CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s000

OTHER REVIEW(S)

PMR/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/BLA # NDA 205832
Product Name: OFEV (Nintedanib)

PMR/PMC Description: Conduct an open-label trial to evaluate the pharmacokinetics, safety and tolerability of nintedanib in patients with hepatic impairment (Child-Pugh Classification A and B) compared to healthy subjects

PMR/PMC Schedule Milestones:

Final Protocol Submission:	NA
Trial Completion:	03/2015
Final Report Submission:	09/2015
Other:	NA

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

Currently OFEV (nintedanib) is not recommended in patients with moderate or severe hepatic impairment. Availability of this information will (b) (4) help in guiding better dosing decision for OFEV in mild hepatic impairment patients. This is not a pre-approval requirement, as it will delay the approval of this breakthrough therapy for a larger population.

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."

OFEV (nintedanib) is not available to patients with moderate or severe hepatic impairment (b) (4) As nintedanib is eliminated primarily by hepatic metabolism and biliary excretion, hepatic impairment is likely to increase plasma nintedanib concentrations. A systematic evaluation of PK in patients with (b) (4) hepatic impairment will help in guiding better dosing recommendations for nintedanib to minimize the risk of serious adverse events due to increased drug exposure.

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 trial will be an open-label, pharmacokinetic trial in subjects with varying degree of hepatic impairment.

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)
☐ 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

Continuation of Question 4

☐ 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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

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.*

_____

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/s/

SALLY M SEYMOUR
09/25/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 11, 2014
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 205832
Product Name and Strength:	Ofev (nintedanib) Capsules, 100 mg, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date:	September 4, 2014
OSE RCM #:	2014-979-1
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions were resubmitted by the Applicant because a discrepancy was noted between the proposed package insert (PI) and carton labeling regarding the 100 mg capsules and the corresponding 120.40 mg nintedanib ethanesulfonate equivalent. No recommendations were made during our previous label and labeling review.[1]

CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective and we do not have any additional recommendations.

[1] McMillan, T, Worthy, K. and Merchant, L. Label and Labeling Review for OFEV (NDA 205832). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 July 16. 8 p. OSE RCM No.: 2014-979.

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/s/

TERESA S MCMILLAN
09/11/2014

KENDRA C WORTHY
09/12/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: August 29, 2014

TO: Jessica K. Lee, Pharm.D., Regulatory Project Manager
Miya Paterniti, M.D., Medical Officer
Banu Karimi-Shah, M.D., Team Leader
Division of Pulmonary Allergy and Rheumatology Products (DPARP)

FROM: Anthony Orencia, 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 Thompson, M.D.
Team Leader, GCP Assessment Branch,
for Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205832

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG: nintedanib

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: breakthrough therapy review

INDICATION: Treatment of adult patients with idiopathic pulmonary fibrosis (b) (4)

CONSULTATION REQUEST DATE:	June 27, 2014
INSPECTION SUMMARY GOAL DATE (original):	August 22, 2014
INSPECTION SUMMARY GOAL DATE (extended):	September 2, 2014
DIVISION ACTION GOAL DATE (original):	September 2, 2014
DIVISION ACTION GOAL DATE (revised):	October 1, 2014
PDUFA DATE:	January 2, 2015

I. BACKGROUND:

Idiopathic Pulmonary Fibrosis (IPF) is characterized by progressive fibrotic destruction of the lung. The average life expectancy in individuals with IPF is low. Nintedanib is a receptor tyrosine kinase inhibitor (TKI) for platelet derived growth factor/receptor (PDGR/R α/β), fibroblast growth factor/receptor (FGF/R 1-3), vascular endothelial growth factor/receptor (VEGF/R 1-3) and Fms-like tyrosine-protein kinase (Flt-3). It is also an inhibitor of the non-receptor tyrosine kinase, Lck (lymphocyte-specific tyrosine kinase).

For this new molecular entity (NME) application, DPARP requested that a high-level sponsor audit for this specific NDA be completed. Specifically, the audit was to assess the adequacy of sponsor oversight of the Italian, U.K., and U.S. clinical site monitoring for the associated study protocols.

Study 1199.30
This study was a randomized, double-blind, placebo-controlled, parallel design clinical trial comparing four active drug arms to placebo over a one year treatment period, with progressive inclusion of higher dosage arms after adequate Data Monitoring Committee assessment. The primary study objective was to investigate the efficacy and safety of four dose strategies (50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid) of BIBF 1120 (nintedanib) treatment for 12 months, compared to placebo in patients with IPF. The primary efficacy criterion, according to the study protocol, was the yearly rate of decline in forced vital capacity (FVC). This study was monitored by the Center for Rare Lung Diseases at the University of Modena and Reggio Emilia- Policlinico Hospital clinical site in Modena Italy. A total of 679 subjects were enrolled.

Study 1199.32
This study was a randomized, double-blind, placebo-controlled, parallel design trial comparing 150 mg BIBF 1120 bid (nintedanib) to placebo over a 52 week treatment period. The primary objective was to investigate the efficacy and safety of BIBF 1120 (nintedanib) 150 mg bid in patients with IPF. The primary study efficacy endpoint was the annual rate of decline in FVC. This study was monitored by the National Institute for Health Research, Southampton Respiratory Biomedical Research Unit clinical site, Southampton Center for Biomedical Research University Hospital Southampton NHS Foundation Trust in the U.K. A total of 718 subjects were enrolled.

Study 1199.34
This study was also a randomized, double-blind, placebo-controlled, parallel design clinical trial comparing a 150 mg bid active drug treatment group to placebo over a 52-week treatment period. The primary study objective was to investigate the efficacy and safety of 150 mg bid of BIBF 1120 (nintedanib) treatment for 12 months, compared to placebo in patients with IPF. The primary efficacy endpoint was the annual rate of decline in FVC. This study was monitored by the University of California San Francisco clinical site. A total of 794 subjects were enrolled.

II. RESULTS:

Name of CI Location	Protocol/ Number of Subjects Enrolled (n)	Inspection Date	Classification*
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Rd. P. O. Box 368 Ridgefield, CT 06877	Sponsor's oversight of the clinical trial for the following protocols: Protocol 1199.30 N=679 Protocol 1199.32 N=718 Protocol 1199.34 N=794	July 14-24, 2014	Preliminary: NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

SPONSOR

1. **Boehringer Ingelheim Pharmaceuticals, Inc.**
   Ridgefield, CT

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from July 14 to 24, 2014.

The inspection evaluated the following documents for the selected studies and monitoring clinical sites/personnel: (1) organization and personnel including review of written agreements with contract research organizations (CROs), (2) registration of studies on clinicaltrials.gov, (3) selection and monitoring of clinical investigators including agreements, non-compliance, and training (including protocol specific and GCP training), (4) selection of monitors, monitoring procedures, plans and reports for the three selected clinical sites, (5) quality assurance (QA) including the audit plan and QA audits, (6) safety and adverse event reporting, (7) financial disclosure, (8) data collection and handling, and (9) test article integrity and accountability.

b. General observations/commentary:

The sponsor generally maintained adequate oversight of the clinical trial. Monitoring of the investigator sites was adequate. Appropriate steps were taken by the sponsor to bring noncompliant sites into compliance. There was no evidence of under-reporting of adverse events. There were no GCP noncompliant sites reported.

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

c. Assessment of data integrity:

The sponsor monitoring appeared reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Boehringer Ingelheim Pharmaceuticals, Inc. was audited to inspect the sponsor's responsiblities in maintaining adequate oversight of the clinical trial sites and monitors for the following study protocols: Protocol 1199.30, Protocol 1199.32, and Protocol 1199.34.

The preliminary regulatory classification for the sponsor inspection is No Action Indicated (NAI). Data submitted by this sponsor appears reliable in support of the requested indication.

Note: *The inspectional observations noted above are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated, if conclusions on the current*

inspection report changes significantly, upon receipt of the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Orencia, 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 Thompson, M.D.
Team Leader, GCP Assessment Branch,
for Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
08/29/2014

JANICE K POHLMAN
08/29/2014

SUSAN D THOMPSON
08/29/2014

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

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

Memorandum

Date: August 18, 2014

To: Jessica Lee, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

cc: Kathleen Klemm, Team Leader, OPDP

Subject: NDA 205832
OPDP labeling comments for Nintedanib capsules for oral use

In response to DPARP's consult request dated May 22, 2014, OPDP has reviewed the proposed draft labeling (Package Insert [PI] and Carton and Container Labeling) for Nintedanib capsules for oral use (nintedanib) and offers the following comments. OPDP's comments on the proposed Patient Package Insert (PPI) were incorporated into a collaborative review by the Division of Medical Policy Programs (DMPP) and OPDP, and were provided under separate cover on August 15, 2014.

OPDP's comments on the PI are provided directly below and are based on the draft marked-up labeling titled "NDA 205832_nintedanib_BIproposed labeling_8_12_14_SCPI_MP.docx" that was provided via email from DPARP on August 12, 2014.

OPDP has also reviewed the proposed carton and container labeling submitted by the sponsor on June 5, 2014 (eCTD sequence #0003), and available at:

- \\cdsesub1\evsprod\nda205832\0003\m1\us\l5946a.pdf
- \\cdsesub1\evsprod\nda205832\0003\m1\us\ct5945a.pdf
- \\cdsesub1\evsprod\nda205832\0003\m1\us\l5949a.pdf
- \\cdsesub1\evsprod\nda205832\0003\m1\us\ct5948a.pdf

We have no comments at this time on the proposed carton and container labeling.

Thank you for your consult. OPDP appreciates the opportunity to provide comments on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
08/18/2014

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

PATIENT LABELING REVIEW

Date:	August 14, 2014
To:	Badrul Chowdhury, M.D. Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, MSN, FNP-BC, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Roberta Szydlo, RPh, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	nintedanib
Dosage Form and Route:	capsules
Application Type/Number:	NDA 205832
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On May 2, 2014, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application for nintedanib capsules. Nintedanib capsules are indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Nintedanib for the treatment of patients with IPF was granted Orphan Drug Designation on June 29, 2011. The IPF clinical development program also received Fast Track Designation on May 31, 2013, based on the life-threatening nature of the disease and the serious unmet medical need in the U.S.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on May 22, 2014, and May 22, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for nintedanib capsules.

2 MATERIAL REVIEWED

- Draft nintedanib PPI received on May 2, 2014, and received by DMPP on August 12, 2014.
- Draft nintedanib PPI received on May 2, 2014, and received by OPDP on August 12, 2014.
- Draft nintedanib Prescribing Information (PI) received on May 2, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on August 12, 2014.
- Draft nintedanib Prescribing Information (PI) received on May 2, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 12, 2014.
- Approved pazopanib (VOTRIENT) comparator labeling dated June 3, 2014.

3 REVIEW METHODS

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 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- 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 and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
08/14/2014

ROBERTA T SZYDLO
08/14/2014

MELISSA I HULETT
08/15/2014

LASHAWN M GRIFFITHS
08/15/2014

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

IND or NDA	NDA 205832
Brand Name	(b) (4)
Generic Name	Nintedanib (BIBF 1120)
Sponsor	Boehringer Ingelheim, Inc.
Indication	Treatment of idiopathic pulmonary fibrosis (IPF)
Dosage Form	Soft gelatine capsule
Drug Class	BIBF 1120 is a potent, orally available triple kinase inhibitor targeting VEGFR, PDGFR, and FGF receptors (FGFR).
Therapeutic Dosing Regimen	200 mg twice daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	BIBF 1120 monotherapy: 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients.
Submission Number and Date	SDN 001; 02 May 2014
Review Division	DPARP

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

1 SUMMARY

1.1 Overall Summary of Findings

No significant QTc prolongation effect of BIBF 1120 200 mg BID was detected in this QT study. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline in QTcF was 6.4 ms observed on Day 15.

In this randomized, open -label, parallel-group phase II study, 96 previously untreated patients with renal cell cancer received BIBF 200 mg BID and sunitinib 50 mg QD. Patients receiving sunitinib did not take part in the ECG evaluation. 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 BIBF 1120 200 mg BID (FDA Analysis)

Day	Time (hour)	ΔQTcF (ms)	90% CI (ms)
1	5	-1.3	(-4.3, 1.8)
15	7	3.1	(-0.2, 6.4)

Based on the Phase I dose escalation trials with BIBF 1120 monotherapy, the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. Available PK data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg BIBF 1120 once daily. Maximum BIBF 1120 plasma concentrations occurred mainly 1 h to 4 h after administration; steady state was reached at latest within 9 days of starting treatment. The mean terminal half-life was between 7 h to 19 h. There was no detectable deviation from dose-proportionality.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a dedicated study in renal cell cancer patients, QT/QTc measurements were recorded and showed that a single oral dose of 200 mg nintedanib as well as multiple oral doses of 200 mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

2.2 QT-IRT'S PROPOSED LABEL

The sponsor's proposed labeling seems acceptable. We defer the final labeling decisions to the review division.

