package Insert for Bosulif and do not have any comments. Note that this review was based upon the August 30, 2012 version of the label.

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/s/

JAMES S DVORSKY
09/04/2012

Division of Hematology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 203341

Name of Drug: BOSULIF® (bosutinib) Tablets, 100 mg and 500 mg.

Applicant: Wyeth Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: November 17, 2011

Receipt Date: November 17, 2011

Background and Summary Description:

This new drug application provides for the use of BOSULIF® (bosutinib) Tablets, 100 mg and 500 mg for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy

Review

NDA 203341 bosutinib label was reviewed by the DHP RPM staff which made several proposed formatting changes.

Recommendations

Regulatory Project Manager	Date
Chief, Project Management Staff	Date

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/s/

DIANE C HANNER
09/04/2012

JANET K JAMISON
09/04/2012

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The required drug-drug interaction trial will likely be a crossover trial to evaluate the effect of a moderate CYP3A4 inhibitor on the pharmacokinetics of bosutinib.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/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.

RCK _____
 (signature line for BLAs)

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/s/

DIANE C HANNER
08/31/2012

ROBERT C KANE
09/04/2012

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: Bosulif (bosutinib)

PMC Description: The Applicant agrees to continue to follow patients (on treatment and in protocol defined post-treatment follow-up) enrolled in Study 200-WW at least an additional 2 years past the March 28, 2011 cut-off date. The Final Report will consist of an updated report containing, at a minimum, data through March 28, 2013.

PMC Schedule Milestones:	Final Protocol Submission:	<u>NA</u>
	Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>12/2015</u>
	Other:	<u>NA</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

At the time of database lock, the median duration of follow-up for the primary efficacy population of patients with second-line CML who were imatinib-resistant was 30.5 months (range: 0.7 to 58 months). Many of the median durations of response had not been reached. The median durations of response would be an important additional piece of information for prescribers. The safety and efficacy of bosutinib over a longer time period will enhance understanding of the drug and its use in patients with CML.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Extended follow-up of ongoing trial will enhance knowledge of the safety profile and will enhance knowledge of duration of efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMC refers to continuation of the ongoing pivotal trial, Trial 200-WW which is a single arm, multi-center trial of oral daily dosing of 500 mg of bosutinib for patients with chronic phase, accelerated phase and blast phase CML.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

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

PMR/PMC Development Coordinator:

- This 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.*

____RCK_____
(signature line for BLAs)

Reviewer, DO YOU WANT TO REQUEST THE SPONSOR TO:

[REDACTED] (b) (4)

Submit the protocol for FDA review and concurrence before commencing the trial? No

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/s/

DIANE C HANNER
08/31/2012

ROBERT C KANE
09/04/2012

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

PATIENT LABELING REVIEW

Date: August 24, 2012

To: Ann Farell, 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: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Drug Name (established name): BOSULIF (bosutinib)

Dosage Form and Route: tablets for oral use

Application Type/Number: 203341

Applicant: Wyeth Pharmaceuticals, Inc.

1 INTRODUCTION

On November 17, 2011, Wyeth Pharmaceuticals, Inc. submitted an Original New Drug Application (NDA) 203341 under section 505(b) of the Federal Food, Drug and Cosmetic Act, for BOSULIF (bosutinib) tablets. The Applicant's proposed indication for BOSULIF (bosutinib) tablets is for the treatment of chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy.

On November 18, 2011, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for BOSULIF (bosutinib) tablets.

This review is written in response to a request by Division of Hematology Products (DHP) for Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for BOSULIF (bosutinib) tablets.

2 MATERIAL REVIEWED

- Draft BOSULIF (bosutinib) tablets Patient Package Insert (PPI) received on November 17, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on August 22, 2012.
- Draft BOSULIF (bosutinib) tablets Prescribing Information (PI) received on November 17, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on August 22, 2012.
- Approved Sprycel (dasatinib) comparator labeling dated October 7, 2011.

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. In our review of the PPI the target reading level is at or below an 8th grade 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 have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP 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/

LATONIA M FORD
08/28/2012

BARBARA A FULLER
08/28/2012

LASHAWN M GRIFFITHS
08/28/2012

Executive CAC

Date of Meeting: July 17, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Supervisor and Alternate Member
Shawna Weis, Ph.D., DHOT, Presenting Reviewer

Author of Draft:

Shawna Weis

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

NDA #203341

Drug Name: Bosutinib

Sponsor: Wyeth (Pfizer)

Background:

Bosutinib is an Abl and Src kinase inhibitor that is undergoing development for Ph(+) CML in adult patients with resistance or intolerance to prior therapy. Bosutinib was negative in the Ames and *in vitro* chromosome aberration assays, both with and without activation by Arochlor-induced S9 extracts. Bosutinib was also negative in the *in vivo* micronucleus assay in rats. A protocol (SPA) and supporting toxicity data were submitted to the CAC for the 2-year rat study in June of 2009, and concurrence was obtained on dose selection for this study. All males were terminated during Week 91 due to excessive mortality. Females were terminated during Week 100.

Rat Carcinogenicity Study

Sprague-Dawley rats were dosed daily by oral gavage in a 10 mL/kg dose volume. Doses were 0 (water), 0 (vehicle), 0 (vehicle), 1.5, 5, and 15 mg/kg/day for females and 0 (water), 0 (vehicle), 0 (vehicle), 2.5, 7.5, and 25/15 mg/kg/day for males. Due to the large number of deaths, doses were reduced for males in the high dose cohort during Study Week 78, and then suspended during Study Week 79 until termination in Study Week 86.

Each dose group consisted of 60 males and 60 females, plus an appropriate number of toxicokinetic satellite cohorts to permit confirmation of exposure and toxicokinetic assessment on Study Day 182. Doses were administered by gavage in a vehicle suspension (0.5% carboxymethylcellulose 2% polysorbate 80, and 0.06% glacial acetic acid). Three control groups, (two vehicle and one water group), were employed in this study.

This study was relocated from the Sponsor facility in Chazy, NY to the CRO site in (b) (4)

during week 36 of dosing.

Plasma exposure levels achieved in this study were up to 1.5-3-fold (AUC_{τ}) greater than those anticipated clinically at the 500 mg/day dose level.

Executive CAC Recommendations and Conclusions (Rat):

- The Committee agreed that the study was acceptable, but noted that moving an ongoing carcinogenicity study is undesirable and rendered historical control data difficult to interpret due to numerous differences between the two sites.
- The Committee concurred that the study was negative for drug-induced neoplasms.

David Jacobson-Kram, Ph.D.

Chair, Executive CAC

cc:\

/Division File, NDA 203341; DHP

/Haleh Saber; DHOT

/Shawna Weis, DHOT

/Diane Hanner, CSO/PM, DHP

/Adele Seifried, OND IO

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/s/

ADELE S SEIFRIED
07/18/2012

DAVID JACOBSON KRAM
07/18/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 28, 2012

TO: Diane Hanner, Regulatory Project Manager
Karen McGinn, M.S.N., C.R.N.P., Clinical Analyst
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203341

APPLICANT: Wyeth Pharmaceuticals, Inc.

DRUG: bosutinib
NME: Yes
THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATION: adult chronic myelogenous leukemia

CONSULTATION REQUEST DATE: February 9, 2012 (Signed)
INSPECTION SUMMARY GOAL DATE: July 2, 2012
DIVISION ACTION GOAL DATE: September 17, 2012
PDUFA DATE: September 17, 2012

I. BACKGROUND:

The most common phenotype of Philadelphia chromosome positive leukemia is chronic myelogenous leukemia (CML), which is most frequently associated with a 210 kD BCR-Abl fusion protein. BCR-Abl is a transcript resulting from the 9:22 chromosomal translocation responsible for formation of the Philadelphia (Ph) chromosome. This fusion protein (BCR-Abl), with constitutive tyrosine kinase activity, consists of the breakpoint cluster region (BCR) and Abelson kinase (Abl). Bosutinib is an orally bioavailable inhibitor of both Src-family and Abl kinases. Unlike imatinib, dasatinib and nilotinib, bosutinib exhibits no significant inhibition of c-kit or PDGFR proteins.

A single adequate study was submitted in support of this NDA. Two U.S. clinical sites were selected for clinical audit. A brief summary of the submitted study is given below.

Protocol 3160A4-200-WW

Protocol 3160A4-200-WW was an open-labeled, continuous daily dosing, Phase I and II safety and efficacy study of bosutinib in patients with Philadelphia chromosome positive (Ph+) leukemias. Phase I was a dose-escalation study in chronic phase CML subjects to establish the maximum tolerated drug dose in this subject population [Part 1]. Study 3160A4-200-WW [Part 2] was a safety and efficacy study of 500 mg daily bosutinib in chronic phase, imatinib resistant/refractory CML subjects, and subjects with advanced Philadelphia chromosome positive leukemia. The primary objective was to determine the proportion of patients attaining a major cytogenetic response with imatinib-resistant chronic phase CML, who have no prior Src, Abl, or Src-Abl kinase inhibitor exposure other than imatinib, and to determine the population pharmacokinetic parameters of bosutinib. DHP directed OSI to focus on the Phase II clinical efficacy and safety aspects of this NDA in the clinical site audits.

Efficacy was defined primarily via analysis of peripheral blood and bone marrow findings. The efficacy endpoints constituted (1) major cytogenetic response for CML subjects in their chronic phase and (2) hematologic response for advanced Ph+ leukemia subjects (i.e., in the accelerated or blast phase). A cytogenetic response at 24 weeks for chronic CML subjects was defined as a complete plus a partial cytogenetic molecular response to treatment. Quantitatively, this was based on a log reduction from baseline in the BCR-Abl/Abl ratio. A partial cytogenetic response was defined as less than three log reduction from baseline in the BCR-Abl/Abl ratio. A major cytogenetic response was defined as a three or greater log reduction from standardized baseline in the BCR-Abl/Abl ratio. A complete cytogenetic response was defined as an undetectable BCR-Abl fusion protein. A complete hematologic response for advanced Ph+ patients was defined as (i) bone marrow blast percentage value of 5 or less, (ii) platelet count over 100,000 or $100 \times 10^9/L$, (iii) total white blood cells within the clinical site's upper limit of normal, (iv) absolute neutrophil count over 1,000 or $1.0 \times 10^9/L$, (v) basophil count less than 20%, (vi) absence of other significant findings such as promyelocytes or blasts in the peripheral blood, and (vii) absence of extramedullary involvement.

II. RESULTS:

Name of CI City, State	Protocol/Study Site	Insp. Date	Final Classification*
Jorge Cortes, M.D. Houston, TX	3160A4-200-WW Site #001	May 9 to 18, 2012	Preliminary: NAI
Hanna Khoury, M.D. Atlanta, GA	3160A4-200-WW Site #017	March 22 to April 2, 2012	VAI
Wyeth Pharmaceuticals, Inc. Groton, CT	Sponsor Sites #001 and #017	April 24 to 30, 2012	Preliminary: NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Jorge Cortes, M.D./Protocol 3160A4-200-WW Site #001

Houston, TX

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from May 9 to 18, 2012. A total of 96 subjects were screened, 81 subjects were enrolled, and 21 subjects completed the study. An audit of 20 enrolled subjects' informed consent forms was performed.

An audit of 16 subjects' records 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.

b. General observations/commentary:

Source documents, for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings, and no discrepancies were noted. There was no under-reporting of serious adverse events. The primary efficacy endpoint was verifiable. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Hanna Khoury, M.D./ Protocol 3160A4-200-WW Site #001

Atlanta, GA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from March 22 to April 2, 2012. A total of 34 subjects were screened and enrolled, and 30 subjects completed the study. A 100% audit of screened subjects' informed consent forms was performed.

An audit of 11 subjects' records 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.

b. General observations/commentary:

Source documents for randomized subjects whose records were audited were verified against the case report forms and NDA subject line listings, and no discrepancies were found. There was no under-reporting of serious adverse events. The primary efficacy endpoint was verifiable. There were no limitations during conduct of the clinical site inspections by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for failure to obtain continuing IRB review and approval, prior to the expiration date of the study. Specifically:

1. Continuing IRB approval was granted from 11/01/2006 to 4/30/2007. However, the clinical investigator did not obtain continued approval before study expiration on 4/30/2007. Subsequently, continuing IRB approval was granted from 5/2/2007 to 11/1/2007.
2. Continuing IRB approval was granted from 5/2/2007 to 11/1/2007. However, the clinical investigator did not obtain continued approval before the study expiration date. Request for continuing review was submitted on 11/20/2007.

Subsequently, continuing IRB approval was granted from 2/26/2008 to 8/25/2008.

3. Continuing IRB approval was granted from 2/12/2009 to 8/11/2009. However, the clinical investigator did not obtain continued approval before the study expiration date on 8/11/2009. Subsequently, continuing IRB approval was granted from 8/13/2009 to 2/12/2010.

Findings on the Form FDA 483 related to IRB approval were discussed with the review division clinical team. The observations cited above were not considered significant.

Additional observations in the ORA field investigator's Establishment Inspection Report regarding potential discrepancies between source documentation and NDA data listings were addressed and documented in correspondence between the clinical site investigator and sponsor. Based on further evaluation by DHP, these items, such as aspicular (Subject #412 and Subject #441) or inadequate (Subject #440) bone marrow samples were not considered significant, as these patients had peripheral blood samples that verified response at the same time points and had sufficient bone marrow aspirates at other timepoints.

ORA also audited primary efficacy endpoints to include cytogenetic responses for CML subjects in their chronic phase, and noted that the clinical site was in compliance. However, DHP noted that its final review will not include the BCR-Abl fusion product change from baseline as a molecular response efficacy measure as part of the efficacy assessment and drug product labeling. Approximately 25% of samples were not obtained; thus, DHP deemed the information insufficient to analyze and correlate with the patient's clinical status.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

SPONSOR

3. Wyeth Pharmaceuticals, Inc.

Groton, CT

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from April 24 to 30, 2012.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA Form 1572s, monitoring reports, and training of staff and site monitors.

b. General observations/commentary:

The Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the Sponsor inspection.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 2 open-labeled study, two U.S. clinical investigator sites for Protocol 3160A4-200-WW, plus the Sponsor, were inspected in support of this application.

No regulatory deficiencies were observed for Jorge Cortes (Site #001) and Sponsor sites. Minor regulatory deficiencies were observed for Hanna Khoury, M.D. (Site #017), for failure to obtain continuing IRB review and approval, prior to the expiration date of the study. Based on review of inspectional findings for these clinical investigators and the Sponsor, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

ANTHONY J ORENCIA
06/28/2012

JANICE K POHLMAN
06/28/2012

SUSAN D THOMPSON
06/28/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: June 11, 2012

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol A. Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Bosulif (Bosutinib) Tablets
100 mg and 500 mg

Application Type/Number: NDA 203341

Applicant: Pfizer, Inc. (Wyeth Pharmaceuticals, Inc.
is a wholly-owned subsidiary of Pfizer, Inc.)

OSE RCM #: 2011-4353

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's evaluation of the proposed container labels and insert labeling for Bosulif (Bosutinib) Tablets for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the proposed labels and labeling for Bosulif (Bosutinib) Tablets (NDA 203341) on November 17, 2011.

