

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205832Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205832 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ofev Established/Proper Name: nintedanib Dosage Form: Capsules, 100 mg and 150 mg		Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):
RPM: Jessica Lee		Division: DPARP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		For ALL 505(b)(2) applications, two months prior to EVERY action: <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>1/2/2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 1
 (*confirm chemical classification at time of approval*)

- | | |
|--|---|
| <input checked="" type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) AP and date(s) AP Oct 15, 2014
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 6/5/14
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	7/7/14 7/3/14
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 6/24/14 DMEPA: <input type="checkbox"/> None 7/16/14; 9/12/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 8/15/14 OPDP: <input type="checkbox"/> None 8/18/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None

Administrative / Regulatory Documents

❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	6/24/14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A due Orphan Exemption</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	5/15/14; 6/2/14; 6/4/14; 6/5/14; 6/9/14; 6/13/14; 6/18/14; 6/23/14; 6/25/14; 6/27/14; 6/30/14; 7/2/14; 7/3/14; 7/11/14; 7/15/14; 7/23/14; 7/29/14; 8/11/14; 8/21/14; 8/25/14; 9/9/14; 9/15/14; 9/30/14; 10/1/14; 10/2/14; 10/7/14; 10/10/14; 10/14/14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg Cancelled by BI
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 12/1/10
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 8/11/14
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 9/11/14
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/15/14
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/10/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/9/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 9/25/14 (1)
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review CDTL Memo 10/9/14
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	6/16/14; 9/3/14
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 16 of the Clinical Review dated 9/3/2014

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None QT-IRT 7/23/14 Hepatology 9/23/14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	9/11/14 <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 8/29/14
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/7/14; 9/3/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/12/14; 9/3/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 9/22/14
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 9/5/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/11/14; 8/22/14; 8/22/14; 8/28/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 7/17/14
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 7/16/14 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review	10/9/14
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review	
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	6/5/14; 6/13/14; 8/14/14; 9/3/14; 9/4/14; 9/16/14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed	
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	5/30/148/22/14	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None	6/3/14
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		6/5/14
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: <input checked="" type="checkbox"/> Acceptable 8/22/14 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable	
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation	
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)	

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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
10/15/2014

EXCLUSIVITY SUMMARY

NDA # 205832

SUPPL #

HFD #

Trade Name Ofev Capsules 100, and 150 mg

Generic Name nintedanib

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known October 15, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

5-years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Jessica Lee, PharmD
Title: Regulatory Health Project Manager
Date: 9/15/2014

Name of Office/Division Director signing form: Badrul A. Chowdhury, MD, PhD
Title: Director, DPARP

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

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

/s/

JESSICA K LEE
10/15/2014

BADRUL A CHOWDHURY
10/15/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014 to NDA 205832, is currently under review. Attached are our revisions to your proposed package insert (PI) received on October 10, 2014.

Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit your concurrence to the attached label as soon as possible, but no later than close of business today, October 14, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

18 Pages Draft Labeling have been Withheld in Full as B4(CCI/
TS) Immediately Following this Page

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

/s/

JESSICA K LEE
10/14/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014 to NDA 205832, is currently under review. Attached are our revisions to your proposed package insert (PI) received on October 9, 2014.

Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit your response by 1:00 PM, Friday, October 10, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
10/10/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014 to NDA 205832, is currently under review. Attached are our revisions to your proposed package insert (PI) received on October 6, 2014.

The following new revisions were made:

1. Section 6: Adverse Reactions

- A small imbalance in hypothyroidism events was noted in your clinical development program. This adverse reaction has also been noted with other drugs in the same class. As a result, language was added after the common adverse reactions table in this section to reflect this adverse reaction.

2. Section 14: Clinical studies

-  (b) (4)
- We note your proposed revisions to the title of the Kaplan-Meier curve. The timing of follow-up is already included on the x-axis, we maintain our previous position regarding the title.
- We also maintain our position  (b) (4) for Study 1, as the phase 2 study was not part of the pre-specified mortality analysis.
- We do not agree with your proposed changes to the y-axis of the Kaplan-Meier figure. Refer to our previous comment to “break’ the y-axis at 50%. To further clarify, the scale should then proceed to count by 10’s.