3 BACKGROUND

3.1 PRODUCT INFORMATION

BIBF 1120 is a small molecule, triple kinase inhibitor of VEGFR 1 to 3, FGFR 1 to 3, as well as PDGFR α and ß in the low nanomolar range.

3.2 MARKET APPROVAL STATUS

BIBF 1120 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

BIBF 1120 base had an IC50 value of 4.0 μM on hERG mediated potassium current in HEK293 cells. Action potential configuration: In isolated papillary muscles from guinea pigs, BIBF 1120 base had no effect on APD90 in concentrations up to 10 μM.

Intravenous doses of 3, 10 and 30 mg/kg BIBF 1120 were administered to anaesthetized telemetered pigs for the measurement of haemodynamic parameters. Heart rate was only increased by about 10 beats/min at 30 mg/kg, which was probably due to the drop in arterial blood pressure. The QT interval duration decreased throughout the protocol and the QRS duration tended to increase with the highest dose, but was quickly reversible upon stopping the infusion.

3.4 PREVIOUS CLINICAL EXPERIENCE

At the planning stage of this clinical trial (as of July 2008), a total of 704 patients and 59 healthy volunteers had been treated with doses up to 450 mg in Phase I and Phase II clinical trials. Phase I dose selection studies revealed that BIBF 1120 was generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms and reversible elevations of liver enzymes. The predominant AEs after monotherapy with BIBF 1120 were nausea, diarrhea, vomiting, abdominal pain, and fatigue of mostly low to moderate intensity. Dose limiting toxicities were dose-dependent hepatic enzyme elevations. These liver enzyme elevations were not accompanied by a simultaneous increase in bilirubin. Grade 3 liver enzyme increases (CTCAE Version 3, R04-0474) were reported in the dose groups of 250 mg twice daily or higher. The increases in liver enzymes were reversible and usually occurred within the first 2 months of treatment.

Unlike other compounds in this therapeutic class, hypertension or thromboembolic events were rare and did not suggest an increased frequency as a consequence of therapy with BIBF 1120. Combination of BIBF 1120 with other anti-cancer drugs revealed a similar AE profile compared to BIBF 1120 monotherapy, except for the chemotherapy-related toxicities.

Appendix 6.1 summarizes the key clinical cardiac safety. There is no clear difference from the placebo treatment.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of BIBF 1120's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report 1199.26 (and its interim report U11-2411-01) for BIBF 1120, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, open-label, parallel-group Phase II study comparing the efficacy and tolerability of BIBF 1120 versus sunitinib in previously untreated patients with renal cell cancer

4.2.2 Protocol Number

1199.26 /U11-2411-01

4.2.3 Study Dates

17-Jun-2010 – 01-Feb-2011

4.2.4 Objectives

The objectives of this clinical trial were to compare the efficacy and safety of BIBF 1120 in patients suffering from renal cell cancer (RCC) to sunitinib and to investigate the effects of BIBF 1120 on the heart rate (HR) corrected QT interval (QTcF).

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, open-label, parallel-group phase II study.

4.2.5.2 Controls

The sponsor did not use placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were two treatment arms:

- Vargatef™ (BIBF 1120) soft gelatine capsules 200 mg bid (dose reduction to 150 mg bid or 100 mg bid in case of relevant AEs).
- Sunitinib (Sutent®) hard capsule 50 mg qd (dose reduction to 37.5 mg qd or 25 mg qd in case of relevant AEs).

BIBF 1120 was given continuously (treatment courses of 4 weeks), while sunitinib was given in courses of 4 weeks followed by 2 weeks without treatment. Treatment was to be continued until patients died, experienced disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST), experienced unacceptable AEs, or withdrew consent for any other reasons.

4.2.6.2 Sponsor's Justification for Doses

Available PK data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg BIBF 1120 once daily. Maximum BIBF 1120 plasma concentrations occurred mainly 1 h to 4 h after administration; steady state was reached at latest within 9 days of starting treatment. The gMean terminal half-life was between 7 h to 19 h. There was no detectable deviation from dose-proportionality. The main metabolite of BIBF 1120 was BIBF 1202 which was further glucuronidated *in vitro* to the BIBF 1202-glucuronide via the UDP glucuronosyltransferase (UGT) 1A1 enzyme in the liver and via UGT1A1, UGT1A7, UGT1A8 and UGT1A10 in the intestine. In humans, 93.4% of total [14C] radioactivity was excreted in the faeces within 120 h after oral administration of BIBF 1120. Only 0.7 % of total [14C] radioactivity was eliminated via the urine. The PK parameters of BIBF 1120 or of cytotoxic co-medication did not change in combination treatment.

Based on the Phase I dose escalation trials with BIBF 1120 monotherapy, the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg

twice daily in Japanese patients with a manageable safety profile in advanced cancer patients.

In this randomized, open-label, parallel-group Phase II study comparing the efficacy and tolerability of BIBF 1120 versus sunitinib in previously untreated patients with renal cell cancer, patients were randomised in a 2:1 ratio to receive either 200 mg BIBF 1120 bid given continuously in 4-week cycles, or 50 mg sunitinib given once daily in 6-week cycles (4 weeks of sunitinib followed by 2 weeks without treatment). The dosages of 200 mg bid BIBF 1120 or 50 mg qd sunitinib could be reduced if a patient experienced drug-related AEs.

Reviewer's Comment: The selection of doses in the study is acceptable.

4.2.6.3 Instructions with Regard to Meals

BIBF 1120 was to be swallowed unchewed with about 200 ml water after food intake at approximately the same time every day, i.e., in the morning and in the evening to ensure a dosing interval of approximately 12 h.

Reviewer's Comment: Acceptable. There is no clear food effect on BIBF 1120 PK.

4.2.6.4 ECG and PK Assessments

The time schedule for ECG assessments as well as PK blood sampling on Day -1 (baseline), Day 1 (single dose of BIBF 1120), and Day 15 (steady state of BIBF 1120) is depicted in the table below (Table 2).

Table 2. Flow Chart with Schedule of ECG Assessments and PK Blood Sampling

	Baseline	Treatment Period 1	Treatment Period 1	Treatment Period 1	Treatment Period 2
Visit	**2**	**3**	**4**	**5**	**R2**
Day	**-1[§]**	**1**	**15**	**28**	**28**
ECG time point -0:05 h	X	X	X		
ECG time point +1 h	X	X	X		
ECG time point +2 h	X	X	X		
ECG time point +3 h	X	X	X		
ECG time point +4 h	X	X	X		
ECG time point +5 h	X	X	X		
ECG time point + 6h	X	X	X		
ECG time point +7 h	X	X	X		
ECG time point +10 h	X	X	X		
ECG time point +12 h	X	X	X		
PK time point -0:05 h		X	X	X	X
PK time point +1 h		X	X		
PK time point +2 h		X	X		
PK time point +3 h		X	X		
PK time point +4 h		X	X		
PK time point +5 h		X	X		
PK time point +6 h		X	X		
PK time point +7 h		X	X		
PK time point +10 h		X	X		
PK time point +12 h		X	X		

Reviewer's Comment: The proposed ECG and PK sampling times are appropriate to capture the peak (Tmax = 3 hour in fed subjects) and potential delayed effects.

4.2.6.5 Baseline

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

4.2.7 ECG Collection

Twelve-lead ECGs were obtained at baseline, on days 1 and 15 of the first cycle, and at the end of subsequent cycles.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Ninety-nine subjects were randomized at 13 European centers; of these, 64 received nintedanib. About 1/3 of these discontinued.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Based on the FAS-ECG (the full analysis set), the largest time-matched mean change from baseline of 3.1 ms (90% CI -0.2, 6.4) occurred at 7 h after dosing. Based on the PPS-ECG (the per-protocol set), the largest time-matched mean change from baseline of 2.5 ms (90% CI -0.9, 6.0) was seen at 12 h after dosing. (Using the PPS-ECG the largest overall increase in QTcF from baseline [3.1 ms, 90% CI -0.4, 6.5] was observed just prior to the morning dose on Day 15). The upper limits of the 90% CIs for the adjusted mean changes were clearly below 10 ms at all time points of assessment independent of the analysis set used. All CIs included 0 ms.

On Day 1 of Treatment Course 1, the adjusted mean time-matched changes from baseline in QTcF revealed small decreases between 1 h and 12 h after a single oral dose of 200 mg BIBF 1120. The upper limits of the 90% CIs for the adjusted mean changes were well below 10 ms at all time points of assessment. All CIs included zero except for 2 h and 10 h after dosing.

The sponsor's results are displayed in Table 3 and Table 4.

Table 3: Repeated Measures Analysis of Time-matched Changes in the QTcF Interval [ms] from Baseline to Day 15 (Sponsor's Results)

Time	Day 15 (FAS-ECG)				Day 15 (PPS-ECG)			
[h]	N	Mean (SD)	Adjusted mean (SE)	2-sided 90% CI	N	Mean (SD)	Adjusted mean (SE)	2-sided 90% CI
0	63	3.4 (12.2)	2.6 (2.0)	-0.7, 5.9	52	4.2 (10.4)	3.1 (2.1)	-0.4, 6.5
1	62	0.4 (13.0)	0.4 (2.0)	-2.8, 3.7	51	0.3 (12.6)	0.0 (2.1)	-3.4, 3.5
2	63	-0.9 (12.2)	-1.7 (2.0)	-4.9, 1.6	52	-1.4 (12.0)	-2.4 (2.1)	-5.8, 1.1
3	63	-0.9 (11.0)	-0.5 (2.0)	-3.8, 2.8	52	-1.2 (10.8)	-1.0 (2.1)	-4.4, 2.5
4	61	-1.4 (13.1)	-0.5 (2.0)	-3.8, 2.8	51	-0.9 (13.2)	-0.4 (2.1)	-3.9, 3.0
5	61	-0.9 (8.4)	0.3 (2.0)	-3.0, 3.6	51	-0.8 (8.8)	0.2 (2.1)	-3.3, 3.6
6	62	1.9 (12.0)	2.2 (2.0)	-1.1, 5.5	52	1.7 (12.4)	1.4 (2.1)	-2.0, 4.9
7	61	3.3 (14.7)	3.1 (2.0)	-0.2, 6.4	51	3.0 (14.8)	2.2 (2.1)	-1.2, 5.7
10	60	-0.3 (14.0)	0.1 (2.0)	-3.2, 3.4	50	0.7 (14.5)	0.5 (2.1)	-2.9, 4.0
12	60	1.7 (12.3)	1.6 (2.0)	-1.7, 4.9	50	3.0 (12.3)	2.5 (2.1)	-0.9, 6.0

Note: 0 h denotes the timepoint -0.05 h, CI=confidence interval, SD=standard deviation, SE=standard error

Table 4: Repeated Measures Analysis of Time-matched Changes in the QTcF Interval [ms] from Baseline to Day 1 Based on the FAS-ECG (Sponsor's Results)

Time		Day 1		
[h]	N	Mean (SD)	Adjusted mean (SE)	2-sided 90% CI
1	64	-1.4 (11.0)	-1.6 (1.7)	-4.4, 1.2
2	64	-2.4 (8.2)	-3.1 (1.7)	-6.0, -0.3
3	64	-2.8 (8.9)	-2.6 (1.7)	-5.5, 0.2
4	62	-3.3 (10.8)	-2.6 (1.7)	-5.4, 0.3
5	62	-2.4 (10.2)	-1.4 (1.7)	-4.3, 1.4
6	62	-2.1 (10.2)	-2.0 (1.7)	-4.8, 0.9
7	61	-1.2 (11.6)	-1.5 (1.7)	-4.4, 1.3
10	60	-3.6 (9.9)	-3.6 (1.7)	-6.4, -0.7
12	61	-2.0 (10.3)	-2.2 (1.7)	-5.0, 0.7

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

4.2.8.2.2 Assay Sensitivity

No assay sensitivity analysis was performed because there was no positive control arm.

4.2.8.2.3 Categorical Analysis

On Day 1, 1 patient experienced a new onset (i.e., not present at any time pre-dose) of an absolute QTcF interval >450 ms and <470 ms. On Day 15, 1 patient developed a new onset of an absolute QTcF interval >450 ms and <470 ms and 1 patient developed a new onset of an absolute QTcF interval >470 ms and <500 ms.