1.2 PRODUCT INFORMATION

- Active ingredient: Bosutinib
- Indication of Use: for the treatment of chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance, or intolerance to prior therapy.
- Route of administration: Oral
- Dosage form: Tablets
- Dose and Frequency: 500 mg once daily with food. Dose escalation to 600 mg once daily with food in patients who failed to reach complete hematological response (CHR) by week 8 or a complete cytogenetic response (CCyR) by week 12, at the recommended starting dosage and who did not have Grade 3 or higher adverse reactions. Dose adjustment for non-hematologic toxicities such as elevated liver transaminases and diarrhea, include drug interruption and resuming at a dose of 400 mg once daily. Dose adjustment for hematologic toxicities such as neutropenia and thrombocytopenia, include drug interruption and resuming at a dose reduction by 100 mg once daily. A lower starting dose of 200 mg is recommended in patients with hepatic impairment. No dose adjustment is recommended in patients with renal impairment or the elderly, and no data is available in patients less than 18 years of age.
- How Supplied:
 - 120 tablets per bottle of 100 mg tablets (NDC #0069-0135-01) that are yellow, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "100" on the other
 - 30 tablets per bottle of 500 mg tablets (NDC #0069-0136-01) that are red, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "500" on the other
- Storage: at 25°C (77 °F); excursions permitted to 15- 30°C (59-86°F) [see USP Controlled Room Temperature].

- Container and Closure Systems: The commercial container closure system for Bosutinib 100 mg and 500 mg tablets consists of a high-density polyethylene bottle/closure system with desiccant as outlined in the table below.

HDPE Bottle/Closure System				
Strength	Count	Bottle Size (mL)	Closure Size (mm)	Desiccant Canister
100 mg	120	60	28	1 per bottle
500 mg	30	60	28	1 per bottle

Additionally, the insert labeling suggests the following:

- Procedures for proper disposal of anticancer drugs should be considered. Any unused product or waste material should be disposed of in accordance with local requirements, or drug take back programs.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted November 17, 2011 (no image)
- Trade Container Labels submitted November 17, 2011 (Appendix A)
- Note: Carton Labeling was not submitted since product will not be packaged in cartons as confirmed by Applicant

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

DMEPA identified the following deficiencies in the insert labeling and container labels.

3.1 INSERT LABELING

- The Dosage and Administration and Patient Counseling Information sections provide instructions on how to handle “missed doses”; however, no reference of time was given. Therefore, we recommend adding a time frame to the instructions to improve clarity for patients in both of these sections. For example, “if a dose is missed *beyond 4 hours*, the patient should not”
- Due to the nature of this oncology product, the Patient Counseling Information section should contain additional precaution/warning statements:
 - Regarding crushing and/or cutting to minimize accidental exposure during the process of crushing or cutting the tablet. An example of statement: “Do not crush or cut tablet. Do not touch or handle crushed or broken tablets.”

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Regarding the possibility of anaphylactic shock occurring with this product (two cases were reported during clinical trials) and the importance of patients notifying the prescriber of any hypersensitivity.
- We recommend removing the hyphen between the numbers in the Storage section since a hyphen can be misinterpreted as a negative sign. In addition, the information presented does not comply with current USP standards. Therefore, we recommend revising the storage condition to read “Store at 20°C to 25°C (68°F to 77°F); excursions...” rather than “Store at 25°C (77°F); excursions permitted to 15-30°C ...”
- We recognize that the Applicant uses abbreviations (e.g., Ph+, NCI CTCAE), symbols (e.g., >, <, ≤, ≥), and trailing zeros (e.g., 1.0) in the Dosage and Administration section of the insert labeling.

Generally, the Agency does not approve labeling with the use of abbreviations because they may be misinterpreted. On June 14, 2006, the Agency, in conjunction with ISMP, launched a campaign to warn healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations such as trailing zeros, or symbols. As part of this campaign, FDA agreed not to use such error prone designations in their approved product labeling because they are carried onto the prescribing practice.

However, we recognize that the use of abbreviations for disease processes is common practice in oncology, and none of these abbreviations appear on the Institute of Safe Medication Practices (ISMP) list of Error-Prone Abbreviations, Symbols, and Dose Designations². Therefore, we find it acceptable to use these abbreviations if each abbreviation is fully defined once at its first use.

Because the symbols >, <, ≤, ≥ appear on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations, we recommend using the appropriate terms “greater than, less than, etc...” instead of the symbols as they have been mistaken as the opposite of its intended meaning and practitioners have mistakenly used the incorrect symbol.

Similarly, the use of trailing zeros is also error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. ‘1.0’ is misinterpreted as ‘10’); thus, we recommend removing the trailing zeros where they appear in the insert labeling.

3.2 CONTAINER LABELS

- Trade Container 100 mg and 500 mg Labels
 - Since this is an oncology product, we recommend the addition of the warning statement “Do not crush or cut tablet. Do not touch or handle crushed or broken tablets.” on the front display panel to minimize

² ISMP’s List of Error Prone Abbreviations, Symbols and Dose Designations <http://www.ismp.org/Tools/errorproneabbreviations.pdf>

accidental exposure of the product during crushing or cutting of the tablet. This notation is also consistent with labels of other products within the same therapeutic class.

- To further differentiate this oncology product from other tablets, we recommend the addition of a statement “Cytotoxic Agent” on the front display panel to serve as a reminder to healthcare providers to alert patients to follow proper handling and disposal procedures appropriate for this class of drugs.
- The storage condition statement needs to be revised to comply with current USP designations as “20°C to 25°C (68°F to 77°F); excursions...” rather than “at 25°C (77°F); excursions...”

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication error. We recommend the following:

A. Insert Labeling

1. Include a time frame in the discussion for “missed doses” under the Dosage and Administration, Patient Counseling Information, and Patient Labeling sections. For example, “If a dose is missed *beyond 4 hours*, the patient should not”
2. Add the additional warning statements of “Do not crush or cut tablet. Do not touch or handle crushed or broken tablets.” and “There is a possibility of anaphylactic shock...” under the Patient Counseling Information as a reminder for healthcare providers to obtain detailed hypersensitivity information from the patient.
3. Include the warning regarding anaphylactic shock in the Patient Labeling section and also include common symptoms of anaphylactic shock to assist patients with identification of the event.
4. Revise the Storage section to read “Store at 20°C to 25°C (68°F to 77°F); excursions...” rather than “Store at 25°C (77°F); excursions...” to be consistent with the current USP designations.
5. Remove all trailing zeros present in the insert labeling since the use of trailing zeros is error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. ‘1.0’ is misinterpreted as ‘10’).
6. Replace the symbol < with “less than”, replace the symbol ≤ with “less than or equal to”, replace the symbol > with “greater than”, and replace the symbol ≥ with “greater than or equal to”.

B. Container Labels (100 mg and 500 mg trade bottle)

1. Unbold the dosage form “tablets”. Additionally, ensure the established name (which consists of the active ingredient plus the dosage form) has prominence commensurate with the prominence of

the proprietary name, including typography (size, font, etc.), layout, contrast, and other printing features, as per 21 CFR 201.10(g)(2).

2. Add the statement “Do not crush or cut tablet. Do not touch or handle crushed or broken tablets.” on the front principal display panel.
3. Add the statement “Cytotoxic Agent” on the front principal display panel.
4. Change the wording on the Storage condition statement to read “Store at 20°C to 25°C (68°F to 77°F); excursions...” rather than “Store at 25°C (77°F); excursions...”
5. Ensure that the expiration date and lot number is printed on each container label, as per 21 CFR 201.17 and 21 CFR 201.18. It is unclear from the label images submitted whether there is a placeholder for this information.
6. Relocate the pink circular Pfizer logo (above the proprietary name) to the side panel away from the principal display panel as it detracts from the product name.
7. Delete or decrease prominence of the vertical blue Pfizer graphic as it crowds the label and detracts from other important information such as the product name and strength.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

APPENDICES

Appendix A: (Trade 500 mg and 100 mg Labels)



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/s/

KIMBERLY A DE FRONZO
06/11/2012

ZACHARY A OLESZCZUK on behalf of TODD D BRIDGES
06/11/2012

CAROL A HOLQUIST
06/12/2012

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

NDA	203341
Brand Name	BOSULIF
Generic Name	Bosutinib
Sponsor	Wyeth Pharmaceuticals, INC.
Indication	Treatment of CP, AP, or BP ph(+) in adult patients with resistance or intolerance to prior therapy
Dosage Form	Tablets
Drug Class	Dual inhibitor of Src and Abl tyrosine kinases
Therapeutic Dosing Regimen	500 mg oral once daily with food
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	500 mg
Submission Number and Date	SDN 001/ 17 Nov 2011
Review Division	DHP

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The largest upper bounds of the 2-sided 90% CI for the mean difference between bosutinib 500 mg and placebo, and between ketoconazole 400 mg and placebo were below 10 ms. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole was 10.3 ms which is slightly higher than the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

A single dose, crossover, placebo- and moxifloxacin-controlled study, 70 subjects received bosutinib 500 mg, bosutinib 500 mg plus ketoconazole, placebo, moxifloxacin 400 mg and placebo plus ketoconazole. 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 Bosutinib 500 mg, Bosutinib 500 mg plus Ketoconazole and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Bosutinib 500 mg	8	2.4	(0.3, 4.5)
Bosutinib 500 mg + ketoconazole*	8	7.4	(4.5, 10.3)
Moxifloxacin 400 mg**	6	8.8	(6.7, 10.9)

* Mean (90% CI) $\Delta\Delta\text{QTcF}$ for bosutinib (adjusted for placebo+ketoconazole) when administered with ketoconazole

** Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 6.0 ms

Based on concentration- $\Delta\Delta\text{QTcF}$ analysis, the expected $\Delta\Delta\text{QTcF}$ for the 500-mg dose is 3.8 ms (90% CI: 2.0 to 5.5 ms) at a mean C_{max} of 326 ng/ml (2.9-fold the mean C_{max} of 500-mg bosutinib dose). The steady state exposures of bosutinib following multiple doses of bosutinib with ketoconazole will be higher than what is observed in this study. However, the risk of QT prolongation at these exposures is mitigated by the fact that the proposed label recommends to avoid moderate or potent CYP3A inhibitors with bosutinib and proposes a dose reduction if bosutinib must be coadministered with a moderate or potent CYP3A inhibitor. Hepatic impairment will decrease bosutinib's clearance as it is metabolized by liver. However, exposure data in patients with hepatic impairment is not available. The label recommends decreasing the starting dose of bosutinib to 200 mg in patients with hepatic impairment.

2 PROPOSED LABEL

2.1 SPONSOR PROPOSED LABEL

Sponsor proposed the following language in the label:

(b) (4)

[Redacted text block]

2.2 QT-IRT RECOMMENDED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

The effect of single dose of bosutinib 500 mg and 500 mg with ketoconazole on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) two or three-period crossover thorough QT study in 70 healthy subjects. In a study with demonstrated ability to detect small effects, no significant changes in placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) were observed. The exposure of bosutinib with ketoconazole was 2.9-fold that with bosutinib alone. The dose of 500 mg bosutinib with ketoconazole covers the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Bosutinib is a substituted 4-anilinoquinoline-3-carbonitrile noncytotoxic Src and Abl kinase inhibitor with oral activity in several human tumor xenograft models, including models for Philadelphia chromosome positive chronic myelogenous leukemia (CML).

This application seeks approval for bosutinib for the treatment of chronic, accelerated, or blast phase Ph⁺ chronic myelogenous leukemia (CML) in patients with resistance or intolerance to prior therapy.

3.2 MARKET APPROVAL STATUS

Bosutinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.4

“The potential effects of bosutinib on the rapidly activating, delayed rectifier cardiac potassium ion current (I_{Kr}) were examined in two in vitro hERG assays using patch clamp electrophysiology techniques with stably transfected HEK-293 cells at concentrations of 0.1, 0.3, 1, and 10 μM. (RPT-54968; RPT-56238; RPT-61333; RPT-61223). Bosutinib inhibited the hERG potassium ion current in a concentration-dependent manner with calculated IC₅₀s of 0.3 μM (159 ng/mL) and 0.7 μM (371 ng/mL). The lower of the two values (0.3 μM) is 12.6-fold above the unbound C_{max} in humans (23.8 nM, 12.6 ng/mL) following administration of the 500 mg dose. The metabolites of bosutinib (M5:PF-05312061 and M2:PF-05898965) were also evaluated in hERG assays (PF05312061HERG; PF05898965HERG). PF-05898965 produced a concentration-dependent inhibition of the hERG current with an IC₅₀ of 27.9 μM and PF-05312061 produced a concentration-dependent inhibition of the hERG current with an IC₅₀ of 8.7 μM. The IC₅₀s for the two metabolites in the hERG assays were > 90-fold above the human C_{max} following administration of the 500 mg bosutinib dose for both the M2 (55.5 nM) and M5 (93.1 nM) metabolites.

“In a single-dose oral cardiovascular safety study of bosutinib (RPT-51769), doses of 0, 2, 5, or 10 mg/kg did not produce changes in blood pressure. No abnormal atrial or ventricular arrhythmias were detected in this study and there was no bosutinib-related prolongation of the PR, QRS, or QTc interval of the electrocardiogram (ECG). A statistically significant ($p \leq 0.05$) average baseline corrected heart rate increase of 15% (14 bpm) was observed 17:30 to 24 hours, with the maximum effect at 21:45 hours post dose, following the 10 mg/kg dose administration. At 10 mg/kg, the dose at which there were no effects on blood pressure or ECG measurements in dogs, the unbound C_{max} (27 ng/mL) for males was approximately 2.2-fold the unbound C_{max} in humans (12.6 ng/mL) following administration of the 500 mg dose. The dose at which no effects on heart rate were observed (5 mg/kg) has an associated C_{max} (9 ng/mL) that was slightly below the C_{max} in humans.

“Bosutinib was administered IV (15-minute infusion) to 3 male beagle dogs in single ascending dosages of 3, 7, and 15 mg/kg (RPT-50437). During the 15-minute infusion, heart rates were decreased (11% to 16% compared with baseline). Heart rate decreased at all 3 dosages (5% to 17%) between 2 to 120 minutes after the end of the infusion, but gradually returned to baseline values. During the 2 minutes after the infusion ended, the mean blood pressure increased (4% to 20%) for the 3 dosages. Between 2 and 120 minutes after the end of the infusion, mean blood pressure values returned to near baseline values at all dosages.

“No abnormal atrial or ventricular arrhythmias were detected in any of the ECG tracings examined. The average increase in QTc interval compared with predose value was 8, 5, and 8 milliseconds for 3, 7, and 15 mg/kg, respectively. The unbound C_{max} (183 ng/mL) at the 15 mg/kg dose was approximately 14.8-fold the unbound C_{max} in humans (12.6 ng/mL) following administration of the 500 mg dose. While all of the postdose QT intervals fell within the 95% confidence bounds for this animal population, the study design and small.”

Reviewer’s comments: Bosutinib and its metabolites inhibit hERG currents with low affinity (IC₅₀ within the micromolar range).