Be advised that these labeling changes are not necessarily the Agency’s final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed. We wanted to provide you with our revisions ahead of our scheduled teleconference tomorrow, Wednesday, October 8, 2014, to better inform our discussion. You do not need to respond prior to the teleconference. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
10/07/2014

NDA 205832

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. Attached are our revisions to your proposed Patient Information submitted October 1, 2014.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA by noon, Monday, October 6, 2014. The information can be submitted by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
10/02/2014

Dear Ms. Cherian:

Your submission, dated May 2, 2014 to NDA 205832, is currently under review. We note the submission contains a small imbalance in adverse events of hypothyroidism (Nintedanib 1.1% (n=8), Placebo 0.6% (n=3)). Provide available information for these adverse events, which may include CRFs and/or narratives.

Submit your response by Friday, October 3, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any additional questions please call Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
10/01/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014 is currently under review. Attached are our revisions to your proposed package insert (PI), and patient information submitted September 12, 2014. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA as soon as possible, but no later than noon, Monday, October 6, 2014. The information can be submitted by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
09/30/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014, to NDA 205832 is currently under review. Provide hazard ratios, 95% confidence intervals, and p-value results for the on-treatment time to death for Study 30 and for the pooled on-treatment time to death for all 3 studies to complete the highlighted sections of the table below.

Table 1. Survival Analysis (Studies 30, 32, and 34)			
Death	Number of Events (%)		Hazard Ratio[†] (95% CI), p value[‡]
	Nintedanib 150 mg BID	Placebo	
Study 30	N=86	N=87	
Vital Status	7 (8.1)	9 (10.3)	0.73 [0.27, 1.98], p=0.538
On-treatment[*]	1 (1.2)	12 (14.1)	
Respiratory-related	2 (2.3)	8 (9.2)	0.23 [0.05, 1.07], p=0.06
Study 32	N=309	N=204	
Vital Status	13 (4.2)	13 (6.4)	0.63 [0.29, 1.36], p=0.288
On-treatment	8 (2.6)	9 (4.4)	0.68 [0.26, 1.82], p=0.487
Respiratory-related	10 (3.2)	10 (4.9)	0.61 [0.25, 1.47], p=0.352
Study 34	N=329	N=219	
Vital Status	22 (6.7)	20 (9.1)	0.74 [0.40, 1.35], p=0.300
On-treatment	16 (4.9)	17 (7.8)	0.68 [0.34, 1.35], p=0.221
Respiratory-related	14 (4.3)	11 (5.0)	0.86 [0.39, 1.90], p=0.665
Pooled Studies 32, 34	N=638	N=423	
Vital Status	35 (5.5)	33 (7.8)	0.70 [0.43, 1.12], p=0.140
On-treatment	24 (3.8)	26 (6.1)	0.68 [0.39, 1.19], p=0.160
Respiratory-related	24 (3.8)	21 (5.0)	0.74 [0.41, 1.34], p=0.344
Pooled Studies 30, 32, 34	N=723	N=508	
Vital Status	42 (5.8)	42 (8.3)	0.70 [0.46, 1.08], p=0.096
On-treatment	25 (3.5)	38 (7.5)	
Respiratory-related	26 (3.6)	29 (5.7)	0.62 [0.37, 1.06], p=0.078

[†] Hazard ratio was based on the Cox proportional hazard model with terms for treatment, sex, age, and height.
[‡] p-value based on log-rank test, comparing nintedanib 150 mg BID to placebo
^{*} On treatment for study 30 was defined differently: including on AEs that leading to death with an onset date of the event reported during the treatment period plus 14 days, but which the death may have occurred after the 52 weeks period.