In almost all patients, maximum time-matched increases in QTcF interval were ≤30 ms on Day 1 and Day 15. No patient experienced an increase in QTcF between 30 and 60 ms on Day 1, while 6 patients experienced an increase between 30 and 60 ms on Day 15.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

The main PK characteristics for the parent compound and the major metabolites on Day 1 (AUC0-12, Cmax, tmax) and Day 15 (AUCτ,ss, Cmax,ss, tmax,ss) as well as the accumulation ratios (RA,AUC, RA,Cmax) are given in the following Table 5:

Table 5. PK Characteristics for the Parent Compound and the Major Metabolites on Day 1 and Day 15

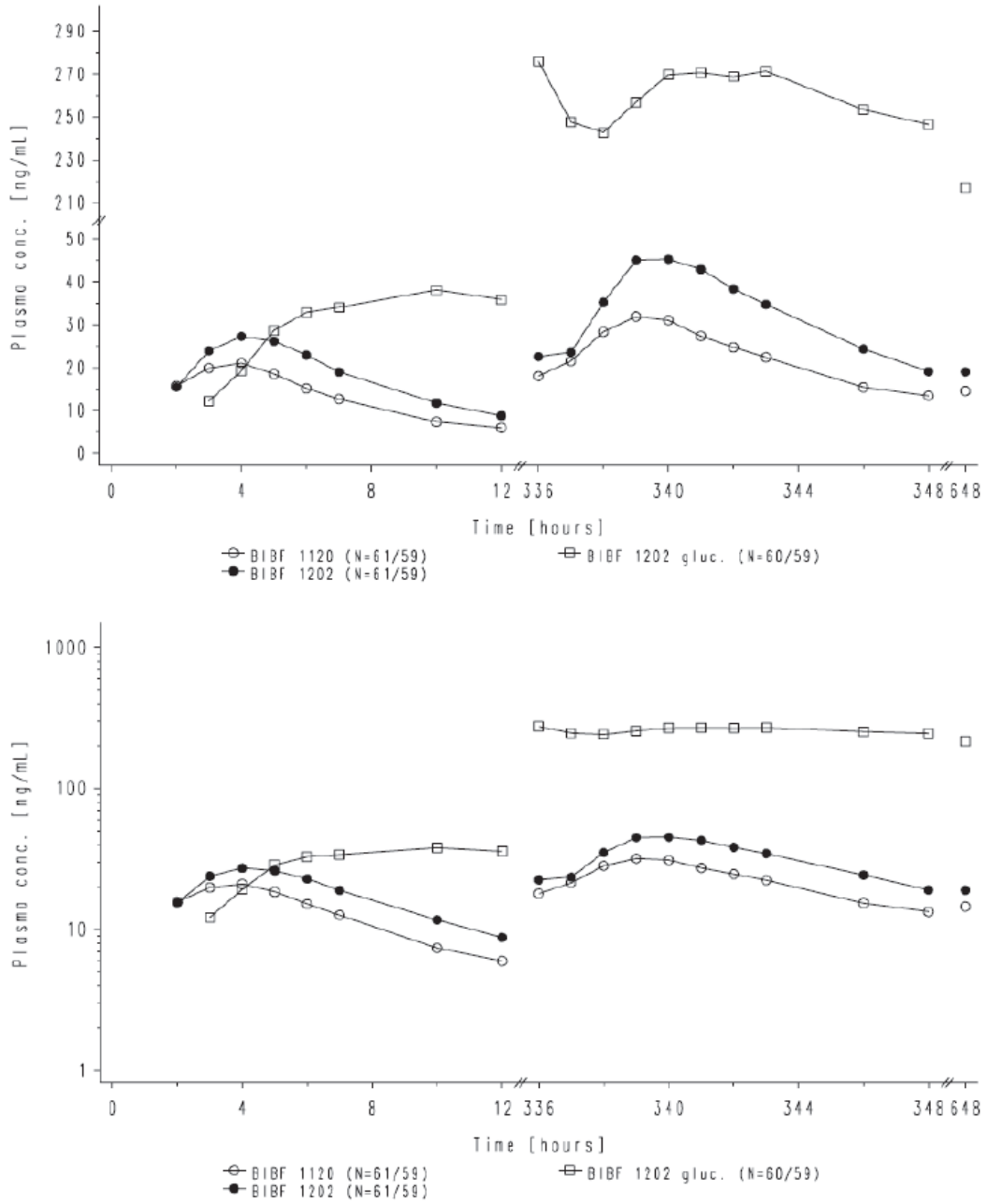
Parameter	Day 1		Day 15	
	N	gMean	N	gMean
		BIBF 1120		
AUC_{0-12} / $AUC_{\tau,ss}$ [ng·h/mL]	59	164	58	270
C_{max} / $C_{max,ss}$ [ng/mL]	61	31.8	61	43.□
t_{max} / $t_{max,ss}$[1] [h]	61	3.08	61	2.92
$R_{A,AUC}$	-	-	56	1.66
$R_{A,Cmax}$	-	-	59	1.33
		BIBF 1202		
AUC_{0-12} / $AUC_{\tau,ss}$ [ng·h/mL]	59	216	59	406
C_{max} / $C_{max,ss}$ [ng/mL]	61	34.8	61	56.5
t_{max} / $t_{max,ss}$[1] [h]	61	3.92	61	3.08
$R_{A,AUC}$	-	-	57	1.89
$R_{A,Cmax}$	-	-	59	1.60
		BIBF 1202-glucuronide		
AUC_{0-12} / $AUC_{\tau,ss}$ [ng·h/mL]	49	329	55	2940
C_{max} / $C_{max,ss}$ [ng/mL]	60	42.0	61	303
t_{max} / $t_{max,ss}$[1] [h]	60	10.1	61	4.05
$R_{A,AUC}$	-	-	45	9.08
$R_{A,Cmax}$	-	-	58	□.12

[1] For t_{max}, $t_{max, ss}$ the median is given

Exposure to the metabolites BIBF 1202 and BIBF 1202-glucuronide was in the same range or higher than the exposure to the parent compound BIBF 1120. Metabolic ratios increased when steady state conditions were compared to the administration of a single oral dose, especially regarding the ratios BIBF 1202-glucuronide /BIBF 1120 and BIBF 1202-glucuronide / BIBF 1202.

BIBF 1120 plasma concentrations increased after oral administration and peak plasma concentrations were achieved mainly around 2 h to 5 h after dosing. In general, BIBF 1120 plasma concentrations declined after reaching Cmax. Although disposition kinetics were observed for a very short time period, it seemed to be comparable after single dose and at steady state (see Figure 1). A slight accumulation was observed when comparing the single dose and steady state plasma concentration-time profiles as reflected by the gMean plasma concentration-time profiles of BIBF 1120 after single and multiple oral dosing. Trough plasma concentrations suggested that steady state was reached on Day 15 and remained stable over the observed time interval.

Figure 1: Geometric Mean Plasma Concentration-Time Profiles of BIBF 1120, BIBF 1202, and BIBF 1202-glucuronide after Single (Day 1) and Multiple (Day 15) Oral Administration of 200 mg BIBF 1120 Bid to Patients with RCC (Upper Graph: Linear Scale; Lower Graph: Semi-Log Scale)



4.2.8.3.2 Exposure-Response Analysis

Mean plasma concentration-time profiles of BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide on Day 1 (single dose) and Day 15 (multiple doses, steady state) are

displayed together with the mean time-matched changes from baseline for QTcF (Figure 2 - Figure 7) with no evident exposure-response relationship.

Figure 2: Relationship between BIBF 1120 Plasma Concentrations and Time-Matched Qtcf Changes from Baseline [ms], Day 1

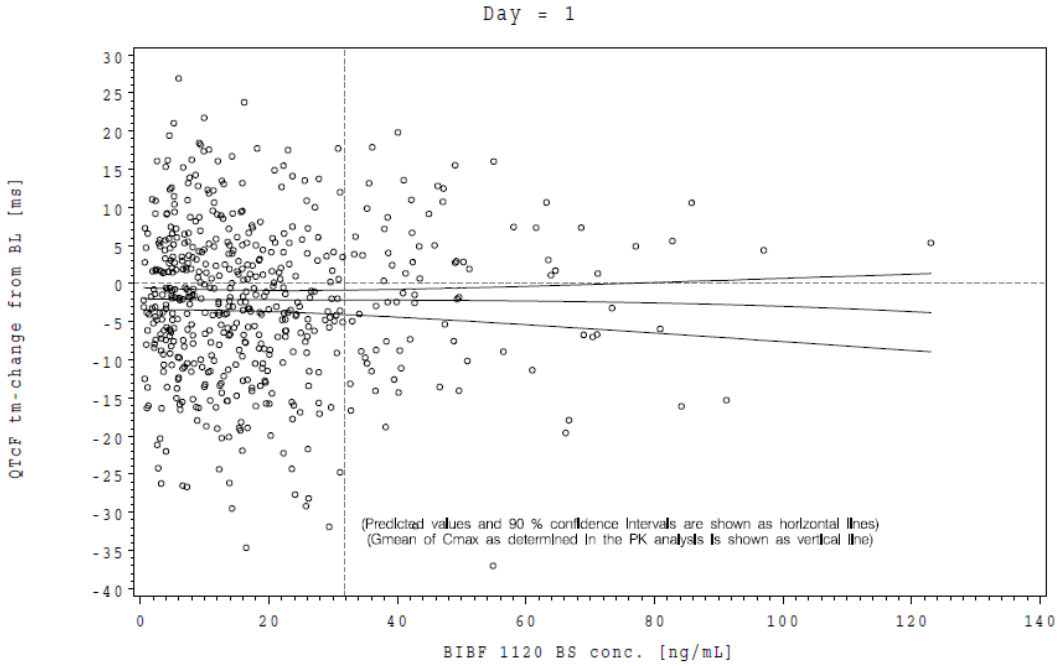


Figure 3: Relationship between BIBF 1120 Plasma Concentrations and Time-matched Qtcf Changes from Baseline [ms], Day 15

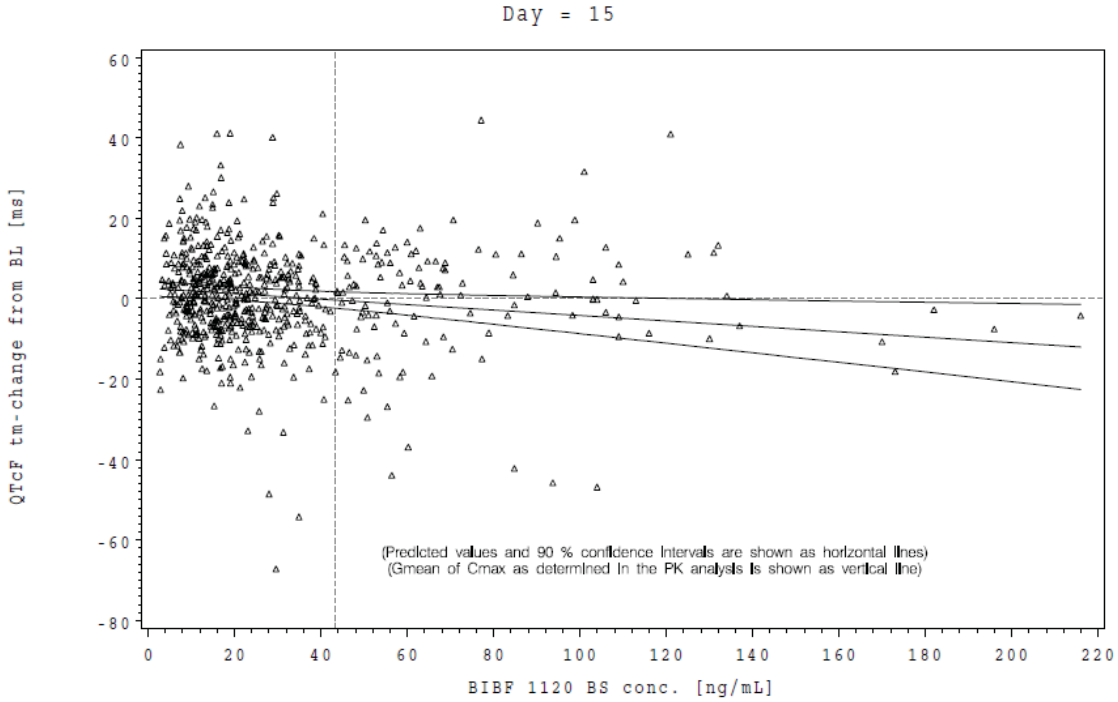


Figure 4: Relationship between BIBF 1202 Plasma Concentrations and Time-Matched Qtcf Changes from Baseline [ms], Day 1