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4, page 285

“Bosutinib was well tolerated when given to healthy subjects as a single 500-mg oral dose alone, and in combination with ketoconazole 400 mg. GI disorders and nervous system disorders accounted for the most commonly reported TEAEs. No cardiac TEAEs, torsade de pointes, sudden death, ventricular arrhythmia, syncope, or seizure were observed following administration of bosutinib or coadministration of bosutinib and ketoconazole. All the TEAEs reported following administration of bosutinib or coadministration of bosutinib and ketoconazole were considered to be mild or moderate. No SAEs or deaths were reported.

From eCTD 2.7.4, page 139

“Cardiac events were reported in 39 (13.5%) CP CML subjects who received bosutinib as second-line treatment. Overall, the most common cardiac TEAEs ($\geq 2\%$) were atrial

fibrillation and palpitations in 7 subjects each (2.4%), and angina pectoris in 6 subjects (2.1%) (Table 73).

“Of the 39 subjects with cardiac TEAEs, 13 subjects had drug-related cardiac TEAEs, 17 subjects had SAEs, and 1 of these subjects died of cardiac failure not considered to be treatment related. Of the other SAEs, 4 events were drug-related, including Grade 4 pericardial effusion, Grade 2 cardiac failure, and 1 subject with concurrent Grade 3 angina unstable and coronary artery disease.

“The remaining SAEs included 4 subjects with atrial fibrillation, 2 subjects each with cardiac failure congestive, pericardial haemorrhage, angina pectoris, and acute MI, and 1 subject each with angina unstable, cardiorenal syndrome, left ventricular dysfunction, pericarditis, extrasystoles, coronary artery stenosis, coronary artery disease, and ventricular fibrillation. The majority of SAEs (with the exception of atrial fibrillation, left ventricular dysfunction, coronary artery stenosis, and cardiac failure congestive) resulted in hospitalization.

“Two (2) subjects discontinued bosutinib treatment due to cardiac events including 1 SAE of Grade 2 drug-related cardiac failure and 1 TEAE of Grade 2 coronary artery disease which was not considered drug related. The maximum toxicity of TEAEs was Grade 1 or 2 in 59.0% of subjects, Grade 3 in 25.6% of subjects, and Grade 4 in 12.8% of subjects. Among subjects with cardiac TEAEs, the median time to first event was 134 days (range, 1 to 1375 days). The median duration of any grade cardiac TEAE was 7 days (range, 1 to 644 days).

Table 2: Treatment-Emergent Cardiac Events Chronic Phase Second-Line Safety Population: Study 3160A4 200-WW

System Organ Class ^a Preferred Term	IM Resistant n=200	IM Intolerant n=88	Total n=288
Any cardiac adverse event	24 (12.0)	15 (17.0)	39 (13.5)
Cardiac disorders	24 (12.0)	14 (15.9)	38 (13.2)
Atrial fibrillation	6 (3.0)	1 (1.1)	7 (2.4)
Palpitations	5 (2.5)	2 (2.3)	7 (2.4)
Angina pectoris	3 (1.5)	3 (3.4)	6 (2.1)
Angina unstable	3 (1.5)	1 (1.1)	4 (1.4)
Bradycardia	1 (0.5)	3 (3.4)	4 (1.4)
Cardiac failure	3 (1.5)	1 (1.1)	4 (1.4)
Cardiac failure congestive	2 (1.0)	2 (2.3)	4 (1.4)
Coronary artery disease	1 (0.5)	2 (2.3)	3 (1.0)
Tachycardia	2 (1.0)	1 (1.1)	3 (1.0)
Acute myocardial infarction	1 (0.5)	1 (1.1)	2 (0.7)
Cardiomyopathy	0	2 (2.3)	2 (0.7)
Coronary artery stenosis	2 (1.0)	0	2 (0.7)
Left ventricular dysfunction	2 (1.0)	0	2 (0.7)
Pericardial effusion	2 (1.0)	0	2 (0.7)
Pericardial haemorrhage	2 (1.0)	0	2 (0.7)
Atrial tachycardia	1 (0.5)	0	1 (0.3)
Atrioventricular block complete	1 (0.5)	0	1 (0.3)
Cardiac failure chronic	1 (0.5)	0	1 (0.3)
Cardiorenal syndrome	0	1 (1.1)	1 (0.3)
Diastolic dysfunction	0	1 (1.1)	1 (0.3)
Dilatation atrial	1 (0.5)	0	1 (0.3)
Extrasystoles	1 (0.5)	0	1 (0.3)
Hypertensive heart disease	1 (0.5)	0	1 (0.3)
Long QT syndrome	0	1 (1.1)	1 (0.3)
Pericarditis	1 (0.5)	0	1 (0.3)
Sinus bradycardia	1 (0.5)	0	1 (0.3)
Supraventricular extrasystoles	0	1 (1.1)	1 (0.3)
Ventricular fibrillation	1 (0.5)	0	1 (0.3)
Investigations	0	1 (1.1)	1 (0.3)
Electrocardiogram QT prolonged	0	1 (1.1)	1 (0.3)

Date of Snapshot: 28MAR11

Abbreviations: IM=imatinib, MedDRA=Medical Dictionary for Regulatory Activities

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have 2 or more different adverse events within the higher level category.

Classifications of adverse events are based on the MedDRA.

Within each system organ class, events are presented in descending order of incidence based on "Total" incidence.

AE4T-BTOX-CAR-CP2L - 04MAY11 20:24

Source: eCTD 2.7.4, Table 73

“CP CML Third-Line. Cardiac TEAEs were reported for 13 subjects (11%) with CP CML who received bosutinib as third-line treatment. The most commonly reported cardiac TEAEs for this cohort were atrial fibrillation and pericardial effusion in 3 subjects each.

“Of the 13 subjects with cardiac TEAEs, 7 subjects had drug-related TEAEs, 5 subjects had SAEs, including 2 subjects who died of cardiac TEAEs (MI and acute MI, respectively) not considered to be drug related. Of the 3 non-fatal SAEs, 1 subject was hospitalized for a Grade 1 drug-related pericardial effusion which resolved after a treatment delay and dose reduction; 1 subject was also hospitalized for concomitant SAEs of Grade 3 atrial fibrillation and Grade 1 palpitations that were not drug related and did not result in bosutinib discontinuation; and 1 subject had Grade 4 drug-related pericarditis which resulted in bosutinib discontinuation, but not hospitalization. The 2

additional subjects that discontinued bosutinib due to a cardiac TEAE were the subjects who died of MIs, although for 1 of these subjects, the reason for treatment discontinuation was a TEAE of Grade 2 cardiac failure which occurred concurrently with the SAE of MI. Among subjects with cardiac TEAEs, the median time to first event was 92 days (range, 1 to 1304 days). The median duration of any grade cardiac TEAE was 14 days (range, 1 to 140 days).

“Advanced Leukemia. Cardiac TEAEs were reported in 14 subjects (18.4%) in the AP CML cohort, 9 subjects (14.1%) in the BP CML cohort, and 1 subject (4.2%) in the Ph+ ALL cohort (Table 75). The most commonly reported cardiac TEAEs in the AP CML cohort were pericardial effusion (4 subjects, 5.3%) and tachycardia (2 subjects, 2.6%) and the most commonly reported cardiac TEAEs for the BP CML cohort were tachycardia (4 subjects, 6.3%) and pericardial effusion (2 subjects, 3.1%). In the Ph+ ALL cohort, prolonged ECG QT interval (1 subject, 4.2%) was the only cardiac-related TEAE reported.

“Safety for Studies 3160A4-200-WW, 3160A4-3000-WW and 3160A4-2203-JA are presented in Table 3 and Table 4.

Table 3: Number (%) of Subjects Reporting Drug Related Treatment Emergent Adverse Events (in Descending Order of the Incidences) For Cluster AE Terms- Cardiac(All Grades Related AEs Only) Safety Population

System Organ Class ^a Preferred Term	Treatment			Total n=870
	3000 n=248	200 n=570	2203 n=52	
Any Adverse Event	12 (4.8)	25 (4.4)	3 (5.8)	40 (4.6)
Cardiac disorders	7 (2.8)	22 (3.9)	3 (5.8)	32 (3.7)
Pericardial effusion	0	7 (1.2)	1 (1.9)	8 (0.9)
Cardiac failure	1 (0.4)	3 (0.5)	0	4 (0.5)
Palpitations	1 (0.4)	2 (0.4)	0	3 (0.3)
Angina pectoris	0	2 (0.4)	0	2 (0.2)
Atrial fibrillation	0	2 (0.4)	0	2 (0.2)
Left ventricular dysfunction	0	2 (0.4)	0	2 (0.2)
Ventricular extrasystoles	1 (0.4)	0	1 (1.9)	2 (0.2)
Angina unstable	0	1 (0.2)	0	1 (0.1)
Arrhythmia	0	1 (0.2)	0	1 (0.1)
Arrhythmia supraventricular	1 (0.4)	0	0	1 (0.1)
Atrioventricular block second degree	1 (0.4)	0	0	1 (0.1)
Bradycardia	0	1 (0.2)	0	1 (0.1)
Bundle branch block right	1 (0.4)	0	0	1 (0.1)
Cardiac failure congestive	0	1 (0.2)	0	1 (0.1)
Cardiac tamponade	0	1 (0.2)	0	1 (0.1)
Cardiomegaly	0	0	1 (1.9)	1 (0.1)
Coronary artery disease	0	1 (0.2)	0	1 (0.1)
Coronary artery stenosis	0	1 (0.2)	0	1 (0.1)
Dilatation atrial	0	1 (0.2)	0	1 (0.1)
Long QT syndrome	0	1 (0.2)	0	1 (0.1)
Myocardial infarction	0	1 (0.2)	0	1 (0.1)
Pericarditis	0	1 (0.2)	0	1 (0.1)
Sinus bradycardia	1 (0.4)	0	0	1 (0.1)
Supraventricular extrasystoles	0	1 (0.2)	0	1 (0.1)
Investigations	5 (2.0)	3 (0.5)	0	8 (0.9)
Electrocardiogram QT prolonged	5 (2.0)	2 (0.4)	0	7 (0.8)
Blood pressure increased	0	1 (0.2)	0	1 (0.1)

Date of Snapshot: 3000 - 15NOV2010, 200 - 15NOV2010, 2203 - 15NOV2010. MedDRA System Organ Class (SOC) = Cardiac disorders OR High Level Group Term (HLGT) = Cardiac and vascular investigations (excl enzyme tests).

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences under 'Total' column.

^a Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

AT-SUB-CARD-REL - 14DEC10 15:28

Source: eCTD 2.7.4, Supporting Table 27

Table 4: Number (%) of Subjects Reporting Drug Related Treatment Emergent Adverse Events (in Descending Order of the Incidences) For Cluster AE Terms- Cardiac(Grades 3 and 4 Related AEs Only) Safety Population

System Organ Class ^a Preferred Term	Treatment			Total n=870
	3000 n=248	200 n=570	2203 n=52	
Any Adverse Event	2 (0.8)	9 (1.6)	0	11 (1.3)
Cardiac disorders	1 (0.4)	8 (1.4)	0	9 (1.0)
Atrial fibrillation	0	2 (0.4)	0	2 (0.2)
Cardiac failure	1 (0.4)	1 (0.2)	0	2 (0.2)
Pericardial effusion	0	2 (0.4)	0	2 (0.2)
Angina unstable	0	1 (0.2)	0	1 (0.1)
Arrhythmia	0	1 (0.2)	0	1 (0.1)
Cardiac tamponade	0	1 (0.2)	0	1 (0.1)
Coronary artery disease	0	1 (0.2)	0	1 (0.1)
Coronary artery stenosis	0	1 (0.2)	0	1 (0.1)
Left ventricular dysfunction	0	1 (0.2)	0	1 (0.1)
Pericarditis	0	1 (0.2)	0	1 (0.1)
Investigations	1 (0.4)	1 (0.2)	0	2 (0.2)
Blood pressure increased	0	1 (0.2)	0	1 (0.1)
Electrocardiogram QT prolonged	1 (0.4)	0	0	1 (0.1)

Date of Snapshot: 3000 - 15NOV2010, 200 - 15NOV2010, 2203 - 15NOV2010. MedDRA System Organ Class (SOC) = Cardiac disorders OR High Level Group Term (HLGT) = Cardiac and vascular investigations (excl enzyme tests).

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences under 'Total' column.

a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

AE-T-SUB-CARD-REL34 - 14DEC10 15:28

On: 15 Oct 2011 15:28

Source: eCTD 2.7.4, Supporting Table 28

Reviewer's comments: Drug related QT prolongation was reported in several studies (including grade 3 and 4 cases). Cases of cardiac failure, pericardial effusion, atrial fibrillation, ventricular tachycardia were reported, none of them was ruled as related to study drug. No Torsade de pointes was reported. A high proportion of deaths occurred within 30 days of study treatment. Main causes of death were disease progression, infection and acute cardiac decompensation.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 68268. The sponsor submitted the study report 3160A4-105-US for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Final Report: A Single Dose, Crossover, Placebo- And Moxifloxacin-Controlled Study Of The Effects Of Bosutinib On Cardiac Repolarization In Healthy Adult Subjects.

4.2.2 Protocol Number

Protocol 3160A4-105-US

4.2.3 Study Dates

18 Jun 2009 to 12 Aug 2009

4.2.4 Objectives

Primary objective was to assess the effect on corrected QT interval (QTc) after administration of bosutinib.

Secondary objectives were to characterize the pharmacokinetic (PK)/pharmacodynamics (PD) relationships and to provide additional safety information.

4.2.5 Study Description

4.2.5.1 Design

“This study was a randomized, single-dose, double-blind (with respect to bosutinib), crossover, placebo- and open-label moxifloxacin-controlled study in healthy subjects, conducted at a single investigational site. The study was conducted in 2 parts with treatments in each part randomly assigned utilizing a crossover design. Part A consisted of 3 periods in which subjects were administered a single dose of test article (bosutinib 500 mg, placebo, or moxifloxacin 400 mg) in a fed state. Part B consisted of 2 periods in which subjects were administered a single dose of test article (bosutinib 500 mg or placebo) concomitantly with ketoconazole 400 mg in a fed state. Subjects were randomly assigned to 1 of 12 dosage administration sequences, which consisted of a combination of each of the 5 treatment arms: bosutinib, placebo, moxifloxacin, bosutinib coadministered with ketoconazole, and placebo coadministered with ketoconazole (see Table 5). Each bosutinib dose was separated by a minimum 14-day washout period. Each bosutinib dose was separated by a minimum 14-day washout period.”

Source: Study protocol, page 16

Table 5: Sponsor’s Randomization Sequence for Study 3160A4-105-US

Part A			Part B	
Sequence	Period 1	Period 2	Period 3	Period 4
1	A	C	B	D
2	A	C	B	E
3	A	B	C	D
4	A	B	C	E
5	C	A	B	D
6	C	A	B	E
7	C	B	A	D
8	C	B	A	E
9	B	A	C	D
10	B	A	C	E
11	B	C	A	D
12	B	C	A	E

Treatment groups: A=Placebo; B=Moxifloxacin 400-mg tablets; C=bosutinib (5x100-mg tablets);
D=Placebo (5 capsules) coadministered with ketoconazole (2x200-mg tablets);
E=bosutinib (5x100-mg capsules) coadministered with ketoconazole (2x200-mg tablets).