Submit your response by Thursday, September 18, 2014. The information can be submitted to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any additional questions please call Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: MPaterniti/9.15.14

Initialed by: BKarimiShah/9.15.14
LJafari/9.15.14

Finalized by: JLee/ 9.15.14

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/s/

JESSICA K LEE
09/15/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014 is currently under review. Attached are our revisions to your proposed package insert (PI), and patient information following the September 2, 2014 teleconference. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA by September 11, 2014. The information can be submitted by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
09/09/2014



NDA 205832

MID-CYCLE COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director
Regulatory Affairs

Dear Ms. Cherian:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 11, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 11, 2014 at 11:00 am – 12:00 pm

Application Number: NDA 205832
Product Name: nintedanib (Ofev)
Indication: Idiopathic Pulmonary Fibrosis (IPF)
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Banu Karimi-Shah, MD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Banu Karimi-Shah, MD, Clinical Team Leader, DPARP
Miya Paterniti, MD, Clinical Reviewer, DPARP
Marcie Wood, PhD, Supervisory Pharmacology/Toxicology, DPARP
Luqi Pei, PhD, Pharmacology/Toxicology Reviewer, DPARP
Satjit Brar, PhD, Lead Clinical Pharmacologist, Division of Clinical Pharmacology II
Jianmeng Chen, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology II
Anshu Marathe, PhD, Pharmacometrics, Division of Pharmacometrics
Craig Bertha, PhD, Acting CMC Lead, Division of New Drug Quality Assessment III
Arthur Shaw, PhD, Chemist, Division of New Drug Quality Assessment III
David Petullo, MS, Lead Mathematical Statistician, Division of Biometrics II
Yongman Kim, PhD, Mathematical Statistician, Division of Biometrics II
Peter Starke, MD, Associate Director for Labeling, DPARP
Nichelle Rashid, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Tamra Meyer, PhD, Epidemiologist, Division of Epidemiology I, OSE
Dipti Kalra, Safety Evaluator, Division of Pharmacovigilance I
Jasmine Gatti, MD, Medical Officer, Division of Pharmacovigilance I
Jessica Lee, PharmD, Regulatory Project Manager, DPARP

APPLICANT ATTENDEES

Sabine Luik, MD, Sr. VP, Medicine & Regulatory Affairs, US
Tunde Otulana, MD, Sr. VP, Clinical Development & Medical Affairs, US
Rozsa Schlenker-Herceg, MD, Global Team Member Medicine and Clinical Lead
Carl Coeck, MD, Global co-Team Member Medicine
Thomas Notter, MD, Global Pharmacovigilance

Craig Conoscenti, MD, Clinical Development and Medical Affairs, US
Susanne Stowasser, MD, Global Medical Affairs, Respiratory
Michele Brun, Global Clinical Operations
Bernd Krist, PhD, Team Member Research & Development
Florian Colbatzky, PhD, Toxicologist
Stefan-Lutz Wollin, PhD, Nonclinical Pharmacologist
Matthias Freiwald, PhD, Clinical Pharmacologist
Shoreh Shabrang, CMC Regulatory Affairs, US
Klaus-Helge Ibs, PhD, Global CMC Regulatory Affairs
Torsten Sokoliess, PhD, CMC, Research & Development
Omar Sefiani, Programmer
Florence LeMaulf, Project Statistician
Inga Tschoepe, co-Project Statistician
Katy Pelling, co-Project Statistician
Kamila Sroka-Saidi, PhD, Project Medical Writer
Friedrich Schmidt, Team Member Operations
Fee Alexandra Ruehmkorf, International Project Leader
Claude Petit, PhD, Executive Director, Biostatistics, US
Ursula Hueppe, PhD, Regulatory Area Lead, Global Respiratory
Jeff Snyder, Executive Director, Drug Regulatory Affairs, Respiratory, US
James Segretario, PhD, Director, CMC Regulatory Affairs
Gertrud Herzog, Global Regulatory Affairs
Terry Keyser, Drug Regulatory Affairs, US Labeling
Donato Forlenza, Drug Regulatory Affairs, US
Ann Cherian, Drug Regulatory Affairs, US

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

2.0 INFORMATION REQUESTS

A Chemistry, Manufacturing, and Controls (CMC) Information Request will be sent out to Boehringer Ingelheim (BI) by Close of Business today, August 11, 2014 or early tomorrow, August 12, 2014.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Non-Clinical:

The Division recommended the following two (2) changes to the proposed labeling: 1) changing the pregnancy category for nintedanib to D (b) (4) and 2) (b) (4) Pregnancy category "D" is in line with the Agency's experience with kinase inhibitors.