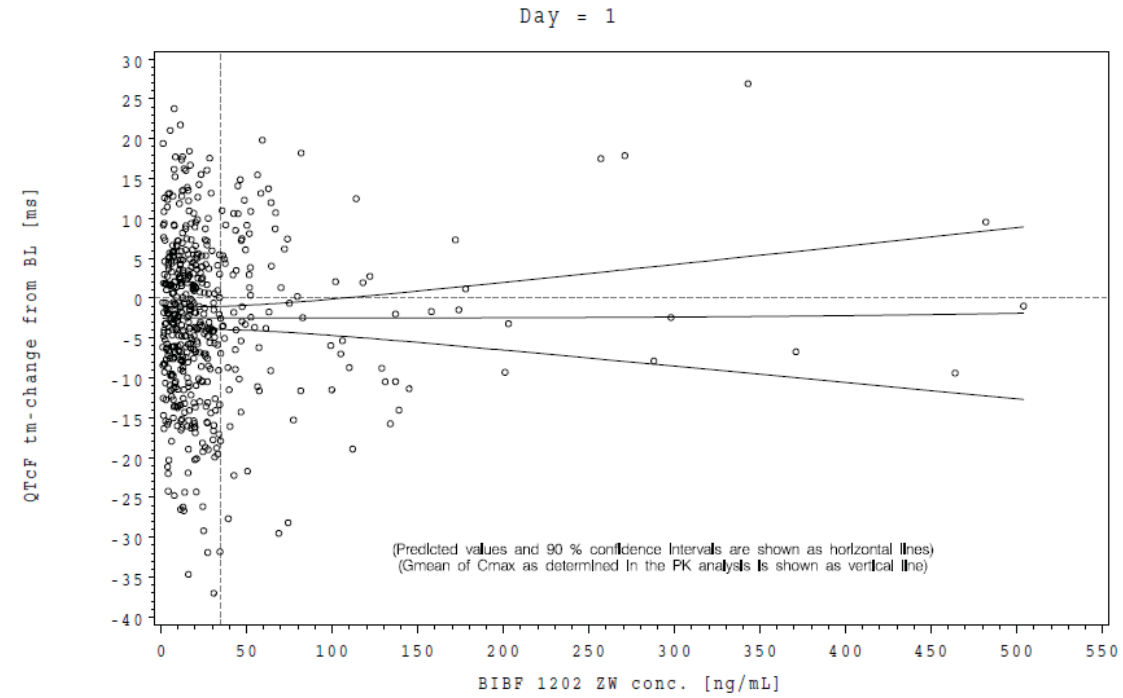


Figure 5: Relationship between BIBF 1202 Plasma Concentrations and Time-matched QTcF Changes from Baseline [ms], Day 15

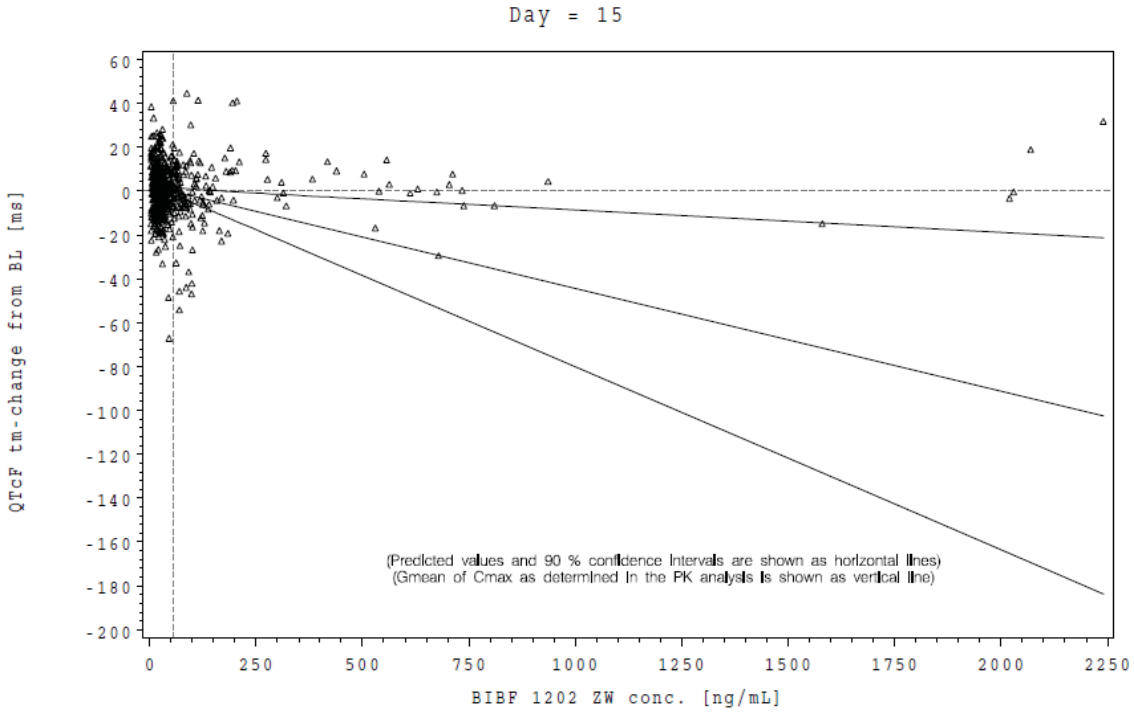


Figure 6: Relationship between BIBF 1202-glucuronide Plasma Concentrations and Time-Matched Qtcf Changes from Baseline [ms], Day 1

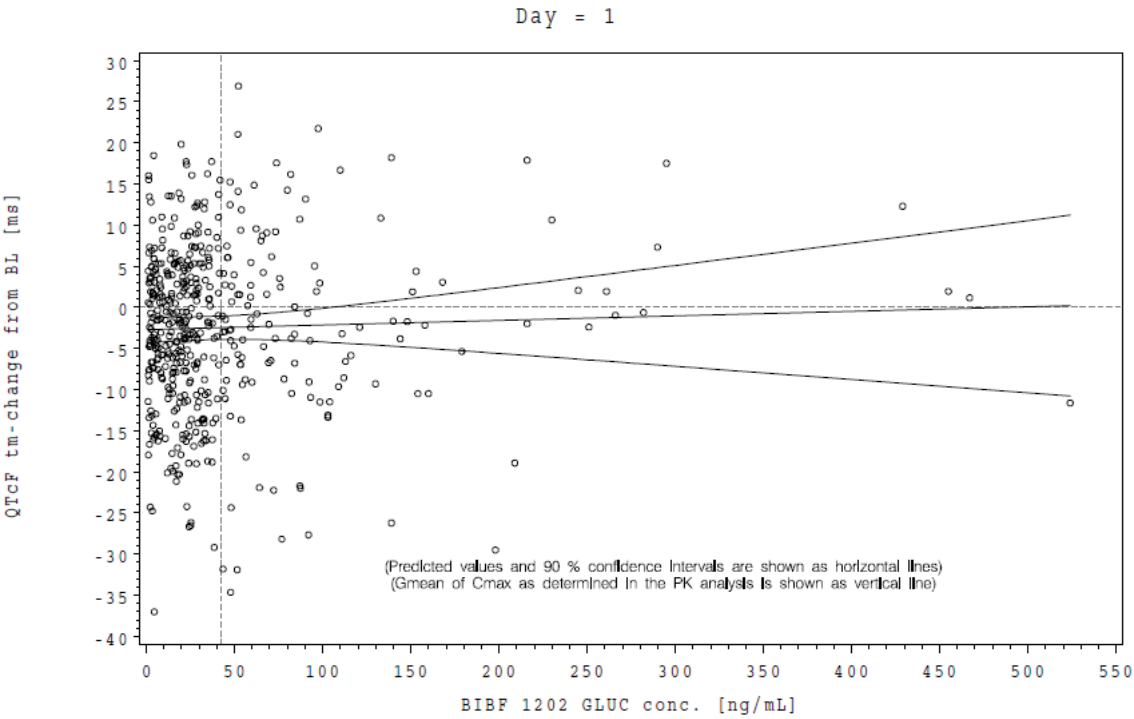
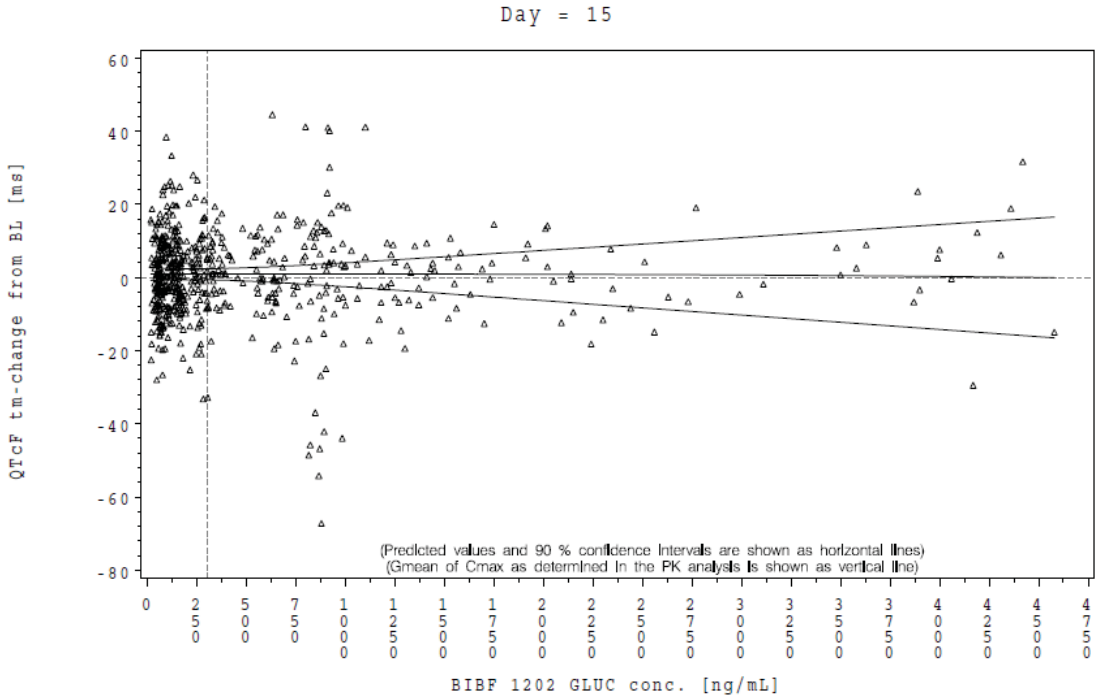


Figure 7: Relationship between BIBF 1202-glucuronide Plasma Concentrations and Time-Matched Qtcf Changes from Baseline [ms], Day 15



Reviewer's Analysis: A plot of ΔQTc vs. drug concentrations is presented in Figure 10 - Figure 12.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcB, QTcF and QTcN). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

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 6, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

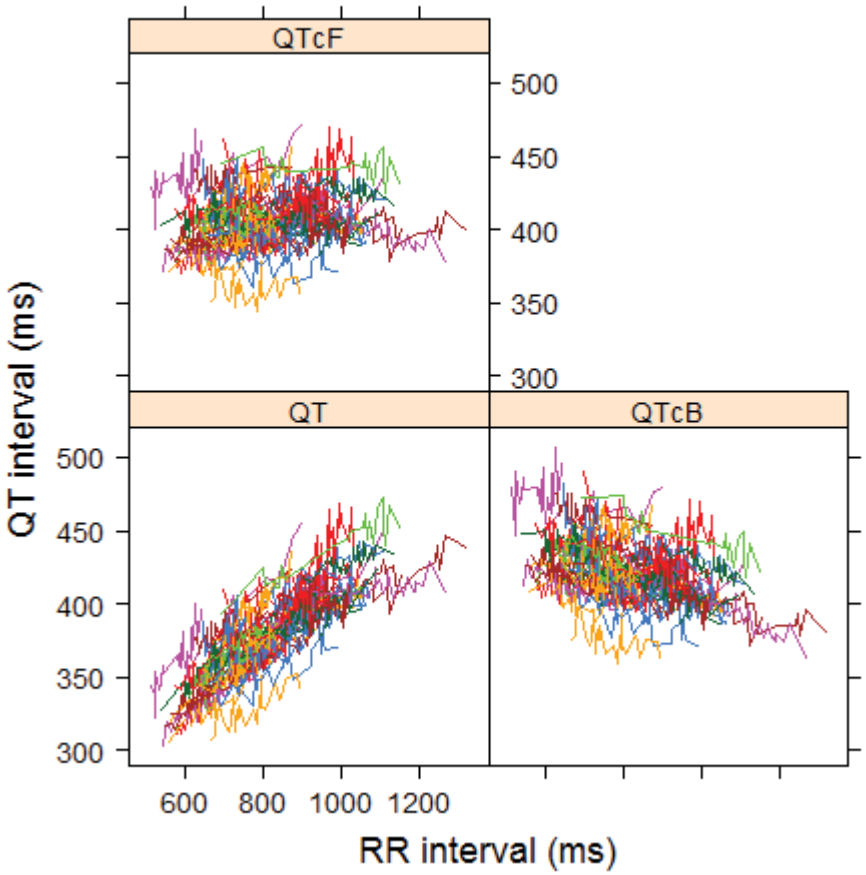
Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcB		QTcF		QTcN	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
BIBF 1120 200 mg BID	64	0.00882	64	0.00403	64	0.00414

*The table and later statistical analyses were based on the full analysis set (FAS-ECG).

The relationship between different correction methods and RR is presented in Figure 8.

Figure 8: QT, QTcB, 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 BIBF 1120 200 mg BID

The primary endpoint is the mean change from baseline in QTcF (ΔQTcF). The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes time as a fixed effect and baseline as a covariate. The analysis results are listed in the following tables.