4.2.5.2 Controls

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

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.5.4 Treatment Arms

The study was conducted in 2 parts (part A, therapeutic dose comparison; and part B, suprathreshold dose comparison). Subjects were randomly assigned to 1 of 12 dosage administration sequences, which consisted of each of the following treatment arms:

A=Placebo

B=Moxifloxacin (1x400-mg tablets)

C=Bosutinib (5x100-mg capsules)

D=Placebo (5 capsules) coadministered with ketoconazole (2x200-mg tablets)

E=Bosutinib (5x100-mg capsules) coadministered with ketoconazole (2x200-mg tablets).

Each bosutinib dose was separated by a minimum 14-day washout period.

4.2.5.5 Sponsor’s Justification for Doses

“In phase 2 and 3 studies in CML, bosutinib is being administered at doses of 500 mg with food. Single dose bosutinib 500 mg (fed) in healthy subjects achieves C_{max} of approximately 100 ng/ml. These single dose plasma exposures represent approximately half the steady state C_{max} of bosutinib (fed) observed in cancer patients receiving bosutinib 500 mg daily (mean of 197 ng/ml) due to accumulation with repeated dosing. Considering the half-life of parent bosutinib in healthy subjects (33 hours in 3160A4-103) and the observed extent of accumulation, a multiple dose study design would be

preferred for evaluating cardiac repolarization. Nevertheless, a multiple dose cardiac repolarization study of bosutinib in healthy subjects is not feasible due to the high frequency of NCI CTC Grade 3 and higher TEAEs (59.4%) observed with administration of multiple doses of bosutinib in cancer patients (3160A4-200).

“Supratherapeutic plasma concentrations of bosutinib are achievable when single dose bosutinib 500 mg (fed) is coadministered with multiple doses of ketoconazole. In study 3160A4-1114, single dose bosutinib (fed) administered in the presence of ketoconazole was tolerated by healthy subjects up to a dose of 600 mg. The median C_{max} achieved by coadministration of 500 mg bosutinib (fed) with ketoconazole was 419 ng/ml. This safely achievable plasma exposure in healthy subjects is greater than the highest C_{max} reported for 48 out of 49 patients with CML (based on preliminary PK data from 3160A4-200) and 2.8-fold greater than the median (range) steady state C_{max} of 149 ng/mL (27 to 483 ng/mL) in CML patients. Therefore, single 500 mg (fed) doses of bosutinib will be administered with ketoconazole in the “supratherapeutic” period of the study.”

Source: ClinPharm Table

Reviewer’s Comment: The doses selected for the study are acceptable.

4.2.5.6 Instructions with Regard to Meals

“Test article was administered orally with 240 mL of room-temperature water, according to the randomization sequence (see Table 5-1) on study day 1 of each study period, at approximately 0800 hours. During each period in part A, test article (bosutinib, moxifloxacin, or placebo) was administered orally on day 1, at approximately 0800 hours with 240 mL of room-temperature water, after completion of a standard meal.

“After a 9-day outpatient washout period, the subjects participated in part B, which consisted of 2 periods. During each period in part B, test article (bosutinib or placebo) was administered orally on day 1, concomitantly with ketoconazole after completion of a standard meal.”

Source: csr-79951 report, page 21

Reviewer’s Comment: Administration of bosutinib with food is acceptable since exposures are increased when bosutinib is administered in fed state. In phase 2 and 3 studies in CML, bosutinib is being administered at doses of 500 mg with food. Also, in the package insert the sponsor recommends that bosutinib dose is to be administered with food.

4.2.5.7 ECG and PK Assessments

“Twelve (12)-lead electrocardiograms (ECGs) were recorded at screening, on day -1, and before and after dose administration in all the study periods for part A and part B of the study. With the exception of the screening visit and admission (study day -1) for parts A and B, triplicate ECG recordings were obtained on day 1 at -1 hour, -0.5 hour, and 0 hour (immediately before dose administration), and at 1.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours after test article administration in all periods.

“Blood samples were collected to measure concentrations of bosutinib and metabolites (M5 [N-desmethyl bosutinib] and M2 [oxydechlorinated bosutinib]), moxifloxacin (period in which moxifloxacin is administered during part A), or ketoconazole (both periods of part B) on study day 1 within 2 hours before test article administration (hour - 2) and at 1.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours after test article administration in all periods.”

Source: csr-79951 report, page 17-18

Reviewer’s Comment: Based on the reported T_{max} of 4-6 hours for bosutinib and its metabolites, the timing of ECGs and PK assessments is acceptable.

4.2.5.8 Baseline

The Sponsor used the average of 3 pre-dose QTc values as baseline.

4.2.6 ECG Collection

Triplicate 12-lead ECG were taken 1-2 minutes apart before investigational product administration on day 1: 1 hour, 0.5 hour, and immediately before investigational product administration.

XML files of annotated electrocardiograms (ECGs) that are generated were in accordance with HL7 industry standards.

4.2.7 Sponsor’s Results

4.2.7.1 Study Subjects

Sixty (60) subjects were enrolled in this study and all were men. The median age of enrolled subjects was 28.5 years (range, 18 to 50 years). Forty-nine (49) subjects (81.7%) completed the study. Eleven (11) subjects (18.3%) prematurely discontinued participation in the study.

A summary of the demographic characteristics of enrolled subjects is presented in Table 6.

Table 6: Demographic and Baseline Characteristics: Safety Population, Study 3160A4-105-US

Characteristic	All Subjects (n=60)
Age (year)	
N	60
Mean	30.57
Standard deviation	9.82
Minimum	18
Maximum	50
Median	28.5
Sex, n (%)	
Male	60 (100)
Race, n (%)	
American Indian or Alaska Native	1 (1.67)
Black or African American	12 (20.00)
Native Hawaiian or Other Pacific Islander	1 (1.67)
White	46 (76.67)
Ethnic origin, n (%)	
Hispanic or Latino	1 (1.67)
Non-Hispanic and Non-Latino	59 (98.33)
Baseline height (cm)	
N	60
Mean	176.93
Standard deviation	6.78
Minimum	161
Maximum	191
Median	177
Baseline weight (kg)	
N	60
Mean	81.4
Standard deviation	12.46
Minimum	57.6
Maximum	111
Median	82.9
Body mass index (kg/m²)	
N	60
Mean	25.95
Standard deviation	3.38
Minimum	19.56
Maximum	32.04
Median	26.64

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3160A4/105/CDRs/3160-105 demo4.htm - 14DEC09 15:55

Source: CSR, Table 6-1.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint proposed by the sponsor was the change from baseline mean differences between bosutinib 500 mg and placebo (therapeutic dose), and between

bosutinib 500 mg plus ketoconazole (supratherapeutic dose) and placebo plus ketoconazole in population-specific correction (QTcN). The sponsor used an analysis of covariance (ANCOVA) and it included baseline as a covariate, sequence, treatment, period, and treatment by time interactions as fixed effects, and subject as random effect. The sponsor's results based on QTcN were listed in Table 7 and Table 8. The upper bounds of the 90% CI for QTcN were less than 10 ms at all post-dose time points for both the therapeutic and the supratherapeutic doses. The sponsor also performed the same analysis using QTcF, and the results were listed in Table 9 and Table 10.

Table 7: Sponsor's Results of Δ QTcN and $\Delta\Delta$ QTcN for Bosutinib 500 mg

Test	Time	Estimate	Standard Error	90% CI
QTc Population Correction	1.5	1.99	1.22	(-0.01, 3.99)
QTc Population Correction	3	0.75	1.22	(-1.25, 2.75)
QTc Population Correction	4	-1.56	1.22	(-3.56, 0.44)
QTc Population Correction	5	-0.81	1.22	(-2.81, 1.19)
QTc Population Correction	6	0.98	1.22	(-1.02, 2.98)
QTc Population Correction	8	-0.17	1.22	(-2.17, 1.84)
QTc Population Correction	12	-0.95	1.22	(-2.96, 1.06)
QTc Population Correction	24	1.52	1.22	(-0.48, 3.53)
QTc Population Correction	48	2.52	1.22	(0.51, 4.52)
QTc Population Correction	72	2.56	1.22	(0.54, 4.57)

Abbreviations: CI=confidence interval; QTc=corrected QT interval; QTcN= QTc based on a population-specific correction formula.

Source: Sponsor's CSR Table 9-6 on page 74/351

Table 8: Sponsor's Results of Δ QTcN and $\Delta\Delta$ QTcN for Bosutinib 500 mg Plus Ketoconazole

Test	Time	Estimate	Standard Error	90% CI
QTc Population Correction	1.5	1.01	1.42	(-1.33, 3.35)
QTc Population Correction	3	-0.65	1.42	(-2.99, 1.69)
QTc Population Correction	4	-0.25	1.42	(-2.59, 2.09)
QTc Population Correction	5	-1.00	1.42	(-3.34, 1.34)
QTc Population Correction	6	3.99	1.42	(1.64, 6.32)
QTc Population Correction	8	4.48	1.42	(2.14, 6.82)
QTc Population Correction	12	3.44	1.42	(1.11, 5.78)
QTc Population Correction	24	-1.22	1.42	(-3.56, 1.12)
QTc Population Correction	48	-2.62	1.42	(-4.96, -0.27)
QTc Population Correction	72	-0.54	1.43	(-2.88, 1.81)

Abbreviations: CI=confidence interval; QTc=corrected QT interval; QTcN= QTc based on a population-specific correction formula; *Source: Sponsor's CSR Table 9-6 on page 76/351*

Table 9: Sponsor's results of Δ QTcF and $\Delta\Delta$ QTcF for Bosutinib 500 mg

Test	Time	Estimate	Standard Error	90% CI
QTcF Interval	1.5	2.33	1.16	(0.41, 4.24)
QTcF Interval	3	1.88	1.16	(-0.04, 3.78)
QTcF Interval	4	0.37	1.16	(-1.54, 2.28)
QTcF Interval	5	-0.8	1.16	(-2.79, 1.04)
QTcF Interval	6	1.92	1.16	(0.00, 3.83)
QTcF Interval	8	2.46	1.17	(0.54, 4.38)
QTcF Interval	12	0.7926	1.17	(-1.13, 2.71)
QTcF Interval	24	2.09	1.17	(0.17, 4.01)
QTcF Interval	48	2.29	1.17	(0.37, 4.21)
QTcF Interval	72	2.33	1.17	(0.40, 4.25)

Abbreviations: CI=confidence interval; QTc=corrected QT interval; QTcN= QTc based on a population-specific correction formula; *Source: Sponsor's CSR Table 9-6 on page 78/351*

Table 10: Sponsor’s results of Δ QTcF and $\Delta\Delta$ QTcF for Bosutinib 500 mg Plus Ketoconazole

Test	Time	Estimate	Standard Error	90% CI
QTcF	1.5	0.26	1.38	(-2.01, 2.52)
QTcF	3	0.49	1.38	(-1.78, 2.76)
QTcF	4	1.55	1.38	(-0.72, 3.82)
QTcF	5	-1.24	1.38	(-3.51, 1.03)
QTcF	6	3.48	1.38	(1.21, 5.75)
QTcF	8	7.36	1.38	(5.09, 9.63)
QTcF	12	5.78	1.38	(3.51, 8.04)
QTcF	24	1.93	1.38	(-0.34, 4.19)
QTcF	48	-0.40	1.39	(-2.67, 1.87)
QTcF	72	1.34	1.38	(-0.94, 3.61)

Abbreviations: CI=confidence interval; QTc=corrected QT interval; QTcN= QTc based on a population-specific correction formula.

Source: Sponsor’s CSR Table 9-7 on page 79/351

Reviewer’s Comments: We will provide our independent analysis results in Section 5.2. We used QTcF as primary endpoint. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole is 10.3 ms.

4.2.7.2.2 Assay Sensitivity

The sponsor used the same model to analyze Δ QTcF effect for moxifloxacin. The results are presented in Table 11. The lower limit of the 2-sided 90% CI for the mean difference was above 5 ms. The sponsor concluded that this study has established the assay sensitivity.

Table 11: Sponsor’s results for $\Delta\Delta\text{QTcF}$ for Moxifloxacin 400 mg

Test	Time	Estimate	Standard Error	90% CI
QTc Interval	1.5	7.28	1.15	(5.37, 9.18)
QTc Interval	3	8.12	1.16	(6.21, 10.02)
QTc Interval	4	8.41	1.16	(6.50, 10.31)
QTc Interval	5	7.54	1.16	(5.63, 9.45)
QTc Interval	6	8.97	1.16	(7.06, 10.88)
QTc Interval	8	8.02	1.16	(6.11, 9.93)
QTc Interval	12	7.90	1.16	(5.98, 9.81)
QTc Interval	24	6.29	1.16	(4.38, 8.20)
QTc Interval	48	2.33	1.16	(0.42, 4.24)
QTc Interval	72	2.33	1.17	(0.40, 4.26)

Source: Sponsor’s CSR Table 13.12 on page 255/351

Reviewer’s Comments: We will provide our independent analysis result in Section 5.2. Our results are similar to the sponsor’s findings.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc >450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject’s absolute QTc >500 ms and ΔQTc >60 ms.

4.2.7.3 Safety Analysis

Eleven (11) subjects (18.3%) prematurely discontinued participation in the study, only two because of AEs (drug hypersensitivity and urticaria).

From CSR, page 34

“At least 1 TEAE was reported for 53 subjects (83.3%) in any treatment group. Thirty-nine (39) subjects (69.6%) reported at least 1 TEAE while receiving bosutinib alone, 38 subjects (70.4%) while receiving bosutinib and ketoconazole, 22 subjects (37.9%) while receiving moxifloxacin, 17 subjects (34.7%) while receiving placebo and ketoconazole, and 15 subjects (25.9%) while receiving placebo alone. No subjects had TEAEs during the post-study period.

“GI disorders and nervous system disorders accounted for the most commonly reported TEAEs. The TEAEs reported for \square 10% of subjects, regardless of severity were diarrhea (36 subjects, 60%); nausea (34 subjects, 56.7%); headache (33 subjects, 55%); abdominal pain (15 subjects, 25%); dizziness (13 subjects, 21.7%); fatigue (11 subjects, 18.3%); and application site dermatitis and vomiting (9 subjects each, 15%). All TEAEs reported

during the study were either considered to be mild (30 subjects, 50%) or moderate (22 subjects, 36.7%), except for syncope (severe), reported by subject 105-001-000038 after receiving moxifloxacin. The TEAE resolved at the time of study completion and it was considered to be not related to the test article. No cardiac TEAEs, torsade de pointes, sudden death, ventricular arrhythmia, syncope, or seizure were observed following administration of bosutinib or coadministration of bosutinib and ketoconazole.”