Clinical Pharmacology:

Based on previous interactions with BI (i.e., End-of-Phase 2 and pre-NDA meetings), the Division indicated that BI will need to conduct a hepatic impairment study. The Division informed the Applicant that the ongoing hepatic impairment study will be listed as a Post Marketing Requirement (PMR).

5.0 ADVISORY COMMITTEE MEETING

The Division confirmed that an Advisory Committee will be not be held for this application.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The Division informed the Applicant that tentative dates for the labeling teleconference and the Late-Cycle Meeting are September 2, 2014 and September 11, 2014, respectively. The Applicant asked and the Division confirmed that the Late-Cycle Meeting could be held as a teleconference.

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/s/

JESSICA K LEE
08/26/2014

Dear Ms. Cherian:

Your submission dated May 2, 2014 is currently under review. Attached are our revisions to your proposed package insert (PI), and patient information leaflet. Comments regarding some changes are embedded within the product label. The following comments provide additional clarification as to some of the changes made in the attached label. The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

General Comments

1. You should replace "TRADENAME" with OFEV, throughout the package insert and patient package insert.
2. Update the table of contents and reference numbers throughout package insert to reflect the current order of the sections.
3. Ensure that you are using the correct terminology throughout the labeling. 'Dose' is a term used to denote a single dose of a drug, whereas 'dosage' is the term used to denote the dosing regimen, e.g., 150 mg twice daily.
4. For ease of communication, study identification numbers were changed to Studies 1, 2 and 3 (for 1199.30, 1199.32, and 1199.34, respectively).
5. Given the recommended change in Pregnancy Category (b) (4) to D, we removed statements throughout the package insert and patient information leaflet (b) (4). Ensure that no other edits are necessary to PI or PPI to reflect the change in pregnancy category.
6. Sections in the package insert that relate to liver safety and monitoring are under active review and a topic of internal discussion at the current time. Further revisions to these sections will be forthcoming as the label continues to be reviewed.

Comments Pertaining to Specific Sections of the Package Insert

1. Section 1: Indication
 - a. The indication was broadened to be "treatment of IPF" based on the efficacy information provided in Section 14.
2. Section 5: Warnings and precautions
 - a. Warnings/precautions regarding (b) (4) were removed as these were based on mechanism of action rather than a safety signal observed in the clinical development program.

- b. [REDACTED] (b) (4) were removed as these are not considered to be clinically relevant.
 - c. The order of the warnings/precautions was changed to list the events in decreasing order of importance/relevance. For example, given the recommended change in pregnancy category [REDACTED] (b) (4) to D, embryofetal toxicity was moved from 5.1 to 5.3.
2. Section 6: Adverse Reactions
 - a. The section has been updated to include Study 1199.30 in the pooled safety data.
 - b. [REDACTED] (b) (4) has been removed from this section to avoid redundancy with [REDACTED] (b) (4).
3. Section 12: Clinical Pharmacology/Pharmacokinetics
 - a. Update your clinical pharmacology section based on the draft guidance “Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format.” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf>)
 - b. You stated that [REDACTED] (b) (4). Update the numbers, preferably with oral doses in IPF patients or healthy subjects. If different accumulations were observed in different studies, use the higher number in the label (e.g. accumulation is up to xx fold). Under the annotated label, provide the source study/data to support the claim in the label (not just general “see summary of clinical pharmacology”).
 - c. Under elimination/excretion, you stated that [REDACTED] (b) (4). The half-life value reported should usually be the half-life based on the time to reach steady state (i.e., the effective half-life). Replace this statement with effective half-life in IPF or healthy subjects.
 - d. For renal impairment, update the information with results of your popPK report in IPF patients (pop PK 1199-0030-0032-0034).
4. Section 13 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - a. Effects of nintedanib on female fertility in rats were added to this section.
5. Section 14: Clinical Studies
 - a. This section was substantially reorganized to be presented by efficacy variable. Study 1199.30 was included among the pivotal studies, rather than being regarded as supportive, as it was similar in design/duration to the phase 3 studies.
 - b. The figure from Study 1199.32 was chosen to be representative of the primary efficacy analysis for each study.
 - c. A cumulative responder analysis has been conducted and included in this section. Figure 2 has been added to show a cumulative responder distribution

of change from baseline in percent predicted forced vital capacity, rather than to focus on a specific cut-point. Descriptions of the results at a cut-off of (b) (4) FVC decline are included in the text.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the NDA ASAP, or latest by September 2, 2014 at 10 am EST. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
08/25/2014