Table 7: Analysis Results of ΔQTcF for BIBF 1120 200 mg BID on Day 1

	ΔQTcF (ms): Day 1					
Time (hour)	**N**	**Mean**	**SD**	**LSmean**	**SE for LSmean**	**90% CI for LSmean**
1	64	-1.4	11.0	-1.5	1.8	(-4.6, 1.5)
2	64	-2.4	8.2	-3.1	1.8	(-6.2, -0.1)
3	64	-2.8	8.9	-2.5	1.8	(-5.6, 0.5)
4	62	-3.3	10.8	-2.5	1.8	(-5.5, 0.6)
5	62	-2.4	10.2	-1.3	1.8	(-4.3, 1.8)
6	62	-2.1	10.2	-1.9	1.8	(-4.9, 1.2)
7	61	-1.2	11.6	-1.6	1.8	(-4.6, 1.5)
10	60	-3.6	9.9	-3.6	1.8	(-6.6, -0.5)
12	61	-2.0	10.3	-2.1	1.8	(-5.2, 1.0)

Table 8: Analysis Results of ΔQTcF for BIBF 1120 200 mg BID on Day 15

	ΔQTcF (ms): Day 15					
Time (hour)	**N**	**Mean**	**SD**	**LSmean**	**SE for LSmean**	**90% CI for LSmean**
-0.08	63	3.4	12.2	2.6	2.0	(-0.7, 5.9)
1	62	0.4	13.0	0.4	2.0	(-2.8, 3.7)
2	63	-0.9	12.2	-1.7	2.0	(-4.9, 1.6)
3	63	-0.9	11.0	-0.5	2.0	(-3.8, 2.8)
4	61	-1.4	13.1	-0.5	2.0	(-3.8, 2.8)
5	61	-0.9	8.4	0.3	2.0	(-3.0, 3.6)
6	62	1.9	12.0	2.2	2.0	(-1.1, 5.5)
7	61	3.3	14.7	3.1	2.0	(-0.2, 6.4)
10	60	-0.3	14.0	0.1	2.0	(-3.2, 3.4)
12	60	1.7	12.3	1.6	2.0	(-1.7, 4.9)

The largest upper bounds of the 2-sided 90% CI for the mean change from baseline in QTcF on Day 1 and Day 15 were 1.8 ms and 6.4 ms, respectively.

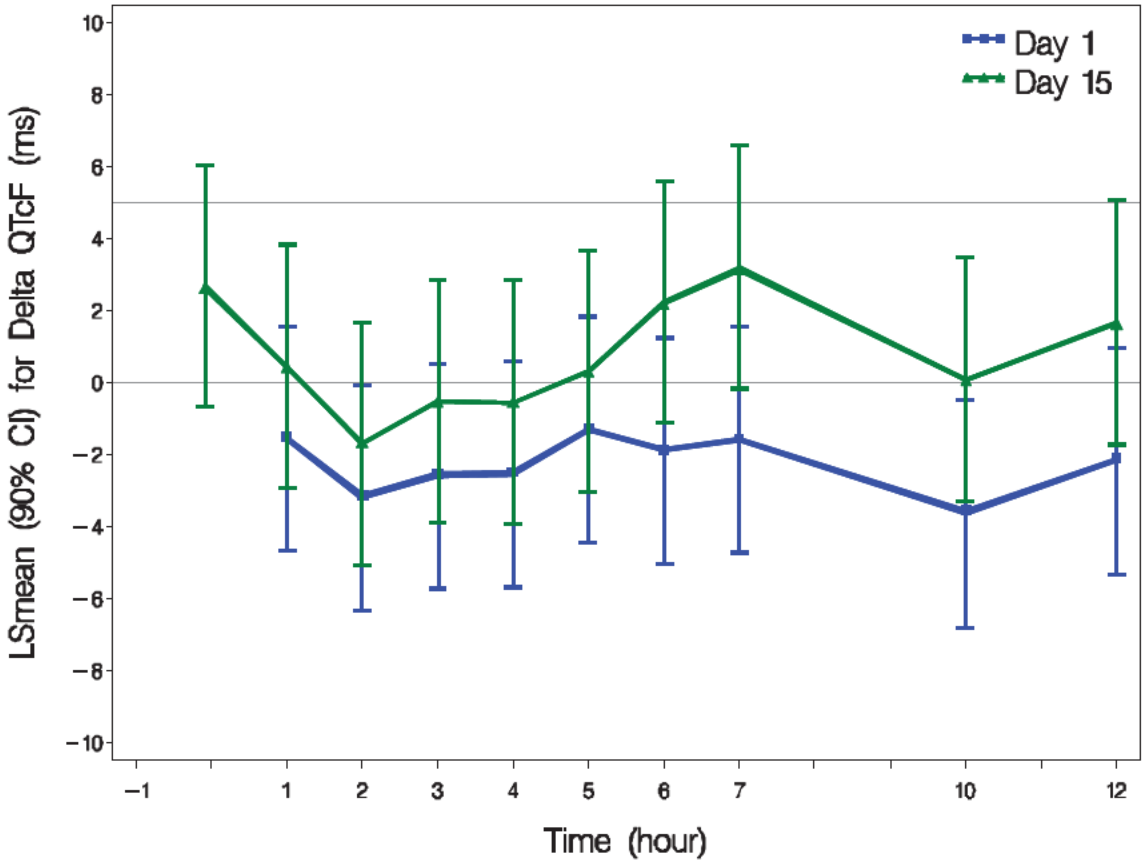
5.2.1.2 Assay Sensitivity Analysis

No assay sensitivity analysis was done by the statistical reviewer because there was no positive control arm.

5.2.1.3 Graph of ΔQTcF over Time

The following figure displays the time profile of ΔQTcF for BIBF 1120 200 mg BID.

Figure 9: Mean and 90% CI ΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 9: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Day	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day -1 and Day 1 Predose	64	691	60 (93.8%)	678 (98.1%)	4 (6.3%)	13 (1.9%)
Day 1	64	568	62 (96.9%)	566 (99.6%)	2 (3.1%)	2 (0.4%)
Day 15	63	624	59 (93.7%)	614 (98.4%)	4 (6.3%)	10 (1.6%)

Table 10 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 10: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Day	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1	64	560	64 (100%)	560 (100%)	0 (0.0%)	0 (0.0%)
Day 15	63	616	57 (90.5%)	607 (98.5%)	6 (9.5%)	9 (1.5%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of the 2-sided 90% CI for the mean change from baseline in HR on Day 1 and Day 15 were 1.8 bpm and 3.0 bpm, respectively. The outlier analysis results for HR are presented in Table 12.

Table 11: Analysis Results of ΔHR for BIBF 1120 200 mg BID

	ΔHR (bpm): Day 1			ΔHR (bpm): Day 15		
Time (hour)	**LSmean**	**SE for LSmean**	**90% CI for LSmean**	**LSmean**	**SE for LSmean**	**90% CI for LSmean**
-0.08				0.9	1.3	(-1.2, 3.0)
1	-0.1	1.2	(-2.1, 1.8)	-0.3	1.3	(-2.4, 1.9)
2	-3.0	1.2	(-5.0, -1.1)	-2.0	1.3	(-4.2, 0.1)
3	-4.0	1.2	(-5.9, -2.0)	-3.3	1.3	(-5.4, -1.2)
4	-2.6	1.2	(-4.5, -0.6)	-3.4	1.3	(-5.5, -1.3)
5	-1.9	1.2	(-3.8, 0.1)	-3.1	1.3	(-5.2, -1.0)
6	-2.3	1.2	(-4.2, -0.3)	-3.8	1.3	(-5.9, -1.7)
7	-1.5	1.2	(-3.5, 0.5)	-2.8	1.3	(-4.9, -0.7)
10	-1.3	1.2	(-3.3, 0.6)	-2.4	1.3	(-4.5, -0.2)
12	-0.1	1.2	(-2.1, 1.8)	-1.6	1.3	(-3.8, 0.5)

Table 12: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Day	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Day -1 and Day 1 Predose	64	55 (85.9%)	9 (14.1%)	64 (100%)	0 (0.0%)
Day 1	64	59 (92.2%)	5 (7.8%)	64 (100%)	0 (0.0%)
Day 15	63	58 (92.1%)	5 (7.9%)	63 (100%)	0 (0.0%)

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 13. The largest upper limits of the 2-sided 90% CI for the mean change from baseline in PR on Day 1 and Day 15 were 7.9 ms and 6.1 ms, respectively. The outlier analysis results for PR are presented in Table 14.

Table 13: Analysis Results of ΔPR for BIBF 1120 200 mg BID

	ΔPR (ms): Day 1			ΔPR (ms): Day 15		
Time (hour)	**LSmean**	**SE for LSmean**	**90% CI for LSmean**	**LSmean**	**SE for LSmean**	**90% CI for LSmean**
-0.08				-2.2	2.6	(-6.5, 2.2)
1	0.4	2.6	(-4.0, 4.8)	-0.7	2.6	(-5.0, 3.7)
2	2.0	2.6	(-2.3, 6.4)	-0.4	2.6	(-4.8, 3.9)
3	2.7	2.6	(-1.7, 7.1)	0.2	2.6	(-4.1, 4.6)
4	2.4	2.6	(-2.0, 6.8)	1.3	2.6	(-3.1, 5.7)
5	2.1	2.6	(-2.3, 6.5)	0.5	2.6	(-3.9, 4.9)
6	3.5	2.6	(-0.9, 7.9)	1.7	2.6	(-2.6, 6.1)
7	2.2	2.6	(-2.2, 6.6)	1.5	2.6	(-2.9, 5.8)
10	1.6	2.6	(-2.8, 6.0)	1.6	2.6	(-2.8, 6.0)
12	2.2	2.6	(-2.2, 6.6)	0.2	2.6	(-4.1, 4.6)

Table 14: Categorical Analysis for PR

	Total N		PR<=200 ms		PR>200 ms	
Day	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day -1 and Day 1 Predose	64	691	55 (85.9%)	620 (89.7%)	9 (14.1%)	71 (10.3%)
Day 1	64	568	55 (85.9%)	498 (87.7%)	9 (14.1%)	70 (12.3%)
Day 15	63	624	53 (84.1%)	553 (88.6%)	10 (15.9%)	71 (11.4%)

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 15. The largest upper limits of the 2-sided 90% CI for the mean change from baseline in QRS on Day 1 and Day 15 were 2.4 ms and 3.3 ms, respectively.

The outlier analysis results for QRS are presented in Table 16.

Table 15: Analysis Results of ΔQRS for BIBF 1120 200 mg BID

	ΔQRS (ms): Day 1			ΔQRS (ms): Day 15		
Time (hour)	**LSmean**	**SE for LSmean**	**90% CI for LSmean**	**LSmean**	**SE for LSmean**	**90% CI for LSmean**
-0.08				0.4	1.3	(-1.8, 2.5)
1	0.2	1.2	(-1.7, 2.1)	0.8	1.3	(-1.4, 2.9)
2	0.1	1.2	(-1.9, 2.0)	-0.0	1.3	(-2.2, 2.1)
3	0.3	1.2	(-1.6, 2.3)	-0.2	1.3	(-2.3, 2.0)
4	0.5	1.2	(-1.4, 2.4)	-0.4	1.3	(-2.6, 1.7)
5	0.3	1.2	(-1.6, 2.3)	0.6	1.3	(-1.6, 2.7)
6	0.4	1.2	(-1.6, 2.3)	0.1	1.3	(-2.0, 2.2)
7	0.3	1.2	(-1.7, 2.2)	0.1	1.3	(-2.0, 2.2)
10	-0.2	1.2	(-2.2, 1.7)	0.2	1.3	(-1.9, 2.4)
12	0.4	1.2	(-1.6, 2.3)	1.1	1.3	(-1.0, 3.3)

Table 16: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Day	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day -1 and Day 1 Predose	64	691	58 (90.6%)	643 (93.1%)	6 (9.4%)	48 (6.9%)
Day 1	64	568	58 (90.6%)	529 (93.1%)	6 (9.4%)	39 (6.9%)
Day 15	63	624	56 (88.9%)	564 (90.4%)	7 (11.1%)	60 (9.6%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationships between ΔQTcF and BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide plasma concentrations are visualized in Figure 10 - Figure 12. It appears there are significant relationships between ΔQTcF and BIBF 1202 and BIBF 1202-glucuronide plasma concentrations, however it seems there is no clinical concerns at the mean steady state C_{max} levels (56.5 and 303 ng/mL) of BIBF 1202 and BIBF 1202-glucuronide.