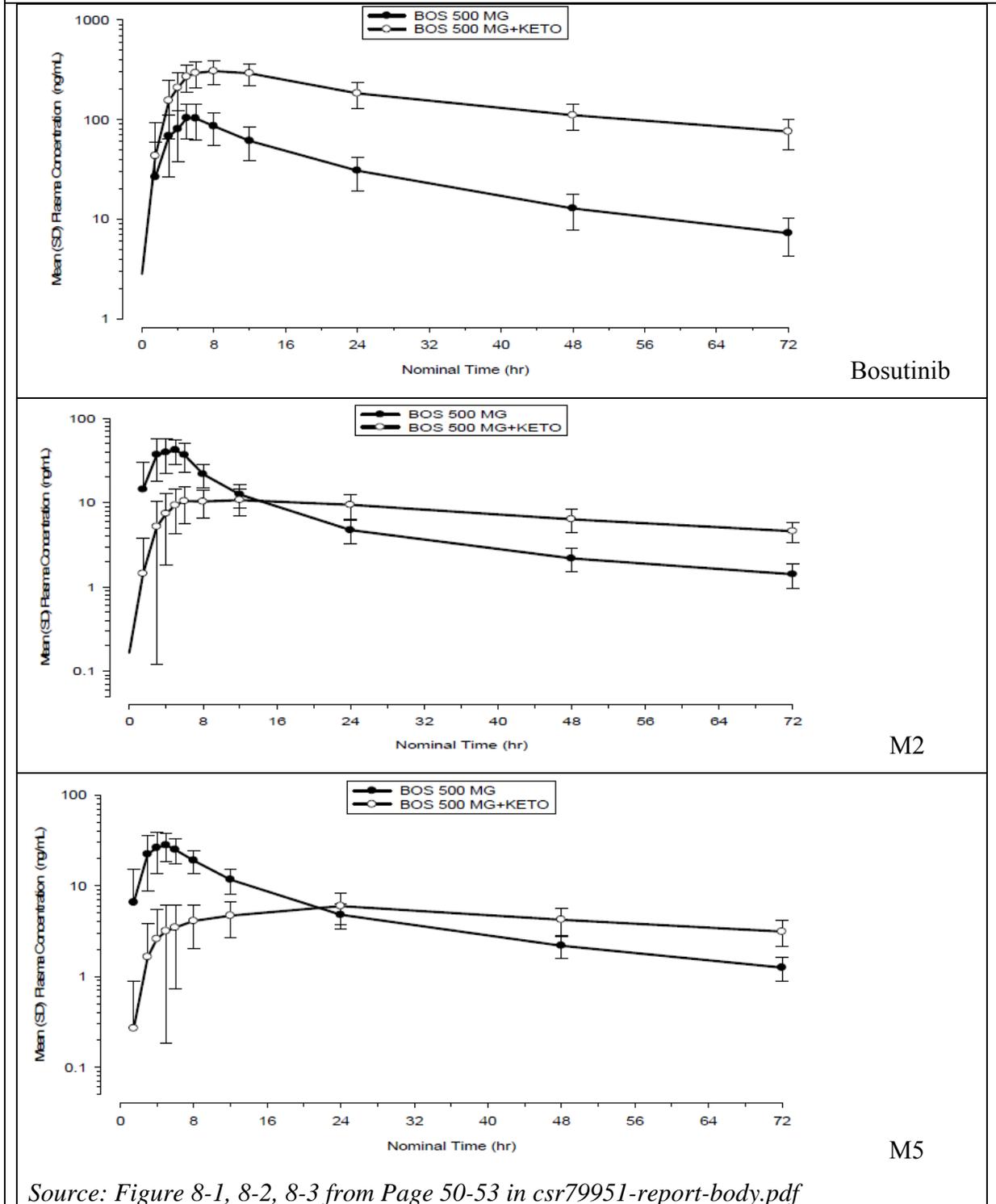
Reviewer’s comments: None of the AEs of interest were reported (ICH E14 guidance). No subjects reported SAEs during this study. No subjects died during the study.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

Mean plasma concentration versus time profiles of bosutinib, M2, and M5 following a single oral dose of bosutinib 500 mg alone and in combination with multiple oral doses of ketoconazole 400 mg in healthy subjects under fed conditions are presented in Figure 1.

Figure 1: Bosutinib and its Metabolites (M1, M5) Plasma Concentration Versus Time Profiles (Mean \pm Standard Deviation) After a Single Oral Dose of Bosutinib 500 mg and in Combination With Multiple Oral Doses of Ketoconazole 400 mg in Healthy Subjects Under Fed Conditions



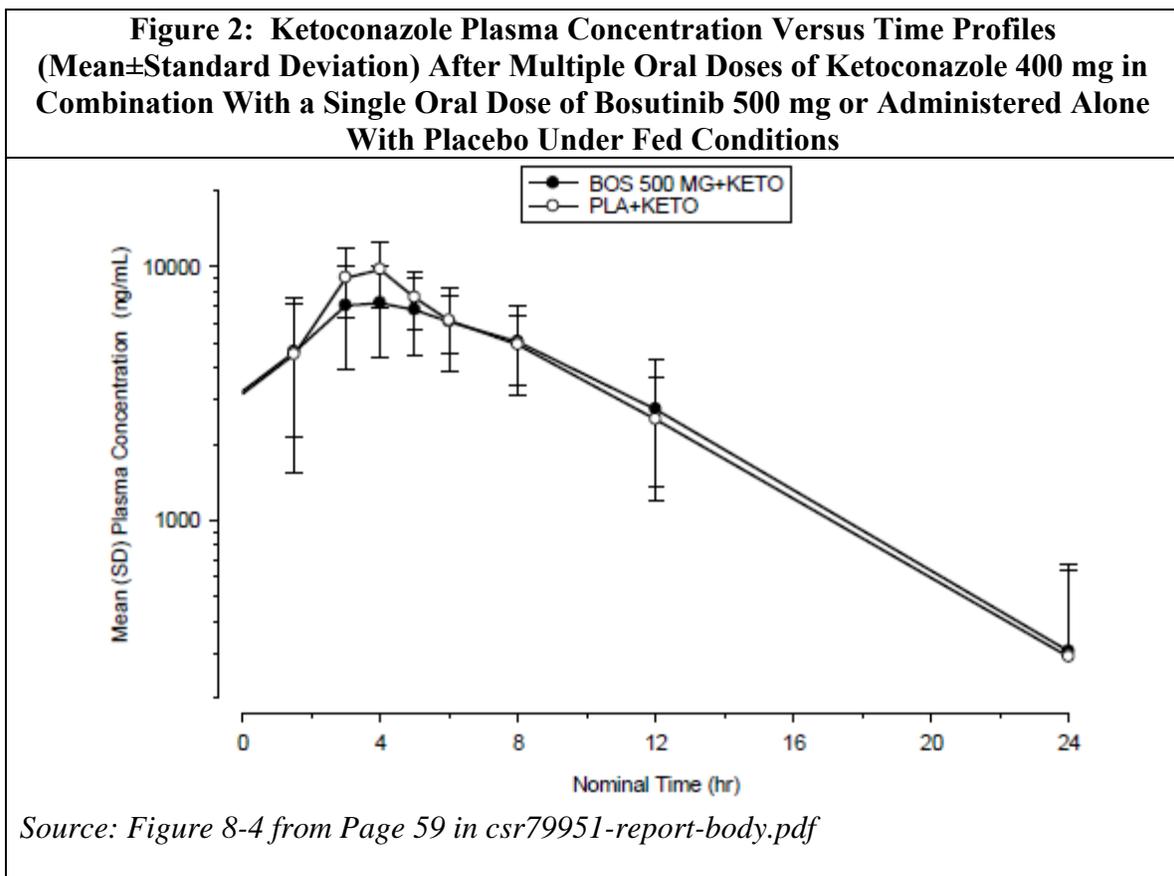
Source: Figure 8-1, 8-2, 8-3 from Page 50-53 in csr79951-report-body.pdf

Summaries of mean PK parameters (C_{max}) of bosutinib, M2, and M5 after a single oral dose of bosutinib 500 mg alone and in combination with multiple oral doses of ketoconazole 400 mg in healthy subjects under fed conditions are presented below.

	Bosutinib 500 mg	Bosutinib 500 mg+Ketoconazole
Bosutinib	114 ± 39.8	326 ± 77.2
M2	31.1 ± 10.8	6.41 ± 3.09
M5	48.8 ± 16.1	12.1 ± 5.13

Source: Tables 8-1, 8-2, 8-3 from Page 53-55 in *csr79951-report-body.pdf*

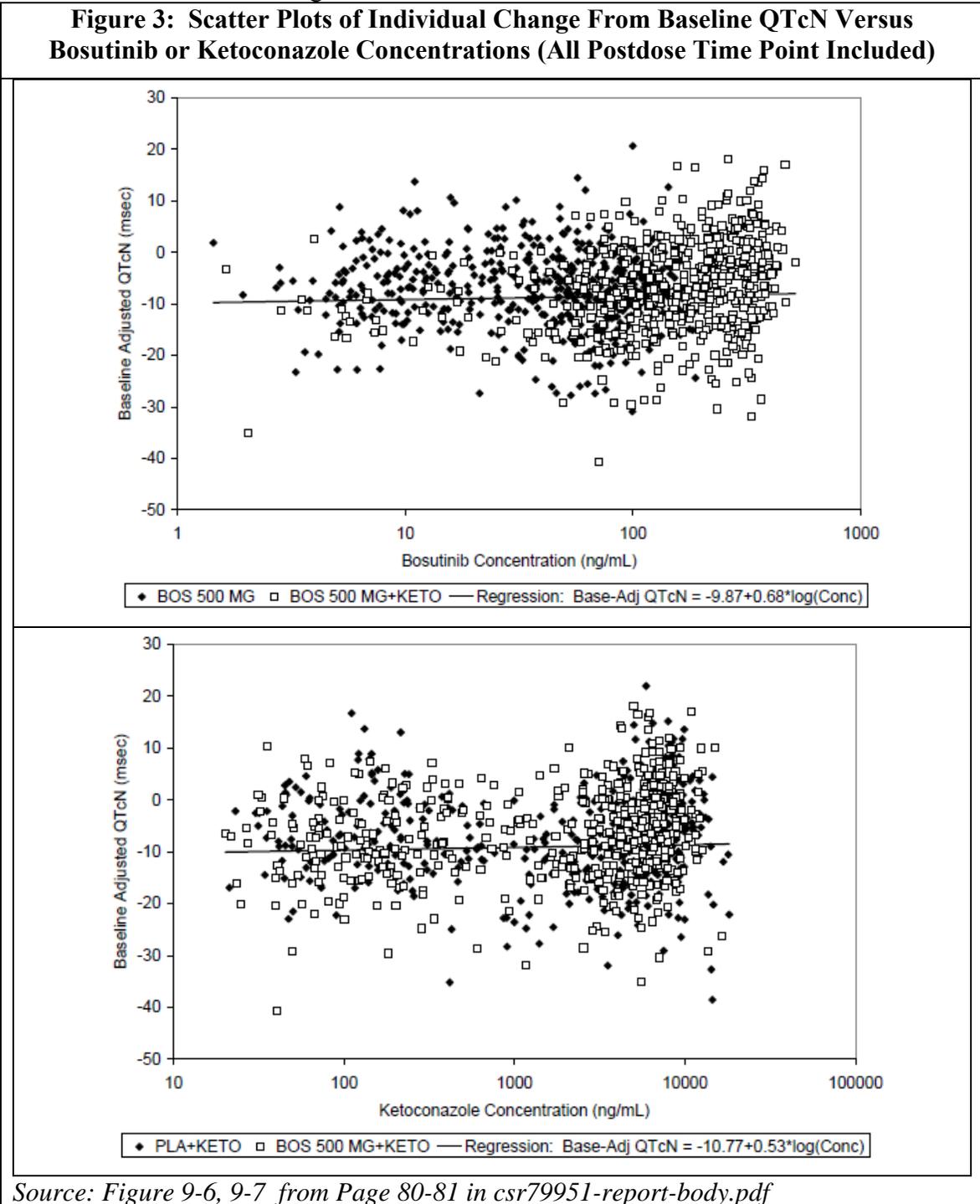
Mean plasma concentration versus time profiles of ketoconazole after multiple oral doses of ketoconazole 400 mg in combination with a single oral dose of bosutinib 500 mg or administered alone with placebo under fed conditions are presented in Figure 2.



4.2.7.4.2 Exposure-Response Analysis

Linear regression models on change from baseline QTcN versus log-transformed concentrations were fit with postdose data for each analyte separately.

The individual QTcN change from baseline values versus bosutinib plasma concentrations after administration of bosutinib 500 mg, and bosutinib 500 mg with ketoconazole is shown in Figure 3.



The linear regression models for both analytes are presented in Table 12.

Table 12: Estimated Coefficients From Regression of Change in QTcN on Log-Transformed Bosutinib and Ketoconazole Concentrations

Analyte	Label	Estimate	P-value	95% CI
Bosutinib	Intercept	-9.87	<0.0001	(-11.84, -7.91)
	Log bosutinib Conc	0.68	0.0008	(0.29, 1.08)
Ketoconazole	Intercept	-10.77	<0.0001	(-12.94, -8.61)
	Log Keto Conc	0.53	<0.0001	(0.29, 0.77)

Abbreviations: CI = confidence interval; Conc = concentration; Keto = Ketoconazole; QTcN = corrected QT interval based on a population-specific correction formula.

Source: Table 9-8 from Page 80 in *csr79951-report-body.pdf*

- The slope coefficient on log-transformed bosutinib concentrations of 0.68 was significantly different from zero (0) (p-value=0.0008) suggesting a slight positive relationship between bosutinib concentrations and change from baseline QTcN.
- The slope coefficient on log-transformed ketoconazole concentrations of 0.53 was significantly different from zero (0) (p-value <0.0001) suggesting a slight positive relationship between bosutinib concentrations and change from baseline QTcN.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 13, it appears that QTcF is better than QTcN, QTcI and QTcB.

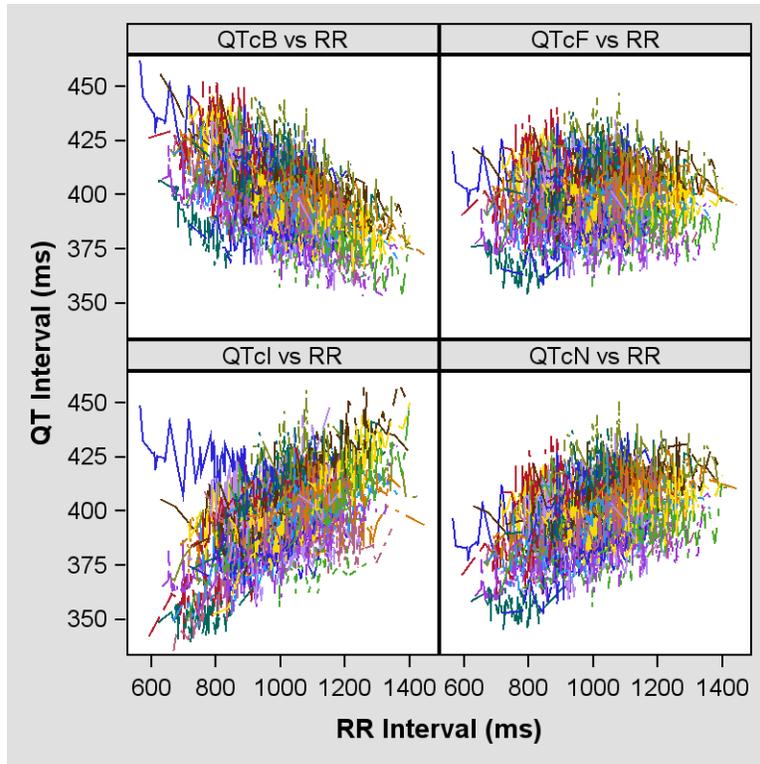
Table 13: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method							
	QTcB		QTcF		QTcI		QTcN	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
BOS 500 MG	56	0.0069	56	0.0012	56	0.0060	56	0.0023
BOS 500 MG+KETO	54	0.0080	54	0.0016	54	0.0068	54	0.0024
MOXI	58	0.0104	58	0.0019	58	0.0044	58	0.0013
PLA	58	0.0065	58	0.0011	58	0.0062	58	0.0023
PLA+KETO	49	0.0074	49	0.0013	49	0.0054	49	0.0021
All	60	0.0073	60	0.0010	60	0.0059	60	0.0017

The QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), Population-specific (QTcN) and Individual correction

(QTcI). A clear trend of QTcN versus RR is still present based on the picture. Therefore, this reviewer used QTcF as the primary endpoint for the analysis.