NDA 205832

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following request for information:

As discussed in the Mid-Cycle teleconference on August 11, 2014, we are considering issuing a Post Marketing Requirement (PMR) for a hepatic impairment study for NDA 205832. Clarify if the dedicated hepatic study is currently ongoing. Provide the protocol of the dedicated hepatic impairment study, along with the timeline of the study, which includes Protocol Submission date (if not ongoing), Study Completion date, and Final Report Submission date.

Submit your response by Monday, August 25, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: JChen/Aug 11, 2014
JLee/Aug 20, 2014

Initialed by: LJafari/Aug 20, 2014
BKarimi-Shah/Aug 20, 2014
SSeymour/Aug 21, 2014

Finalized by: JLee/Aug 21, 2014

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/s/

JESSICA K LEE
08/21/2014



NDA 205832

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Cherian
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Ms. Cherian:

Please refer to your New Drug Application (NDA) submitted May 2, 2014 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nintedanib Capsules.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by August 20, 2014 in order to continue our evaluation of your NDA.

1. Explain why the amount of lecithin in the formulation was chosen to be (b) (4)/capsule when the experiments in Section P.5.6.4.4.3 show that (b) (4) dissolution at (b) (4) minutes was achieved when the amount of lecithin was (b) (4) mg/capsule.
2. Provide a description of the difference between the bottles used for stability testing and the proposed bottles for commercial packaging, as well as the results of USP testing for both bottles (3.2.P.2.4.1.1).
3. Provide the locations of the directions for the (b) (4)
(b) (4)
4. Provide an evaluation of the possible failure modes during the (b) (4)
(b) (4)
5. Provide the test procedure used to (b) (4)
(b) (4)

6. Explain why the

(b) (4)

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Craig Bertha, Ph.D.
Acting CMC Lead
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

CRAIG M BERTHA
08/11/2014

Liu, Youbang

From: Liu, Youbang
Sent: Tuesday, July 29, 2014 5:05 PM
To: 'ann.cherian@boehringer-ingelheim.com'
Cc: 'shohreh.shabrang@boehringer-ingelheim.com'; Lee, Jessica K (ODEII/DPARP)
Subject: Information Request for NDA 205832, Nintedanib Capsules

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Cherian
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Ms. Cherian:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205832, Nintedanib Capsules. We have the following comments and information requests:

- The following dissolution acceptance criterion is recommended: Q = (b) (4) minutes. This recommendation is based on mean in vitro dissolution profile data from the clinical and primary stability batches. Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.

Please acknowledge the receipt of this email and provide the amendment submission by August 4, 2014.

Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

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/s/

YOUBANG LIU
07/29/2014



NDA 205832

**METHODS VALIDATION
MATERIALS RECEIVED**

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

Dear Ann Cherian:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ofev (nintenanib) and to our June 30, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 18, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/23/2014



NDA 205832

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director, Regulatory Affairs

Dear Ms. Cherian:

Please refer to your New Drug Application (NDA), submitted and received May 2, 2014, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nintedanib.

We also refer to your May 28, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that nintedanib for Idiopathic Pulmonary Fibrosis (IPF) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

If the breakthrough therapy designation for nintedanib for IPF is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
07/15/2014

Executive CAC

Date of Meeting: July 15, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Alternate Member
Marcie Wood, Ph.D., DPARP, Pharm Tox Supervisor
Carol M. Galvis, Ph.D., DPARP, Presenting Reviewer

Author of Minutes: Carol M. Galvis, Ph.D.