Figure 10: Δ QTcF vs. BIBF 1120 Concentration

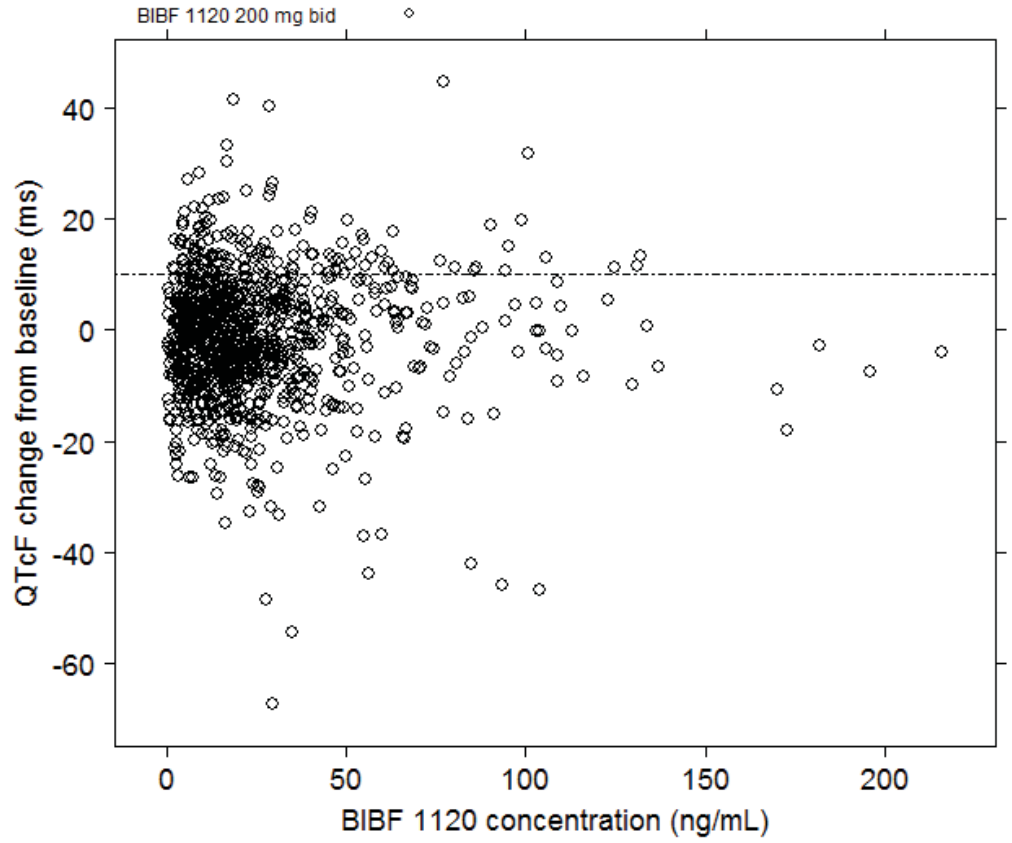


Figure 11: Δ QTcF vs. BIBF 1202 Concentration

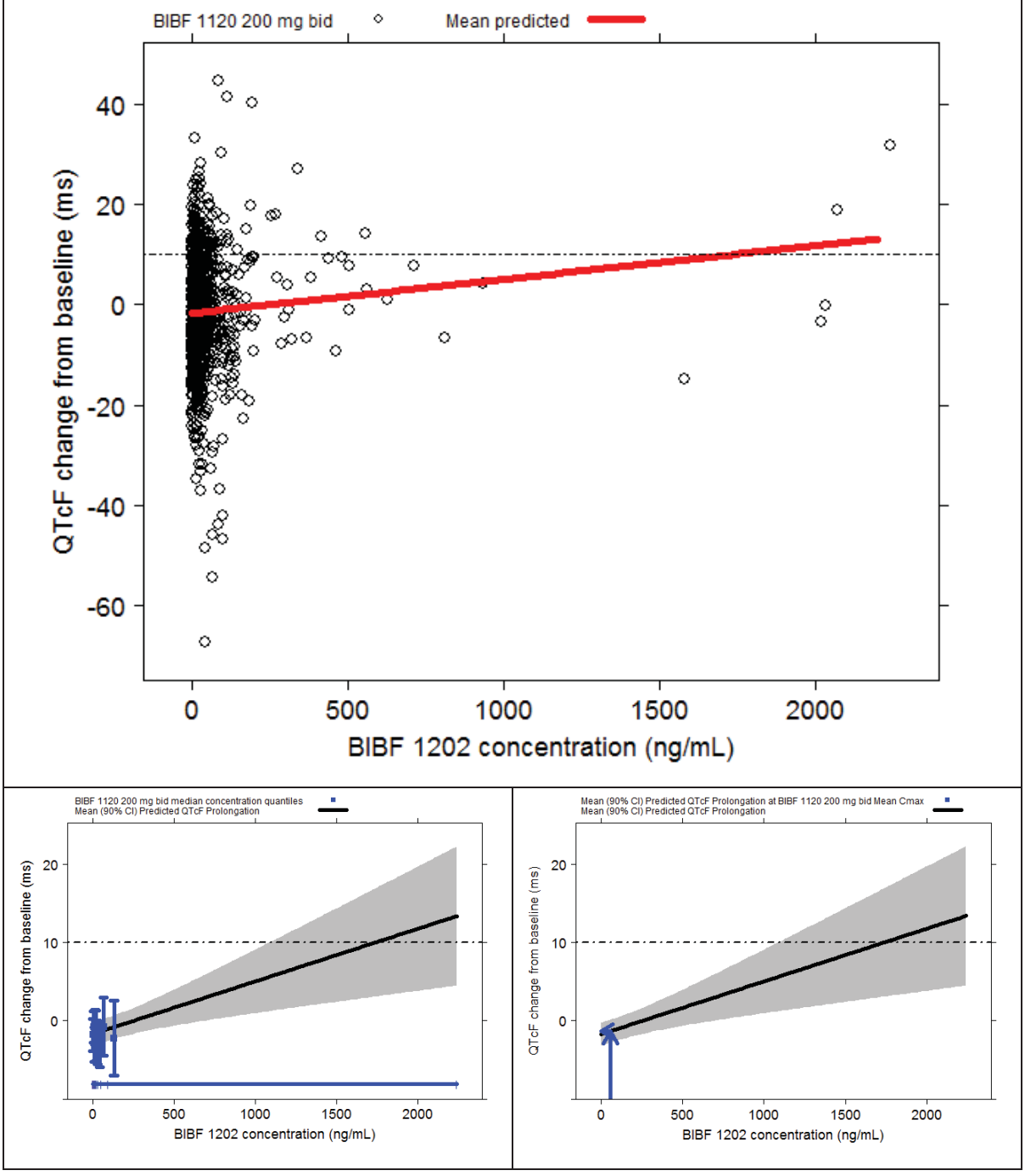
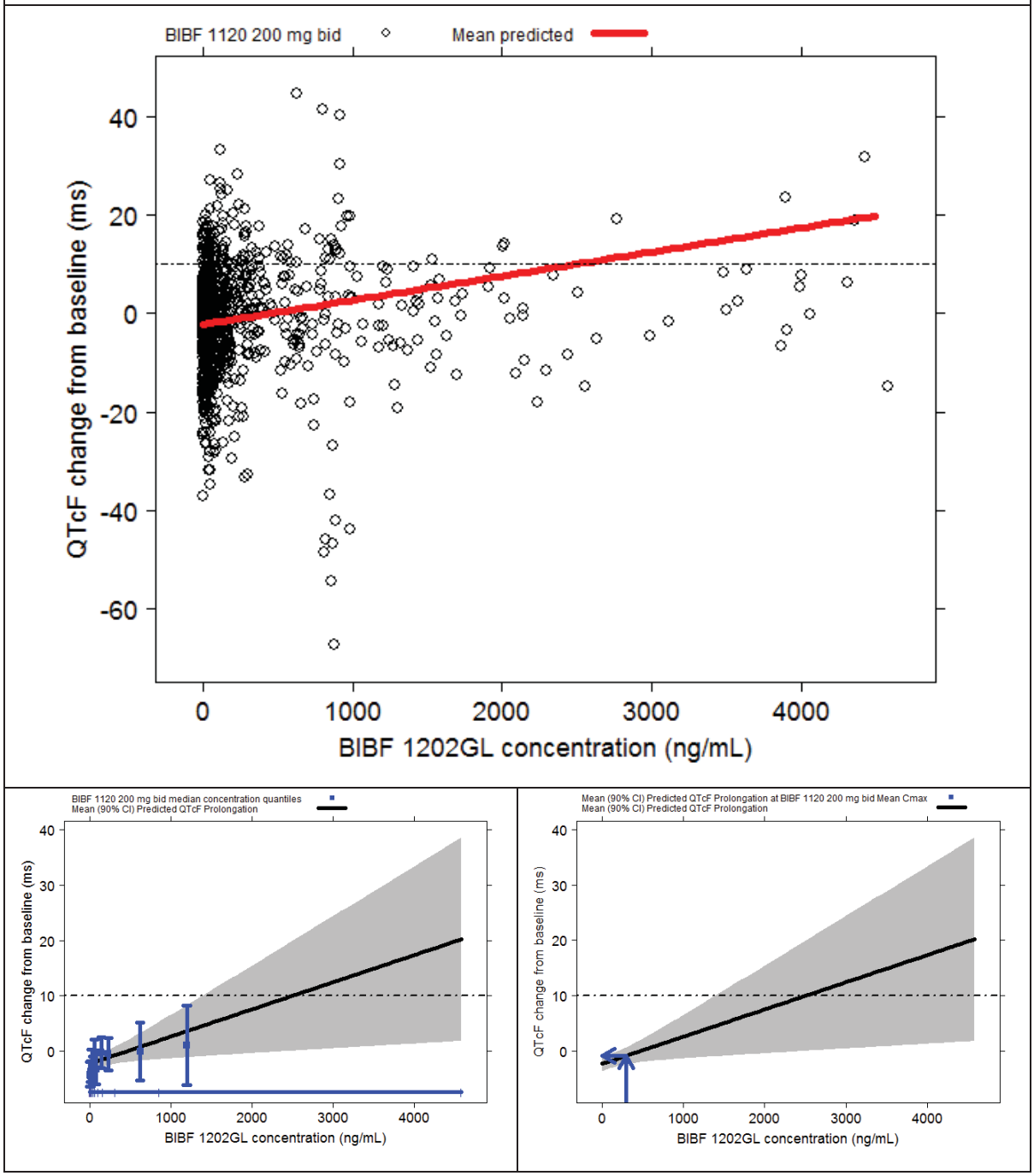


Figure 12: Δ QTcF vs BIBF 1202-glucuronide Concentration



5.4 Clinical Assessments

5.4.1 Safety assessments

There was one death on study drug, attributed to disease progression. There were a variety of grade 1-2 tachyarrhythmias, generally not attributed to study drug. In this assessment, we concur, but with a high background rate, it is difficult to be sure that some of the events are not treatment-related.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	150 mg bid monotherapy; oral administration Based on tolerability, dose adjustment to 100 mg bid possible	
Maximum tolerated dose	Continuous bid administration: 250 mg bid in Caucasians and 200 mg bid in Japanese (obtained from data in cancer patients) Continuous qd administration: 200 mg qd (Study 1199.1); 400 mg qd (Study 1199.4; both data in cancer patients) (Combination with other chemotherapeutic agents in oncology indications: 200 mg bid)	
Principal adverse events	Gastrointestinal disorders (diarrhea, nausea, vomiting) Elevations of liver enzymes (ALT, AST, GGT)	
Maximum dose tested	Single Dose	450 mg (data in cancer patients)
	Multiple Dose	300 mg bid, continuous 450 mg qd, continuous (both: data in cancer patients)
Exposures Achieved at Maximum Tested Dose	Single Dose	gMean (% gCV) of nintedanib after administration of 450 mg (Study 1199.1; N = 3) C_{max}: 76.1 ng/mL (162 %) $AUC_{0-\infty}$: 542 ng·h/mL (185 %)
	Multiple Dose	gMean (% gCV) of nintedanib after administration of 300 mg bid, continuous (Study 1199.1; N = 3): $C_{max,ss}$: 68.6 ng/mL (20.6 %) $AUC_{\tau,ss}$: 366 ng·h/mL (9.57 %) gMean (% gCV) of nintedanib after administration of 300 mg qd, continuous (Study 1199.1; N = 3; for the highest tested dose of 450 mg qd, no steady state PK readouts are available): $C_{max,ss}$: 50.5 ng/mL (137 %) $AUC_{\tau,ss}$: 482 ng·h/mL (128 %)
Range of linear PK	Metaanalysis of Phase I oncology studies 1199.1/2/3/19; analysis of Phase I/II oncology studies 1199.1/3/19/26 50 - 450 mg qd 100 - 300 mg bid	
Accumulation at steady state	Metaanalysis of Phase I oncology studies 1199.1/2/3/19:	