Figure 4: QT, QTcB, QTcI, QTcN and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effects and baseline values as covariate. The analysis results are listed in Table 14, Table 15 and Table 16. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg and placebo is 4.5 ms. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole is 10.3 ms. The largest upper bound of the 2-sided 90% CI for the mean difference between ketoconazole 400 mg and placebo is 6.9 ms.

Table 14: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Bosutinib 500 mg and Moxifloxacin 400 mg

Time (h)	Placebo	BOS 500 MG				MOXI				
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	*Adj. 90% CI
1.5	-9.7	56	-7.5	2.2	(0.2, 4.2)	58	-2.5	7.2	(5.2, 9.2)	(4.5, 9.9)
3	-7.4	56	-5.7	1.7	(-0.3, 3.8)	57	0.6	8.0	(5.9, 10.0)	(5.2, 10.7)
4	-4.1	56	-3.9	0.2	(-1.4, 1.9)	57	4.2	8.3	(6.6, 10.0)	(6.0, 10.6)
5	-1.6	56	-2.5	-1.0	(-3.1, 1.2)	57	5.9	7.4	(5.3, 9.6)	(4.5, 10.4)
6	-5.3	56	-3.5	1.8	(-0.3, 3.9)	57	3.5	8.8	(6.7, 10.9)	(6.0, 11.7)
8	-5.9	56	-3.5	2.4	(0.3, 4.5)	57	2.1	7.9	(5.8, 10.0)	(5.1, 10.8)
12	-5.7	56	-4.9	0.7	(-2.0, 3.4)	57	2.2	7.8	(5.1, 10.5)	(4.2, 11.5)
24	-5.8	56	-3.8	2.0	(-0.2, 4.3)	57	0.4	6.2	(4.0, 8.4)	(3.2, 9.3)
48	-7.2	56	-5.0	2.2	(0.1, 4.3)	57	-4.9	2.3	(0.1, 4.4)	(-0.6, 5.1)
72	-7.2	56	-4.8	2.4	(0.3, 4.5)	56	-4.8	2.4	(0.3, 4.5)	(-0.5, 5.3)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

Table 15: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Bosutinib 500 mg plus Ketoconazole

Time (h)	Placebo	BOS 500 MG+KETO			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF	
	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	-8.2	54	-8.0	0.2	(-2.2, 2.6)
3	-5.8	54	-5.4	0.4	(-1.9, 2.7)
4	-3.5	54	-2.0	1.5	(-0.9, 3.9)
5	2.2	54	0.9	-1.3	(-3.8, 1.2)
6	-3.5	54	0.0	3.5	(1.1, 5.9)
8	-6.5	54	0.9	7.4	(4.5, 10.3)
12	-8.3	54	-2.5	5.8	(3.1, 8.5)
24	-6.2	54	-4.2	1.9	(-0.1, 4.0)
48	-7.6	53	-8.0	-0.4	(-2.9, 2.1)
72	-8.6	53	-7.2	1.4	(-1.1, 3.9)

Table 16: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Ketoconazole 400 mg

	Placebo	KETO			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	-10.3	49	-7.5	2.8	(0.6, 4.9)
3	-7.9	49	-5.2	2.7	(0.6, 4.9)
4	-4.5	49	-2.9	1.6	(-0.5, 3.7)
5	-1.9	49	2.6	4.5	(2.1, 6.9)
6	-5.9	49	-2.7	3.2	(1.0, 5.5)
8	-6.3	49	-5.9	0.3	(-2.1, 2.8)
12	-6.2	49	-7.5	-1.3	(-3.8, 1.2)
24	-6.4	49	-5.4	1.0	(-1.1, 3.1)
48	-7.7	49	-6.9	0.8	(-1.4, 3.1)
72	-8.0	49	-7.6	0.4	(-1.9, 2.8)

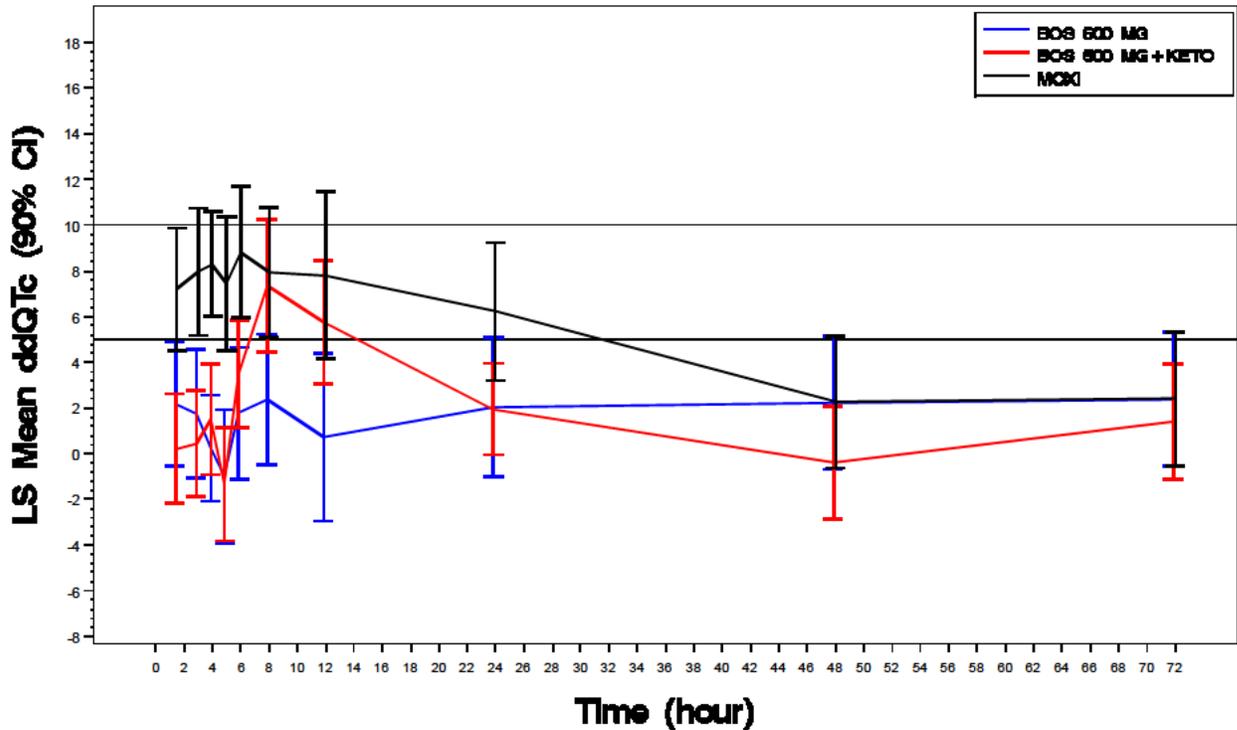
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 14. The largest unadjusted 90% lower confidence interval is 6.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 6.0 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

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

Figure 5 displays the time profile of $\Delta\Delta$ QTcF for bosutinib 500 mg, bosutinib 500 mg plus ketoconazole and moxifloxacin 400 mg.

Figure 5: Mean and 90% CI $\Delta\Delta$ QTcF Time Course for Bosutinib 500 mg, Bosutinib 500 mg plus Ketoconazole and Moxifloxacin 400 mg



5.2.1.3 Categorical Analysis

No subject's QTcF is above 450 ms. No subject's change from baseline is above 30 ms.

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% CI are presented in Table 17 and Table 18. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg and placebo is 5.4 bpm. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole is 6.0 bpm. No subject who experienced HR interval greater than 100 bpm was in both bosutinib 500-mg and bosutinib 500-mg plus ketoconazole groups.

Table 17: Analysis Results of Δ HR and $\Delta\Delta$ HR for Bosutinib 500 mg and Moxifloxacin 400 mg

		Treatment Group										
		BOS 500 MG				MOXI						
		Placebo		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	90% CI
1.5	5.1	56	5.4	0.3	(-1.1, 1.7)	58	6.9	1.8	(0.5, 3.2)			
3	0.7	56	2.2	1.5	(0.0, 2.9)	57	2.6	1.9	(0.4, 3.3)			
4	1.1	56	4.0	2.9	(1.6, 4.2)	57	2.7	1.6	(0.3, 3.0)			
5	6.4	56	6.3	-0.1	(-1.6, 1.4)	57	7.1	0.8	(-0.8, 2.3)			
6	7.1	56	8.4	1.3	(0.1, 2.6)	57	8.7	1.7	(0.4, 2.9)			
8	2.2	56	6.2	4.0	(2.6, 5.4)	57	3.6	1.5	(0.1, 2.9)			
12	5.9	56	8.8	2.9	(1.1, 4.7)	57	7.2	1.4	(-0.5, 3.2)			
24	-1.1	56	-0.3	0.7	(-0.6, 2.1)	57	-1.1	-0.0	(-1.4, 1.3)			
48	-0.1	56	-0.7	-0.6	(-2.2, 1.0)	57	0.1	0.2	(-1.4, 1.8)			
72	2.3	56	1.7	-0.7	(-2.7, 1.4)	56	1.0	-1.3	(-3.3, 0.7)			

Table 18: Analysis Results of Δ HR and $\Delta\Delta$ HR for Bosutinib 500 mg plus Ketoconazole

		Placebo	BOS 500 MG+KETO			
			Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	
1.5	6.3	54	5.0	-1.3	(-2.9, 0.3)	
3	0.4	54	2.3	1.9	(0.5, 3.3)	
4	1.2	54	4.0	2.8	(1.6, 4.1)	
5	6.3	54	6.1	-0.1	(-1.9, 1.6)	
6	7.0	54	6.5	-0.5	(-2.1, 1.0)	
8	1.0	54	5.3	4.3	(2.9, 5.8)	
12	5.0	54	8.6	3.6	(2.0, 5.1)	
24	-1.9	54	2.6	4.5	(2.9, 6.0)	
48	-1.5	53	1.9	3.4	(1.7, 5.2)	
72	1.5	53	4.5	3.0	(1.2, 4.8)	

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 19 and Table 20. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg and placebo is 5.4 ms. The largest upper bound of the 2-sided 90% CI for the mean

difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole is 3.6 ms. Table 21 presents the categorical analysis of HR. Four subjects who experienced HR interval greater than 200 ms were in both bosutinib 500-mg and bosutinib 500-mg plus Ketoconazole groups.

Table 19: Analysis Results of Δ PR and $\Delta\Delta$ PR for Bosutinib 500 mg and Moxifloxacin 400 mg

		Treatment Group									
		BOS 500 MG				MOXI					
		Placebo		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI		
1.5	5.1	56	5.4	0.3	(-1.1, 1.7)	58	6.9	1.8	(0.5, 3.2)		
3	0.7	56	2.2	1.5	(0.0, 2.9)	57	2.6	1.9	(0.4, 3.3)		
4	1.1	56	4.0	2.9	(1.6, 4.2)	57	2.7	1.6	(0.3, 3.0)		
5	6.4	56	6.3	-0.1	(-1.6, 1.4)	57	7.1	0.8	(-0.8, 2.3)		
6	7.1	56	8.4	1.3	(0.1, 2.6)	57	8.7	1.7	(0.4, 2.9)		
8	2.2	56	6.2	4.0	(2.6, 5.4)	57	3.6	1.5	(0.1, 2.9)		
12	5.9	56	8.8	2.9	(1.1, 4.7)	57	7.2	1.4	(-0.5, 3.2)		
24	-1.1	56	-0.3	0.7	(-0.6, 2.1)	57	-1.1	-0.0	(-1.4, 1.3)		
48	-0.1	56	-0.7	-0.6	(-2.2, 1.0)	57	0.1	0.2	(-1.4, 1.8)		
72	2.3	56	1.7	-0.7	(-2.7, 1.4)	56	1.0	-1.3	(-3.3, 0.7)		

Table 20: Analysis Results of Δ PR and $\Delta\Delta$ PR for Bosutinib 500 mg plus Ketoconazole

Time (h)	BOS 500 MG+KETO				
	Placebo	Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	-1.7	54	-3.6	-1.9	(-4.2, 0.4)
3	-4.9	54	-3.9	1.0	(-1.7, 3.6)
4	-2.6	54	-3.6	-1.0	(-2.7, 0.6)
5	-2.2	54	-3.2	-1.1	(-3.1, 0.9)
6	-4.4	54	-3.5	0.9	(-1.4, 3.1)
8	-4.7	54	-5.1	-0.4	(-3.1, 2.3)
12	-4.7	54	-6.7	-2.1	(-4.6, 0.5)
24	-1.2	54	-2.0	-0.8	(-2.8, 1.1)
48	-1.2	53	-3.1	-2.0	(-4.1, 0.1)
72	1.2	53	-1.5	-2.7	(-4.7, -0.7)

Table 21: Categorical Analysis of PR

Treatment Group	Total N	PR < 200 ms	PR \geq 200 ms
BOS 500 MG	56	54 (96.4%)	2 (3.6%)
BOS 500 MG+KETO	54	52 (96.3%)	2 (3.7%)
MOXI	58	57 (98.3%)	1 (1.7%)
PLA	58	57 (98.3%)	1 (1.7%)
PLA+KETO	49	48 (98.0%)	1 (2.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 22 and Table 23. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg and placebo is 2.3 ms. The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole is 2.2 ms. No subject who experienced QRS greater than 110 ms was in both bosutinib 500-mg and bosutinib 500-mg plus ketoconazole groups.