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

NDA # 205-832

Drug Name: Nintedanib Oral Capsules

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Boehringer Ingelheim conducted two carcinogenicity bioassays (2-year oral studies in CD-1 mice and Han Wistar rats) to assess the carcinogenic potential of nintedanib. Both study protocols were discussed with the Executive CAC in a meeting held on September 14, 2010. The doses used in the studies were recommended by the Committee (see meeting minutes dated September 16, 2010 under IND (b) (4)).

Nintedanib was negative in a full battery of genetic toxicology assays (*in vitro* Ames and mouse lymphoma assays and *in vivo* micronucleus assay in rats).

Rat Carcinogenicity Study

In a 2-year bioassay (study number DDB0007), HsdHanTM; WIST rats (60/sex/group) received 0 (vehicle control; 0.5% hydroxyethyl cellulose in demineralized water), 2.5, 5, or 10 mg/kg/day nintedanib orally once daily for 104 weeks. No statistically significant neoplastic findings were observed in male or female rats. In addition, nintedanib did not affect mortality or body weights. AUC and C_{max} increased in a greater than dose-proportional manner across doses and there was evidence of drug accumulation over time. There was not a clear gender difference in AUC or C_{max}.

Mouse Carcinogenicity Study

In a 2-year bioassay (study number DDB0006), CD-1 mice (66/sex/group) received 0 (vehicle control; 0.5% hydroxyethyl cellulose in demineralized water), 5, 15, or 30 mg/kg/day nintedanib orally once daily for 102 weeks (males) or 104 weeks (females). No statistically significant neoplastic findings were observed in male or female mice. Increased mortality was observed in 30 mg/kg males starting approximately on study week 76 and led to termination of this group on study week 102 when the number of animals reached 15 (based on recommendations provided by the Division). The other male groups were terminated on study week 103.

In females, mortality was higher at all nintedanib doses compared to controls but did not follow a dose-response and was not statistically significant. All the female groups were maintained until scheduled necropsy. AUC and C_{max} increased in a greater than dose-proportional manner across doses. There was not a clear evidence of gender difference in AUC or C_{max} or evidence of drug accumulation over time.

Executive CAC Recommendations and Conclusions

Rat

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that there were no drug-related neoplasms in the study.

Mouse

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

/NDA 205-832 Division File, DPARP
/MWood, DPARP
/CGalvis, DPARP
/JLee, DPARP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
07/16/2014

ABIGAIL C JACOBS
07/16/2014

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following request for information:

Statistics:

We found the location for the raw efficacy datasets for study 1199.30 as you described. However, we also need your derived efficacy datasets for an expedited review. Provide the derived efficacy datasets with definitions for study 1199.30 similar to the derived efficacy datasets in the folder of 'analysis' for studies 1199.32 and 1199.34.

Provide your responses as soon as possible, but no later than July 18, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: JLee/July 11, 2014

Initialed by: LJafari/July 11, 2014
DPetullo/July 11, 2014

Finalized by: JLee/July 11, 2014

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/s/

JESSICA K LEE
07/11/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205832

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877-0368

ATTENTION: Ann Cherian
Senior Associate Director, Regulatory Affairs

Dear Ms. Cherian:

Please refer to your New Drug Application (NDA) dated May 2, 2014, received May 2, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nintedanib Capsules, 100 mg and 150 mg.

We also refer to your June 6, 2014, correspondence, received June 6, 2014, requesting review of your proposed proprietary name, Ofev.

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

If any of the proposed product characteristics as stated in your June 6, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
07/07/2014

From: Nabavian, Sadaf
To: ann.cherian@boehringer-ingelheim.com
Cc: [Lee, Jessica K \(ODEII/DPARP\)](#); [Jafari, Ladan](#)
Subject: NDA 205832-FDA Information Request
Date: Thursday, July 03, 2014 2:52:00 PM
Importance: High

Dear Ann:

Please note that we have an additional information request regarding NDA 205832 (Nintedanib). Please note that the request is time sensitive as we are requesting for the responses to the IR by NLT Tuesday, July 8, 2014 . Please let me know if you have any question and/or if I can be of further assistance.

In reviewing your submission dated July 2, 2014, please add the following columns to each of the two dataset, pkeff.xpt and pksaf.xpt. and submit as an amendment to the NDA.