	Accumulation based on C_{max}: 0.978 fold (qd) and 1.04 fold (bid) Accumulation based on AUC_{τ}: 1.08 fold (qd) and 1.38 fold (bid)	
Metabolites	Major metabolites: BIBF 1202: active at some target receptors of nintedanib; plasma exposure not considered a relevant surrogate to judge BIBF 1202's contribution to the clinical effects of nintedanib based on preclinical *in-vivo* models (lack of efficacy of BIBF 1202; highly polar moiety) BIBF 1202 glucuronide: not active at target receptors of nintedanib Minor metabolic pathways via CYP enzymes: CYP dependent metabolites not detected in plasma in the human ADME study (1199.20)	
Absorption	Absolute/Relative Bioavailability	Study 1199.75: gMean absolute bioavailability F = 4.69 %, gCV = 53.4% (N = 12)
	Tmax	Study 1199.161 (reference treatment; N = 31; median and range): Nintedanib: 4.00 hr (3.00 – 6.00 hr) BIBF 1202: 4.00 hr (3.00 – 6.00 hr) BIBF 1202 glucuronide: 10.0 hr (3.00 – 15.1 hr)
Distribution	Vz, Vss	Study 1199.75 (N = 12; 6 mg nintedanib administered as *iv* infusion): gMean V_{ss} = 1050 L; gCV = 45.0 % gMean V_z = 2150 L; gCV = 31.9 %
	% bound	Bound fraction 97.8 % Major binding protein: human serum albumin
Elimination	Route	Study 1199.20 (N = 8): Excretion of total [^{14}C] radioactivity: feces: 93.4 % of dose urine: 0.649 % of dose Total recovery: 92.4 % within 4 days after dosing
	Terminal $t_{1/2}$	Study 1199.161 (reference treatment; N = 31; gMean (gCV%)): Nintedanib: 18.1 hr (34.9 %) BIBF 1202: 11.1 hr (32.4%) BIBF 1202 glucuronide: 28.2 hr (34.6%)
	CL/F or CL	Study 1199.75; N = 12; 6 mg nintedanib administered as *iv* infusion:

		gMean CL = 1390 mL/min (gCV = 28.8 %)
Intrinsic Factors[1]	Age	PopPK of studies 1199.10/13/14/30: Linear increase in bioavailability: Predicted $AUC_{\tau,ss}$ decreased by 16 % for patient at 5th percentile (45 years) relative to median (62 years) of analyzed population Predicted $AUC_{\tau,ss}$ increased by 13 % for patient at 95th percentile (76 years) relative to median
	Sex	PopPK of studies 1199.10/13/14/30: No significant effect of sex on PK after correction for body weight
	Race	PopPK of studies 1199.10/13/14/30: 33 % higher exposure in Chinese, Taiwanese, and Indian patients compared to Caucasians 22 % lower exposure in Korean patients compared to Caucasians Limited data from Black individuals; exposure in the range of Caucasians
Intrinsic Factors[1] (cont'd)	Hepatic & Renal Impairment	PopPK of studies 1199.10/13/14/30: Renal impairment: No significant effect of mild and moderate renal impairment (determined by creatinine clearance) on PK; data for severe impairment too limited Hepatic impairment: non-significant trend to elevated $AUC_{\tau,ss}$ in patients with hepatic impairment at baseline determined by ALT/AST levels > ULN but ≤ 10x ULN and bilirubin levels > ULN but ≤ 1.5x ULN; data in more severe hepatic impairment too limited
Extrinsic Factors[1]	Drug interactions	Drug-drug interaction with ketoconazole (P-gp inhibition; Study 1199.161; reference: N = 31; test: N = 29): Ratio test/reference C_{max}: 179.6 %; 90 % confidence interval 157.6 – 204.8 % Ratio test/reference $AUC_{0-\infty}$: 160.5 %; 90% confidence interval 148.2 – 173.7 % Drug-drug interaction with rifampicin (P-gp induction; Study 1199.162; reference: N = 26; test: N = 25): Ratio test/reference C_{max}: 59.76 %; 90 %

		confidence interval 53.83 – 66.35 % Ratio test/reference $AUC_{0-\infty}$: 50.12; 90 % confidence interval 47.16 – 53.28 %
	Food Effects	Study 1199.17; high-fat, high-caloric meal (reference: N = 15; test: N = 15 for C_{max} and N = 11 for AUC): Ratio test/reference C_{max}: 115.3 %; 90 % confidence interval 84.630 – 157.002% Ratio test/reference $AUC_{0-\infty}$: 120.6 %; 90% confidence interval 95.349 – 152.474 % No difference in exposure observed across studies for different food types: high-fat, high-caloric meal vs. standard or continental breakfast (metaanalysis across studies in healthy volunteers)
Expected High Clinical Exposure Scenario	Simulations based on the PopPK of studies 1199.10/13/14/30 for the hypothetical combination of equally directed covariates increasing exposure: Increase in $AUC_{\tau,ss}$ by 90 % for a patient at the 95th percentile of each covariate value compared to a typical patient defined by the mode/median of the baseline covariate values (covariates included: age, race, smoking habits, body weight) Exposure still within the 90 % prediction interval for an individual typical patient.	
Preclinical Cardiac Safety	**Electrophysiological Assessments *in vitro*** hERG mediated current: BIBF 1120 base had an IC50 value of 4.0 µmol/L on hERG mediated potassium current in HEK293 cells. Action potential configuration: In isolated papillary muscles from guinea pigs, BIBF 1120 base had no effect on APD90 in concentrations up to 10 µmol/L. Based on the results of these two *in vitro* studies, BIBF 1120 base has no demonstrable effect on myocardial repolarization at human therapeutic plasma concentrations [U02-1288]. **Cardiovascular/Respiratory Functions in Rats** Oral doses of 10, 30 and 100 mg/kg BIBF 1120 were given to telemetered rats for measurement of haemodynamics and body temperature. By whole body plethysmographs pulmonary function was measured for seven hours post application. Systemic arterial blood pressure increased dose-dependently. This effect lasted up to the end of the seven hour post-administration observation period. The increase in systolic systemic blood pressure was about 15 mm Hg in the highest dose group. No concomitant change in heart rate was	

observed. Body temperature remained unchanged in all groups. Respiratory rate and tidal volume tended to increase, but only at the highest dose [BIBF 1120 chloride was used in these experiments; U02-1398].

Cardiovascular Function and ECG in Pigs

As cardiovascular function and ECG normally are recorded above the anticipated therapeutic doses (in general a factor of 10), these experiments were regarded as not feasible in dogs, because it was known that rather moderate dose levels of BIBF 1120 may induce severe diarrhea. The pig was therefore chosen as species to investigate cardiovascular function in general pharmacological studies.

Intravenous doses of 3, 10 and 30 mg/kg BIBF 1120 were administered to anaesthetized telemetered pigs for the measurement of haemodynamic parameters. Doses of 3 and 10 mg/kg had little effect on the systolic and diastolic systemic blood pressure. The dose of 30 mg/kg led to a drop in blood pressure (both systolic and diastolic blood pressure fell 15-20 mm Hg) that quickly reversed following termination of the infusion. Heart rate was only increased by about 10 beats/min at 30 mg/kg, which was probably due to the drop in arterial blood pressure. The QT interval duration decreased throughout the protocol and the QRS duration tended to increase with the highest dose, but was quickly reversible upon stopping the infusion [BIBF 1120 chloride was used in these experiments; U02-1674].

NOTE: The heart was not a target organ in any of the repeat-dose toxicology studies performed in mice, rats, rabbits, dogs, Cynomolgus and rhesus monkeys.

Cardiovascular System

Preclinical experiments have focused on cardiotoxicity as a potential effect of inhibition of cabl by imatinib [R07-0018]. BIBF 1120 inhibits the c-abl wild-type kinase with an IC50 of 41 nmol/L. The proposed causal link between occasional cases of heart failure under treatment with imatinib and inhibition of c-abl is difficult to interpret. Imatinib was tested once in a phospholipidosis assay and showed a moderate phospholipidotic potential in the phospholipidosis assay (positive results starting at 6 µM). This may explain the vacuolization of myocardiocytes (light microscopic examination) and occurrence of whorls (electron microscopic examination) [R07-0018]. Vacuolisation of cardiomyocytes was not found in any of the BIBF 1120 toxicity studies in rats (up to 26 weeks), Cynomolgus (up to 13 weeks) and Rhesus monkeys (up to 52 weeks). It is, therefore, not expected that BIBF 1120 has a cardiotoxic potential comparable to imatinib.

Ref: Toxicology Written Summary [n00222772-02].

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/s/

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07/23/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review:	July 16, 2014
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 205832
Product Name and Strength:	Ofev (nintedanib) Capsules, 100 mg, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date:	May 2, 2014 and June 5, 2014
OSE RCM #:	2014-979
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

As part of the evaluation for NDA 205832, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested DMEPA evaluate the proposed container labels, carton labeling, and Prescribing Information for Ofev (Nintedanib) Capsules for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing 100 mg and 150 mg capsules that will be packaged in a 60-count bottle, which is supported by the dosage and administration section for this product. A risk assessment of the proposed Prescribing Information, container labels and carton labeling did not identify any areas of confusion. Thus we find them acceptable from a medication error prospective.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the proposed Prescribing Information, container labels and carton labeling is acceptable from a medication error prospective and we do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ofev (Nintedanib) that Boehringer Ingelheim Pharmaceuticals, Inc. submitted on May 2, 2014.

Table 2. Relevant Product Information for Ofev (Nintedanib)	
Initial Approval Date	N/A
Active Ingredient	Nintedanib
Indication	Maintenance treatment of Idiopathic Pulmonary Fibrosis (IPF)
Route of Administration	Oral
Dosage Form	Capsule
Strength	100 mg, 150 mg
Dose and Frequency	150 mg twice daily; with an option to reduce the dose to 100 mg twice daily due to adverse reactions or liver enzyme elevation **Max dose**: 300 mg/day
How Supplied	HDPE 60 count bottles, brown colored (150 mg) opaque, oblong soft gelatin capsules and peach-colored (100 mg) opaque, oblong soft gelatin capsules-each containing a bright yellow viscous suspension
Storage	25°C (77°F); excursions permitted 15 – 30°C (59°F – 86°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

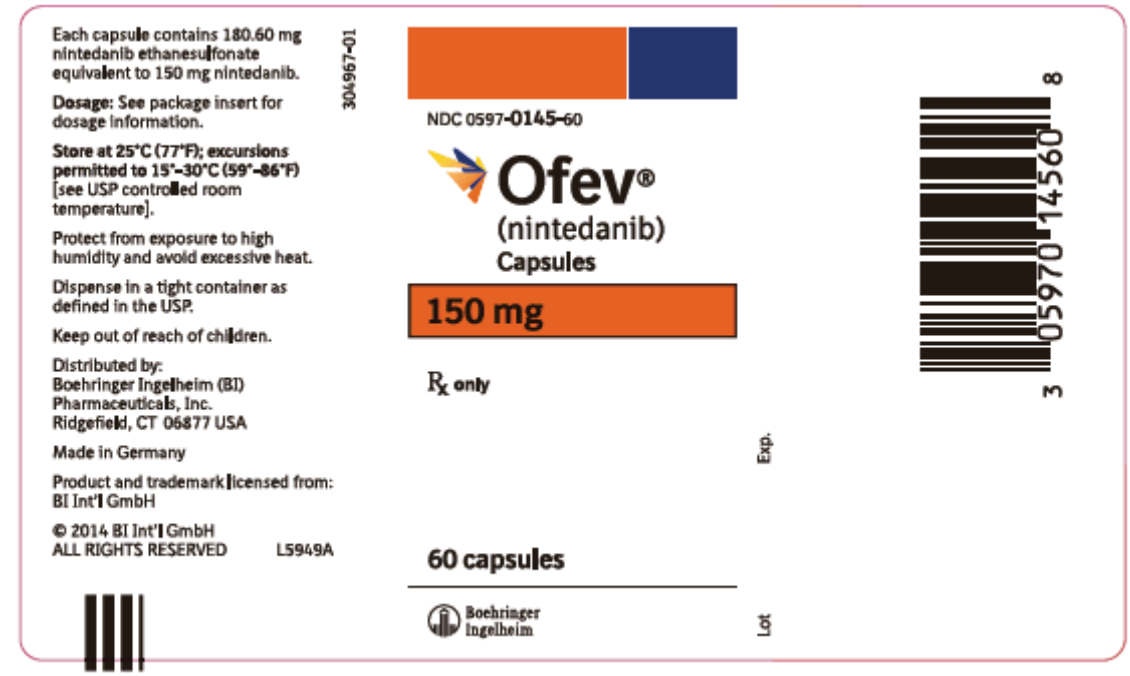
Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Ofev (Nintedanib) labels and labeling submitted by Boehringer Ingelheim on June 5, 2014.