Table 22: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Bosutinib 500 mg and Moxifloxacin 400 mg

	Placebo	BOS 500 MG				MOXI			
	Placebo	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1.5	-0.5	56	-0.2	0.3	(-0.5, 1.2)	58	-0.7	-0.1	(-1.0, 0.7)
3	-1.0	56	-0.2	0.8	(-0.3, 1.8)	57	-1.5	-0.5	(-1.5, 0.5)
4	-1.4	56	-0.7	0.8	(-0.1, 1.6)	57	-0.9	0.6	(-0.3, 1.4)
5	0.4	56	0.5	0.1	(-0.7, 0.9)	57	0.0	-0.4	(-1.2, 0.5)
6	-1.1	56	-0.4	0.8	(-0.2, 1.8)	57	-0.6	0.5	(-0.4, 1.5)
8	-1.5	56	-0.1	1.4	(0.5, 2.3)	57	-1.0	0.5	(-0.4, 1.4)
12	-0.2	56	-0.3	-0.0	(-0.9, 0.8)	57	-0.8	-0.6	(-1.5, 0.3)
24	-0.3	56	-0.2	0.1	(-0.9, 1.2)	57	-0.1	0.2	(-0.8, 1.3)
48	-1.0	56	-0.4	0.6	(-0.3, 1.6)	57	-0.6	0.4	(-0.5, 1.4)
72	-0.2	56	0.1	0.3	(-0.5, 1.2)	56	-0.6	-0.4	(-1.3, 0.4)

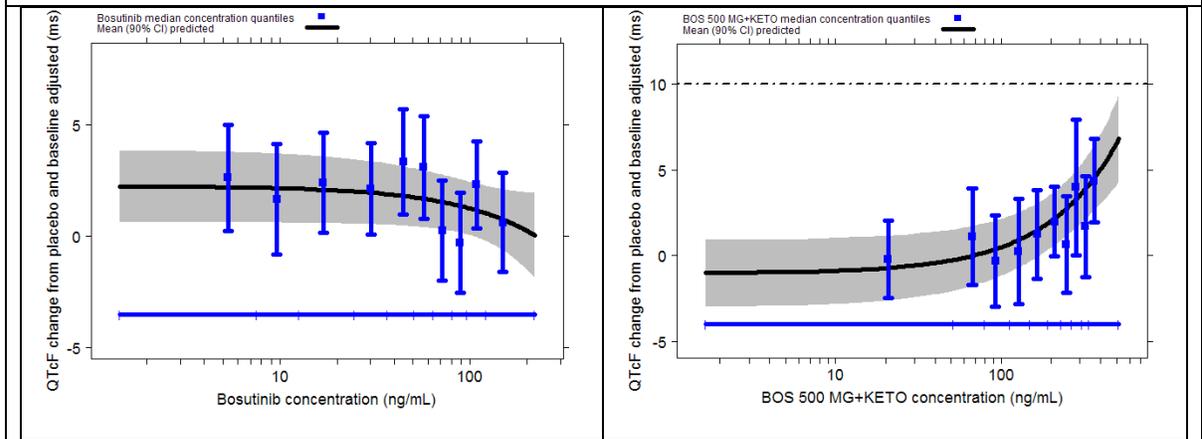
Table 23: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Bosutinib 500 mg plus Ketoconazole

	Placebo	BOS 500 MG+KETO			
		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	-0.2	54	-0.4	-0.2	(-1.0, 0.6)
3	-1.3	54	-0.9	0.4	(-0.7, 1.4)
4	-1.4	54	-0.4	1.0	(0.0, 1.9)
5	-0.1	54	-0.2	-0.1	(-1.3, 1.1)
6	-0.4	54	-0.2	0.2	(-0.7, 1.2)
8	-0.8	54	-0.1	0.7	(-0.3, 1.7)
12	-1.4	54	-0.2	1.2	(0.1, 2.2)
24	-1.2	54	-0.5	0.7	(-0.3, 1.8)
48	-1.7	53	-0.5	1.2	(0.3, 2.1)
72	-0.7	53	0.2	0.9	(-0.1, 1.9)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 1. The relationship between $\Delta\Delta$ QTcF (baseline, placebo corrected) and bosutinib concentrations is shown in Figure 6.

Figure 6: (Left) Scatter Plot Showing Relationship Between $\Delta\Delta$ QTcF (Placebo Corrected QTcF, ms) and Bosutinib Concentrations, (Right) Relationship Between $\Delta\Delta$ QTcF (Placebo + Ketoconazole Corrected QTcF, ms) and Bosutinib concentrations



The estimate of slope and intercept for the relationship between $\Delta\Delta$ QTcF (placebo corrected QTcF or placebo + ketoconazole corrected) and bosutinib concentrations is shown in Table 24.

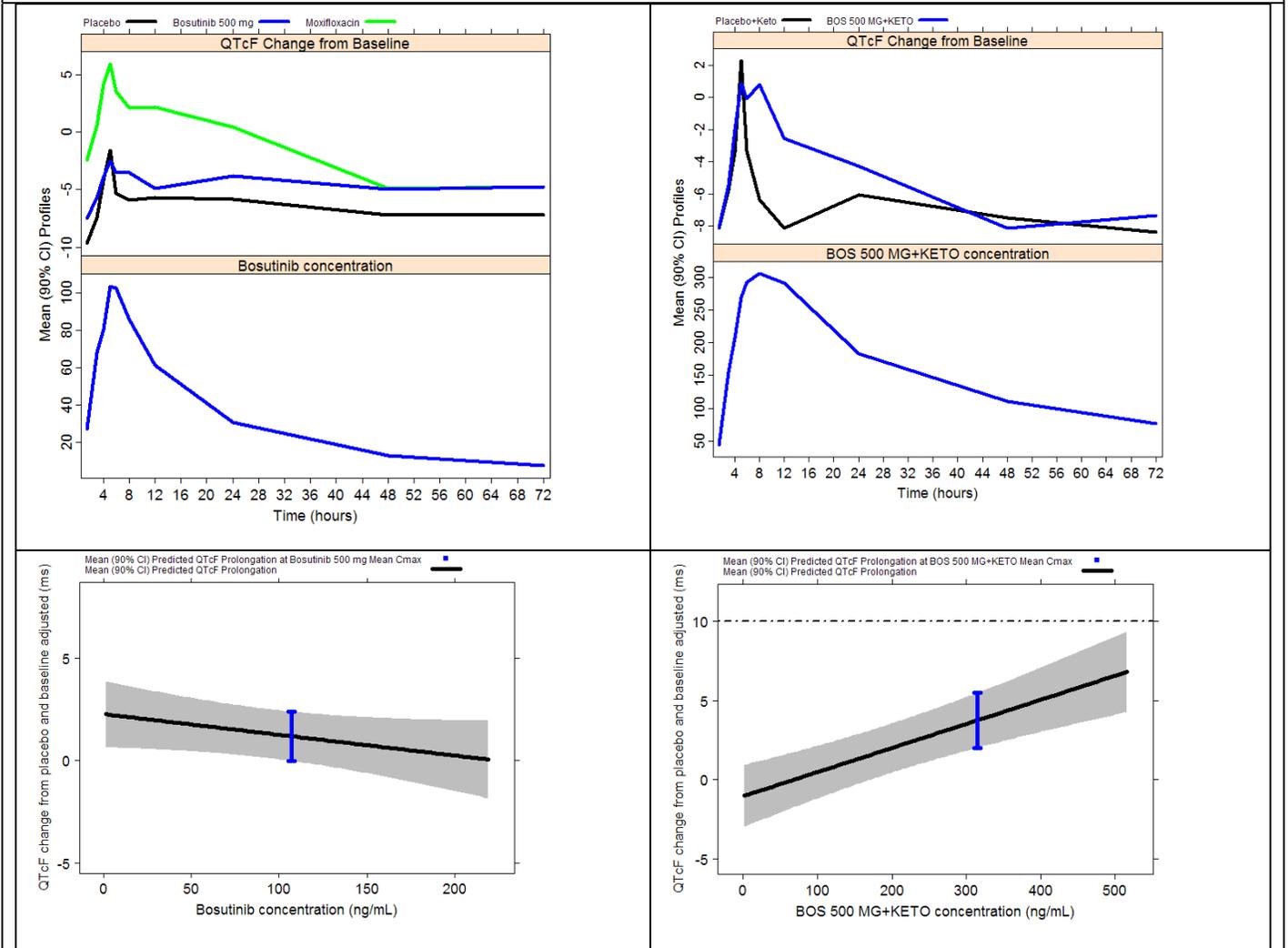
Table 24. Estimates of Intercept and Slope of the Relationship Between Bosutinib Concentrations and $\Delta\Delta$ QTcF

Group	Intercept (ms)	Slope (ms per ng/ml)
Bosutinib Alone	2.27*	-0.01
Bosutinib+Ketoconazole (BOS 500 MG+KETO)	-1.03	0.015**

* p value=0.0230; ** p value=<0.0001

Figure 7 shows the time course of $\Delta\Delta$ QTcF after administration of bosutinib, ketoconazole and bosutinib+ketoconazole. The relationship between bosutinib, ketoconazole concentrations and $\Delta\Delta$ QTcF was analyzed using a linear model with intercept. Based on the model, the predicted $\Delta\Delta$ QTcF at 114 (C_{max} after 500 mg bosutinib dose) and 326 ng/mL (C_{max} after 500 mg bosutinib dose with ketoconazole) is shown in Figure 7. The analysis shows that the mean change in QTcF prolongation due to bosutinib is less than 10 ms.

Figure 7: (Top Left) Time Course of Bosutinib Concentrations and Δ QTcF after Placebo, 500 mg Bosutinib Dose and Moxifloxacin. (Top Right) Time course of Bosutinib Concentrations and Δ QTcF after coadministration of 500 mg Bosutinib and Ketoconazole. (Bottom Left) Predicted $\Delta\Delta$ QTcF at C_{max} of 114 ng/mL (Therapeutic dose of Bosutinib: 500 mg). (Bottom Right) Predicted $\Delta\Delta$ QTcF at C_{max} of 326 ng/mL After Accounting for Ketoconazole Effect on QT Interval (Therapeutic dose of Bosutinib Coadministered with Ketoconazole)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 94% of the ECGs were annotated in the primary lead II, with less than 0.05% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Four subjects had a PR > 200ms. Two in the bosutinib arm and two in the Bosutinib+Keto arm.

No post-baseline PR > 210 ms. No subject had a QRS > 110 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	<p>Include maximum proposed clinical dosing regimen.</p> <p>500 mg oral once daily with food</p>
Maximum tolerated dose	<p>Include if studied or NOAEL dose:</p> <p>The MTD of bosutinib in patients with advanced malignant solid tumors was determined in the dose-escalation study 100-US. Three (3) DLTs were reported for subjects in the 600-mg dose level; grade 3 diarrhea was reported for 2 subjects and grade 3 rash was reported for a third subject. The protocol-defined MTD for oral administration of bosutinib was determined to be 500 mg.</p> <p>On the basis of the MTD determined in study 100-US, the starting dose of bosutinib was 400 mg in study 200 WW in subjects with Ph+ leukemia. Dose escalation continued up to 600 mg. Three (3) subjects each were enrolled in the 400- and 500-mg dose cohorts. Because 1 DLT and several clinically significant grade 2 AEs were observed at the 600 mg dose and early signs of clinical benefit have been observed at all doses, the decision was made to begin dose administration at 500 mg in part 2 of this study and study 3160A4 3000 WW. The 500 mg dose of bosutinib is considered to be tolerable in the subject population.</p>
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events:</p> <p>Among subjects with chronic phase CML (n=257), 237 (92.2%) subjects had at least 1 treatment-emergent adverse events (TEAE). TEAEs have been most frequently associated with gastrointestinal disorders (diarrhea, 74.7%; nausea, 38.1%; vomiting, 30%; abdominal pain upper, 17.9%; and abdominal pain, 14.8%), skin and subcutaneous tissue disorders (rash, 33.5%), and general disorders (fatigue 17.5% and pyrexia, 17.5%). Other commonly reported TEAEs (occurring in $\geq 10\%$ of subjects with CP CML) have been associated with blood and lymphatic system disorders (thrombocytopenia, 22.6%; anemia, 11.3%), investigations (increased levels of alanine aminotransferase [ALT] 11% and increased levels of aspartate aminotransferase [AST], 10% each), nervous system disorders (headache, 14.8%), and respiratory and mediastinal disorders (cough, 11.7%). Grade 3 or higher TEAEs were reported in 51.8% of subjects with chronic phase CML. TEAEs of grade 3 or higher severity that have occurred in 5% or more subjects with CP CML include thrombocytopenia (17.1%), rash (8.6%), diarrhea (8.2%), neutropenia (5.1%), and ALT increased (5.1%). The adverse event profile is comparable in patients with advanced phase CML.</p>

Maximum dose tested	Single Dose	Specify dose: In study 3160A1-103-EU, cohorts of 8 subjects (6 receiving active drug, 2 receiving placebo) were administered bosutinib doses of up to 800 mg or placebo with a high-fat meal. In study 3160A1-1114-EU, cohorts of 8 subjects (6 receiving active drug, 2 receiving placebo) were administered bosutinib doses of up to 600 mg when coadministered with multiple dose of ketoconazole 400 mg QD.
	Multiple Dose	Specify dosing interval and duration: 600 mg once daily oral with food in patients; treatment continued until disease progression or toxicity with PK on study day 15
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC: In healthy subjects at 800 mg oral fed: 216 ng/mL (40%) and 4003 ng.hr/mL (38%) In healthy subjects at 600 mg oral with food in presence of ketoconazole: 426 ng/mL (24%) and 23,000 ng.hr/mL (17%)
	Multiple Dose	Mean (%CV) C _{max} and AUC: Steady State (Day 15): In patients at 600 mg oral with food: 450 ng/mL (63%) and 4675 ng.hr/mL (29%)
Range of linear PK	Specify dosing regimen: In healthy subjects administered single ascending oral doses of 200 mg to 800 mg bosutinib under fed conditions, both C _{max} and AUC of bosutinib increased with increasing dose in a linear fashion. In patients, both the C _{max} and AUC of bosutinib increased with increasing dose from 50 mg to 600 mg.	
Accumulation at steady state	Mean (%CV); specify dosing regimen In patients administered bosutinib on a daily basis, steady state exposure was nearly 2 to 3 fold higher than single dose exposures (mean R ranged from 1.5 to 3.5).	
Metabolites	Include listing of all metabolites and activity: Exploratory screening and analyses of bosutinib metabolites in study 3160A4-103-US were conducted using a Wyeth qualified liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay. In brief, semiquantitative analysis of oxydechlorinated SKI-606 (M2), N-desmethyl SKI-606 (M5), and SKI-606 N-oxide (M6) was performed using pooled plasma samples from 6 subjects at predose and at 2, 4, 8, and 24 hours after oral administration of 400 mg bosutinib under fasted condition. N-desmethyl SKI-606 (M5) was the major circulating	

	<p>metabolite and was present at concentrations of 22% to 74% (at the various time points) relative to bosutinib in healthy subjects. Plasma concentrations of oxydechlorinated SKI-606 (M2) was 5% to 17% (at the various time points) relative to bosutinib in healthy subjects. SKI-606 N-oxide (M6) was present at <10% relative to bosutinib in healthy subjects.</p> <p>Following a single oral dose of 400 mg bosutinib with food in healthy subjects (preliminary data from study 3160A4-1110) the M2 metabolite Cmax and AUC were about 23% and 21% of the parent values, respectively. Cmax and AUC values of the M5 metabolite were 41 and 26% of the parent, respectively.</p> <p>Preliminary data from 14 patients enrolled in the ongoing phase III study 3160A4-3000-WW (i.e. sparse sampling regimen and samples collected at pre-dose and at 3 and 6 hours post-dose on day 28) were evaluated for plasma concentrations of bosutinib, M5 and M2. These preliminary analyses indicate that the steady-state median (range) Cmax for bosutinib, M5 and M2 were 129 ng/mL (6 to 238 ng/mL), 39 ng/mL (range 2 to 98 ng/mL) and 30 ng/mL (2 to 62 ng/mL), respectively. When comparing the steady-state metabolite levels to the parent, the median Cmax for M5 and M2 were about 30% and 23% of the parent drug, respectively.</p> <p>In vitro data indicated that both M2 and M5 had less than 5% of the pharmacological activity of bosutinib.</p>	
Absorption	Absolute/Relative Bioavailability	Mean (%CV): Relative bioavailability of bosutinib tablet to oral solution is approximately 100%. Absolute bioavailability has not been determined as an IV dose form is not available.
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent: After administration of single ascending oral doses of 200 mg to 800 mg bosutinib to healthy subjects under fed conditions, bosutinib absorption was relatively slow, with a median [range] tmax of 6 [3-24] hours. • Median (range) for metabolites: Following a single oral dose of 400 mg bosutinib with food in healthy subjects (preliminary data from study 3160A4-1110), the median tmax [range] for M5 was 4 [1-6] hours, and for M2 metabolite the median tmax [range] was 4 [3-8] hours.
Distribution	Vd/F or Vd	<p>Mean (%CV)</p> <p>Study 3160A4-103-EU at 400 mg Fed</p> <p>Vd/F: 132 L/kg (17%)</p>

	% bound	Mean (%CV) [14C]Bosutinib, within estimated therapeutic and toxicologic concentrations, was highly bound to protein in human plasma. There was no marked change in the percentage of bound [14C]bosutinib at plasma concentrations between approximately 100 (93.8 ± 0.1) and 10,000 ng/mL (93.3 ± 0.3).
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated: Hepatic metabolism and subsequent fecal elimination: percent to be determined in humans • Other routes: Renal minor
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent Study 3160A4-103-EU at 400 mg Fed 32.4 hours (26%) • Mean (%CV) for metabolites: to be determined; preliminary data described above where metabolites concentrations at steady state did not accumulate more than parent or approach those of parent bosutinib, suggest a equal or shorter half-life than parent bosutinib.
	CL/F or CL	Mean (%CV) Study 3160A4-103-EU at 400 mg Fed CL/F: 2.9 L/hr/kg (16%)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC To be determined
	Sex	Specify mean changes in C _{max} and AUC To be determined
	Race	Specify mean changes in C _{max} and AUC: To be determined
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC: Hepatic impairment study currently ongoing. No effect of renal impairment expected based on limited renal elimination. Renal impairment study not planned

Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in C_{max} and AUC:</p> <p>When bosutinib (100mg) was coadministered with multiple dose of ketoconazole (400mg), exposure to bosutinib was increased by approximately 5.2 fold for C_{max}, 7.6 fold for AUC, and 8.6-fold for AUC.</p>
	Food Effects	<p>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat):</p> <p>Preliminary food effect assessment in the single ascending dose study 3160A1-103-EU indicated that exposure to bosutinib was increased approximately 2.52 fold for C_{max} and 2.28 fold for AUC when 200 mg of bosutinib was administered with food compared to fasting conditions. Following oral administration of 400 mg bosutinib with food, C_{max} increased approximately 1.42 fold and AUC about 1.54 fold as compared to fasting conditions. Statistical analysis of preliminary-food effect indicated that there was a statistically significant effect of food on bosutinib exposure (AUC, n=6), when 200 mg and 400 mg bosutinib capsules were administered with food as compared to bosutinib administration under fasting conditions.</p>
Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>In phase 2 and 3 studies in CML, bosutinib is being administered at doses of 500 mg with food. Single dose bosutinib 500 mg (fed) in healthy subjects achieves C_{max} exposures of approximately 100 ng/ml. These single dose plasma exposures represent approximately half the steady state C_{max} of bosutinib (fed) observed in cancer patients receiving bosutinib 500 mg daily (mean of 197 ng/ml) due to accumulation with repeated dosing. Considering the half-life of parent bosutinib in healthy subjects (33 hours in 3160A4-103) and the observed extent of accumulation, a multiple dose study design would be preferred for evaluating cardiac repolarization. Nevertheless, a multiple dose cardiac repolarization study of bosutinib in healthy subjects is not feasible due to the high frequency of NCI CTC Grade 3 and higher TEAEs (59.4%) observed with administration of multiple doses of bosutinib in cancer patients (3160A4-200).</p> <p>Supratherapeutic plasma concentrations are intended to evaluate the cardiac repolarization potential of bosutinib at the higher range of steady state C_{max} achievable in the target patient population influenced by a variety of potential intrinsic or extrinsic variables (ie, food effects, drug-drug interactions). For the purpose of this study, supra-therapeutic</p>	

	<p>plasma concentrations of bosutinib are achievable when single dose bosutinib 500 mg (fed) is coadministered with multiple doses of ketoconazole. In study 3160A4-1114, single dose bosutinib (fed) administered in the presence of ketoconazole was tolerated by healthy subjects up to a dose of 600 mg. The median C_{max} achieved by coadministration of 500 mg bosutinib (fed) with ketoconazole was 419 ng/ml. This safely achievable plasma exposure in healthy subjects is greater than the highest C_{max} reported for 48 out of 49 patients with CML (based on preliminary PK data from 3160A4-200) and 2.8-fold greater than the median (range) steady state C_{max} of 149 ng/mL (27 to 483 ng/mL) in CML patients. Therefore, single 500 mg (fed) doses of bosutinib will be administered with ketoconazole in the “supratherapeutic” period of the study.</p> <p>This approach of utilizing ketoconazole inhibition to achieve supratherapeutic concentrations of the investigation agent (CYP3A substrate) was successfully applied to another Wyeth compound (neratinib) recently. In developing the current bosutinib study, our goal was to remain consistent to the study design utilized for neratinib.</p>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VENKATESH A BHATTARAM
03/20/2012

NITIN MEHROTRA
03/20/2012

MOH JEE NG
03/20/2012

JOANNE ZHANG
03/20/2012

MONICA L FISZMAN
03/20/2012

NORMAN L STOCKBRIDGE
03/20/2012

DSI CONSULT: Request for Clinical Inspections

Date: February 9, 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Name of DSI Primary Reviewer (if known)
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Karen McGinn, M.S.N., C.R.N.P., Clinical Reviewer, DHP
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst,
Clinical Team Leader, DHP
Ann Farrell, M.D., Acting Division Director, DHP

From: Diane Hanner, CSO, DHP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application# NDA 203341 (IND 068268)

Applicant: Wyeth Pharmaceuticals Inc., (subsidiary of Pfizer): (Bosutinib)

Contact information: Carl M. DeJuliis, 500 Arcola Road, Collegeville, PA 19426

NME: YES

Study Population: Chronic Myelogenous Leukemia in adult patients

Study Population includes < 17 years of age (No)

Is this for Pediatric Exclusivity (No)

Proposed Indication: For the treatment of CP, AP, or BP PH(+) CML in adult patients with resistance or intolerance to prior therapy.

PDUFA: 9/17/2012

Target Date: 9/17/2012

Inspection Summary Goal Date: July 2, 2012

II. Background Information

Wyeth (Pfizer) has submitted a new drug application (NDA) for approval of Bosutinib in the second-line setting of chronic myeloid leukemia based upon the results from Study 3160A4-200-WW.

III. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Comments
<p>Site # 001 Jorge Cortes, M.D. The University of Texas M.D. Anderson Cancer Center 1515Holcombe Boulevard, Unit 428 Houston, TX 77030-4009</p>	<p>3160A4-200-WW</p>	<p>81</p>	<p>This site enrolled more patients than any other site. Also, the primary endpoint in patients with second line treatment of chronic phase chronic myeloid leukemia (MCyR =41%) exceeded that of the entire trial population (MCyR=33%).</p>
<p>Site #017 Hanna Jean Khoury, M.D., FACP Winship Cancer Institute Emory University School of Medicine 1365 Clifton Road, NE Atlanta, GA 30322</p>	<p>3160A4-200-WW</p>	<p>34</p>	<p>This site enrolled the second highest number of patients in the US, and the primary endpoint in patients with second line treatment of chronic phase chronic myeloid leukemia (MCyR=50%) exceeded that of the entire trial population (MCyR=33%).</p>

IV. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

We have requested inspections because (please check all that apply):

Enrollment of large numbers of study subjects

High treatment responders (specify): A greater percentage of subjects receiving the study drug as second-line treatment for chronic phase chronic myeloid leukemia enrolled at these 2 U.S. sites achieved the primary endpoint for major cytogenetic response (MCyR) at 24 weeks than was observed for the overall trial population. At site 001 the MCyR was 41% and at site 017 the MCyR rate was 50%. The MCyR for the overall trial population was 33%.

Significant primary efficacy results pertinent to decision-making

There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

Other (specify): a high rate of detection of prostate cancer relative to other centers. One local site was selected since medical reviewers are interested in attending the inspection.

International Inspections:

Reasons for inspections (please check all that apply):

There are insufficient domestic data

Only foreign data are submitted to support an application

Domestic and foreign data show conflicting results pertinent to decision-making

There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

V. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification. If you require any additional information, please contact Diane Hanner (regulatory project manager) at 301-796-4058 or Karen McGinn (clinical reviewer).

Concurrence: (as needed)

Karen McGinn X_____	Clinical Reviewer
Virginia Kwitkowski X_____	Clinical Team Leader
Ann Farrell_____	Division Director (for foreign inspection requests only)

*****Things to consider in decision to submit request for DSI Audit**

- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?
- Are there concerns that the data may be fraudulent or inconsistent?
 - Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
 - Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?
- Is this a new molecular entity or original biological product?
- Is the data gathered solely from foreign sites?
- Were the NDA studies conducted under an IND?

Additional information (Links)

EDR Location: [\\CDSESUB1\EVSPROD\NDA203341\0000](#)

Submission Size: 16993233596

Gateway Location: [\\chdc9681\cderesub\inbound\ectd\ci1321508125756.1263782@llnap32_te](#)

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

/s/

DIANE C HANNER
02/09/2012

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 # 203341 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: Bosulif® Established/Proper Name: Bosutinib monohydrate Dosage Form: oral film coated tablet Strengths: 100 mg and 500 mg		
Applicant: Wyeth Pharmaceutical, Inc Agent for Applicant (if applicable):		
Date of Application: November 17, 2011 Date of Receipt: November 17, 2011 Date clock started after UN:		
PDUFA Goal Date: September 17, 2012 (Standard Review)		Action Goal Date (if different): (TBD)
Filing Date: January 16, 2012		Date of Filing Meeting: December 21, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): For the treatment of CP, AP or BP PH(+) CML in adult patients with resistance or intolerance to prior therapy		
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): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
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 <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <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 <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 [21 CFR 314.55(b)/21 CFR 601.27(b)] <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 (if OTC product): N/A				
List referenced IND Number(s): 068268				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <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 tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
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>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><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. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>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)].</p>			<p>X</p>																	
<p>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> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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 will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>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)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested 5 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<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.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
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), 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)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
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)?	X			Signed by Pfizer not Wyeth
<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>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<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>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA 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></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

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>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		Not required since this is an orphan-designated indication.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
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>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		Ck with Clinical
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (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 labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <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>	X			
Is the PI submitted in PLR format? ⁴				

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

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

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>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
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>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
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>	X			DMEPA 11-18-11 QT consult 12-7-11 Micro 12-12-11 DDMAC 1-6-12
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): April 18, 2007-EOP2 meeting October 23, 2007- (SPA meeting) July 10, 2008- EOP2- CMC meeting	X			

April 22, 2009-Type C- clinical pharmacology- cancelled April 19, 2010-Type C- Clinical Pharmacology- cancelled <i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 23, 2010-Pre-NDA meeting September 28, 2010-Pre-NDA teleconference <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): SPA-carcinogenicity agreement June 18, 2009 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 21, 2011

BLA/NDA/Supp #: 203341

PROPRIETARY NAME: BOSULIF®

ESTABLISHED/PROPER NAME: bosutinib monohydrate

DOSAGE FORM/STRENGTH: Film Coated Tablet/100 mg and 500 mg

APPLICANT: Wyeth Pharmaceutical, Inc (a wholly owned subsidiary of Pfizer, Inc.)

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of CP, AP, or BP Ph(+) CML in adult patients with resistance or intolerance to prior therapy

BACKGROUND: Filing Meeting 12-21-11

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	CDR Diane Hamner, M.P.H., M.S.W., Senior Program Management Officer	Y
	CPMS/TL:	Janet Jamison, RN, Chief, Project Management Staff	Y
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, Clinical Team Leader		Y

Clinical	Reviewer:	Karen McGinn, M.S., R.N., Senior Clinical Analyst	Y
	TL:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, Clinical Team Leader	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NONE	
	TL:	NONE	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NONE	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Elimika Pfuma, Ph.D., Clinical Pharmacology Reviewer, DCP5	N
	TL:	Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5	Y
Biostatistics	Reviewer:	Kallappa Koti, Ph.D., Biostatistics Reviewer, DB 5	Y
	TL:	Mark Rothmann, Ph.D., Team Leader, Biostatistics Reviewer, DB 5	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shwu-Luan Lee, Ph.D., Pharmacologist	Y
	TL:	Haleh Saber, Ph.D., Supervisory Pharmacologist	Y
Statistics (carcinogenicity)	Reviewer:	NONE	
	TL:	NONE	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NONE	
	TL:	NONE	
Product Quality (CMC)	Reviewer:	Joyce Crich, Ph.D., CMC Reviewer, ONDQA, Division 3, Branch 5	

	TL:	Janice Brown, Ph D, CMC Lead	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Robert Mello, Ph.D., Quality Microbiology Reviewer	N
	TL:	Stephen E. Langille. Ph.D., Team Leader Quality Microbiology	N
CMC Labeling Review	Reviewer:	Joyce Crich, Ph.D., CMC Reviewer, ONDQA, Division 3, Branch 5	N
	TL:	Janice Brown, Ph.D.CMC Lead	Y
Facility Review/Inspection	Reviewer:	TBD	
	TL:	TBD	
OSE/DMEPA (proprietary name)	Reviewer:	Latonia Fond	Y
	TL:	Barbara Fuller	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <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
<p>CLINICAL</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
<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 original NME or BLA application, 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> 	<input checked="" type="checkbox"/> YES Date if known: July 24 & 25, 2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <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> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <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
<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>CLINICAL MICROBIOLOGY</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>CLINICAL PHARMACOLOGY</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
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" 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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>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>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input 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

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D.	
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"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p>Additional Comments (I/R) ONDQA-</p> <p>(1) Provide the specific details for the development of the dissolution method (ref section 2.3.P.2) along with the complete dissolution data collected during this development.</p> <p>(2) Provide the multi time-point dissolution data for all the batches used in the PK and clinical studies listed in table 1, under section: 2.3.P.2, which are needed to evaluate the acceptability of your proposed dissolution acceptance criterion.</p> <p>Quality Mircobiology-</p> <p>(3)Please provide a release specification for microbial limits of the drug product or provide an acceptable justification, which would include appropriate supportive data, for not having such a microbial limit specification.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

<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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

DIANE C HANNER
01/13/2012