- Container label
- Carton labeling

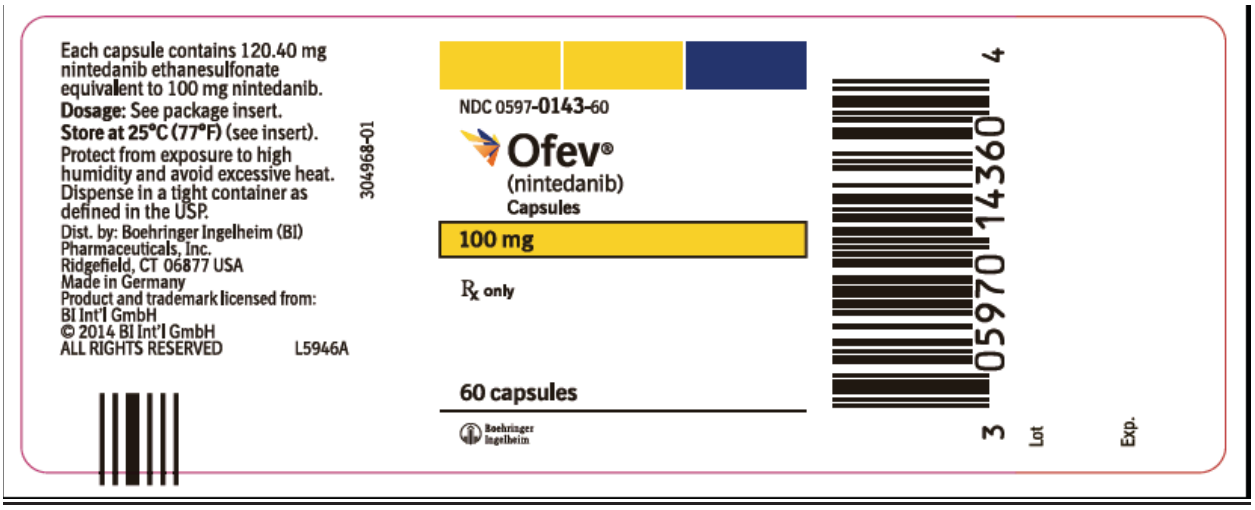
[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 Label and Labeling Images

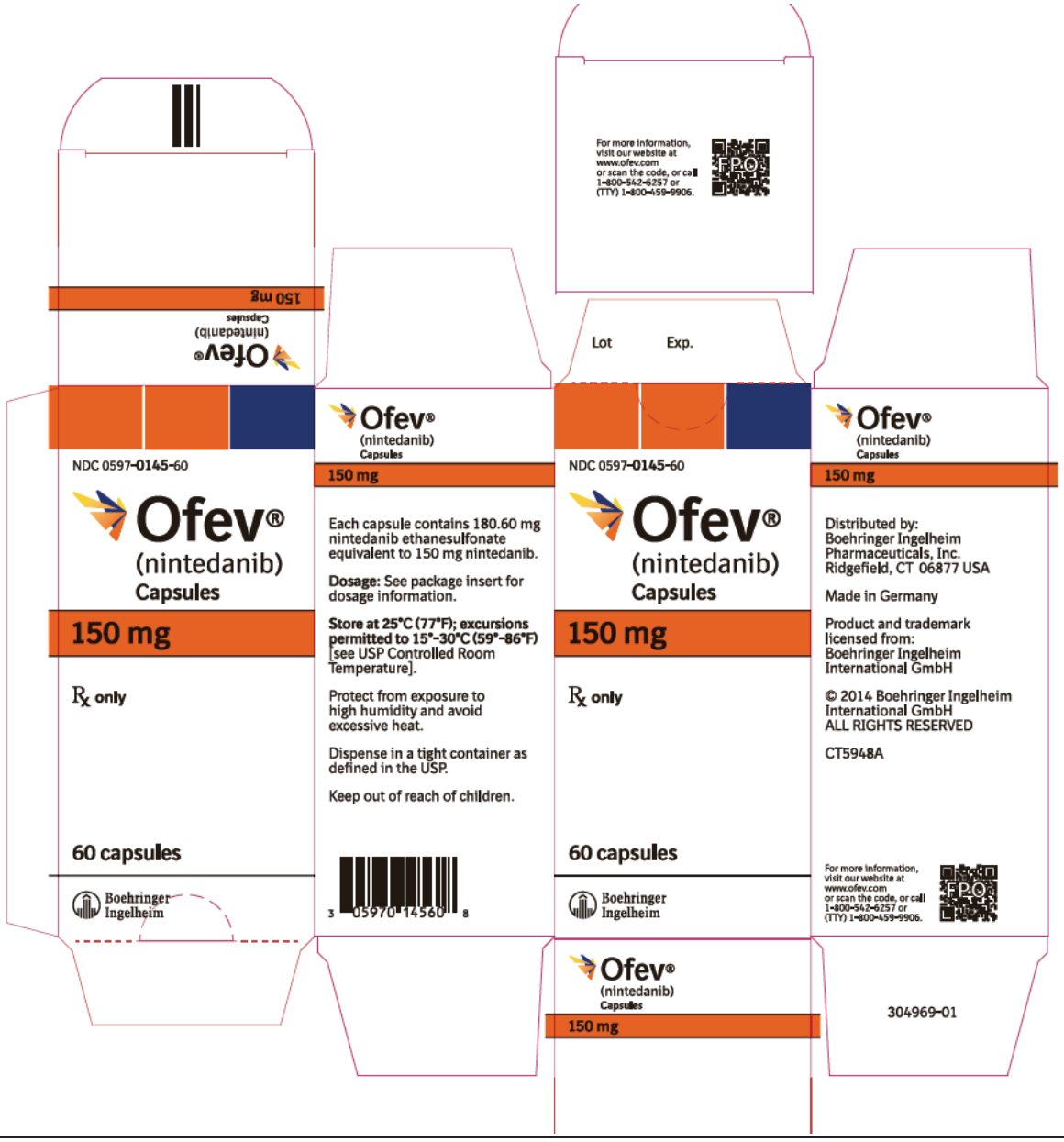
Container Labels 150 mg



Container Labels 100 mg



Carton Labeling 150 mg



Carton Labeling 100 mg

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/s/

TERESA S MCMILLAN
07/16/2014

KENDRA C WORTHY
07/16/2014

LUBNA A MERCHANT
07/16/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: June 27, 2014

To: Ni Khin, M.D. Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D., M.P.H. Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDER OSI PM Track
Anthony Orencia, M.D., Ph.D., Medical Officer, GCPAB, Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Miya Paterniti, M.D. Clinical Reviewer, DPARP/Banu Karimi-Shah, M.D., Clinical Team Leader, DPARP

From: Jessica Lee, Pharm.D./RPM/DPARP

Subject: **Request for Clinical Site Inspections- Sponsor Audit only**

I. General Information

Application#: NDA 205832
IND#: 74,683
Applicant/ Applicant contact information (to include phone/email):
Sponsor:
Boehringer Ingelheim Pharmaceuticals, Inc.

Contact:
Ann Cherian
Senior Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd/ P. O. Box 368
Ridgefield, CT 06877-0368

Phone: 203 798-9988

Drug Proprietary Name: Ofev
Generic Drug Name: nintedanib
NME or Original BLA (Yes/No/Not Applicable*): Yes
Review Priority (Standard or Priority or Not Applicable*): **High Priority Fast Track (Division Goal 9/2/14)**

OSI/DGCPC Consult
version: 09/12/2013

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): Not Applicable

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): Idiopathic Pulmonary Fibrosis (IPF)

PDUFA: 1/2/15
Action Goal Date: 9/2/14
Inspection Summary Goal Date: 8/22/14

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects*	Indication/Primary endpoint and other endpoints for verification
Center for Rare Lung Diseases - University of Modena and Reggio Emilia - Policlinico Hospital - Via del Pozzo 71 - 41100 Modena - ITALIA	1199.30	679	**CONDUCT A HIGH-LEVEL SPONSOR AUDIT AT BOEHRINGER:** **Address sponsor oversight of the Italian, UK or US monitoring sites and the associated study protocol.** Indication: Treatment of idiopathic pulmonary fibrosis (IPF) (b) (4) 1°: Annual rate of FVC decline Key 2°: Time to IPF Exacerbation Key 2°: St. George's Respiratory Questionnaire (SGRQ) score Key 2°: Survival 2°: 5% FVC Responders 2°: 10% FVC Responders
National Institute for Health Research Southampton Respiratory Biomedical Research Unit Southampton Centre for Biomedical Research University Hospital Southampton NHS Foundation Trust Mailpoint 813, Tremona Road, Southampton, UK	1199.32	718	
University of California San Francisco 505 Parnassus Avenue San Francisco, USA	1199.34	794	
*number of patients enrolled			

III. Site Selection/Rationale

Summarize the reason for requesting OSI/DGCPC 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. For example:

Rationale for OSI 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 OSI's thoughts on things to consider in your decision making process*

Given that this is a new molecular entity, for an indication which has no FDA-approved therapies, a DSI consult has been requested for a high level audit of the sponsor site. Note that there are multiple sites (193 sites in 24 countries for Studies 1199.32 and 1199.34; 92 sites in 25 countries (all ex-US) for Study 1199.30) and the data is largely foreign (~85%). Studies 1199.32 and 1199.34 were conducted under IND 74683. For Study 1199.32, site 10001 was closed due to serious non-compliance. The sponsor does not provide further details.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__x__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
__x__ 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):

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).

IV. 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 applicable.

Should you require any additional information, please contact *Jessica Lee* at *301-796-3769 or Miya Paterniti* at 301-796-3337.

******Things to consider in decision to submit request for OSI/DGCPC Audit******

- *Notification by sponsor or applicant that they have identified GCP related concerns at site (such notifications may be submitted to IND or NDA/BLA).*
- *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?*
- *Is the concern related to a study conducted under IND?*
- *Were the NDA studies conducted under an IND?*

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

/s/

JESSICA K LEE
06/27/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

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

Application: NDA 205832

Application Type: New NDA under "The Program"

Name of Drug/Dosage Form: nintedanib/soft gelatin capsules

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Date: 5/2/14

Goal Date: 1/2/15

1. Regulatory History and Applicant's Main Proposals

NDA 205832 was received on May 2, 2014. The applicant is seeking approval for a NME, nintedanib, a tyrosine kinase inhibitor for the proposed indication of Idiopathic Pulmonary Fibrosis. The NDA is under the 6-month "The Program" review.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

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

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

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

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

/s/

JESSICA K LEE
06/24/2014

LADAN JAFARI
06/24/2014

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 # 205832 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: nintedanib Dosage Form: soft gelatin capsules Strengths: 100 mg and 150 mg		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):		
Date of Application: May 2, 2014 Date of Receipt: May 2, 2014 Date clock started after UN:		
PDUFA Goal Date: January 2, 2015	Action Goal Date (if different): 9/2/14	
Filing Date: July 1, 2014	Date of Filing Meeting: June 3, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): Idiopathic Pulmonary Fibrosis		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 74683	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	☒	☐		
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)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
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)].**	☐	☐	☒	
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)]?** ***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 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
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.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*	☐	☒		PREA exempt because of Orphan Designation
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
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? ***If no, request in 74-day letter***	☐	☐	☒	
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)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Received 6/6/14
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	BI provided rationale for no REMS
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
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) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	IRT-QT Consult sent 6/2/14
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 12/1/10 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10/31/13 ***If yes, distribute minutes before filing meeting***	☒	☐		After receipt of preliminary comments dated 10/29/13, BI requested via email to cancel the 10/31/13 Pre-NDA teleconference meeting.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 6/3/14

BLA/NDA/Supp #: NDA 205832

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: nintedanib

DOSAGE FORM/STRENGTH: soft gelatin capsules/ 100 mg and 150 mg

APPLICANT: Boehringer Ingelheim

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Idiopathic Pulmonary Fibrosis (IPF)

BACKGROUND: Boehringer Ingelheim submitted an Original NDA for a NME product, nintedanib, on May 2, 2014. The FDA received the NDA 205832 on May 2, 2014. The applicant is seeking a proposed indication of Idiopathic Pulmonary Fibrosis (IPF). The application is under "The Program" priority review and the PDUFA Goal Date is 1/2/15. The review team decided on an early action for September 2, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Lee	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Banu Karimi-Shah		Y
Clinical	Reviewer:	Miya Paterniti	Y
	TL:	Banu Karimi-Shah	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jianmeng Chen Anshu Marathe	Y Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Yongman Kim	Y
	TL:	David Petullo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Marcie Wood	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Craig Bertha Ying Wang Kareen Riviere (Biopharm)	Y Y Y
	TL:	Eric Duffy Craig Bertha Tapash Ghosh (Biopharm TL)	Y Y N
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Curt Rosebraugh (ODE II Director) Badrul A. Chowdhury (Div Director) Lydia Gilbert McClain (Deputy Div Director) Sally Seymour (Deputy Director for Safety) Peter Starke (Assoc. Director Labeling) Nichelle Rashid (OSE)		Y Y Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☒ YES *High level audit of sponsor site only given international scope of*

If no, explain:	*program* ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined o Reason: ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO

BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Refer to CMC Filing Review 6/5/14	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Mary Parks, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 8/4/14

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

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☐	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • 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 OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	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 in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

JESSICA K LEE
06/24/2014

LADAN JAFARI
06/24/2014