1. predicted AUC
2. Observed steady state Ctrough
3. Predicted steady state Ctrough
4. Predicted Cmax

Please acknowledge the receipt of this email.

With Kind Regards,

Sadaf

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/s/

SADAF NABAVIAN
07/03/2014



NDA 205832

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Cherian
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Ms. Cherian:

Please refer to your New Drug Application (NDA) submitted May 2, 2014 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nintedanib Capsules.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by July 22, 2014 in order to continue our evaluation of your NDA.

A. Regarding the Pharmaceutical Development:

1. Provide data [REDACTED] (b) (4)
2. Provide the differences in formulation or processing that led to two batches 1294830001 and 1251910001 with differing dissolution profiles in Section 3.2.P.2.2.1.6.2
3. Explain why certain operating parameters [REDACTED] (b) (4) are not considered to be potential Critical Process Parameters [REDACTED] (b) (4).
4. Explain [REDACTED] (b) (4) (Batch 1340400001).
5. Provide data to justify the statement in 3.2.P.2.3.3.1.1.4 [REDACTED] (b) (4) [REDACTED] (b) (4)
6. Provide the components and composition of the placebo [REDACTED] (b) (4) used for the experiments in 3.2.P.2.3.3.1.1.4.

B. Regarding the manufacturing procedure

1. Explain (b) (4) (Section 3.2.P.3.3.3.3.1) (b) (4) in P.1.
 2. Provide a detailed narrative description of the manufacturing procedure (b) (4). Revise the master batch record to include these details.
 3. You are advised that the proposed change in the (b) (4) holding times (3.2.P.2.3.1.5.1) must be submitted as a post-approval change.
 4. Explain why the Narrative Description (b) (4) .”
 5. Provide the location in the Executed Batch Record (EBR) of the following steps which are discussed in the Pharmaceutical Development Report but are not in the EBR:
(b) (4)
- C. Regarding the excipients:
1. Provide the incoming specifications (b) (4)
 2. Provide information to show that the USP and Ph. Eur. methods (b) (4) yield comparable results (b) (4).
 3. Provide the specifications for receipt of the Red and Yellow Iron Oxide powders.
- D. Regarding the stability: Provide data to show that there is no leakage of the drug substance from the capsules during storage.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Craig Bertha, Ph.D.
CMC Lead
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

YOUBANG LIU
07/01/2014

CRAIG M BERTHA
07/02/2014



NDA 205832

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Cherian
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
FAX: (203) 791-6262

Dear Ann Cherian:

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

We will be performing methods validation studies on Ofev(nintenanib) 100 mg and 150 mg capsules, as described in NDA 205832.

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

Method, current version

A143073 Assay of BIBF 1120 ES
A143067 Impurities in BIBF 1120 ES
q00215543-01 Assay, Degradation Products, Uniformity of Content and Identification of BIBF 1120 capsules, 100 mg and 150 mg/capsule

Samples and Reference Standards

2 x 200 mg nintenanib (BIBF 1120 ES) reference standard
2 x 200 mg nintenanib (BIBF 1120 ES) drug substance
60 capsules Ofev(nintenanib) 100 mg/capsule
60 capsules Ofev(nintenanib) 150 mg/capsule
50 mg (b) (4) reference standard
50 mg (b) (4) reference standard
50 mg (b) (4) reference standard
100 mg (b) (4) reference standard
50 mg (b) (4) reference standard
50 mg (b) (4) reference standard
50 mg (b) (4) reference standard

Equipment

- 1 Zorbax RRHT (rapid resolution high throughput) StableBond-C18, (b) (4)
- 1 XBridge C18 (b) (4)
- 20 syringe filters (b) (4)
- 1 C18, (b) (4)
- 1 Precolumn C18, (b) (4) and holder

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

Forward these materials via express or overnight mail to:

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

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

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/30/2014

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following request for information:

Clinical Pharmacology/Pharmacometric:

1. Submit your response to the exposure-response analysis information request dated, June 23, 2014, by July 15, 2014.
2. Provide the pooled dataset from studies 1190.30, 1190.32 and 1190.34 with the following variables for ER analysis for safety. There should be one record for each unique ID.
 1. Unique subject ID
 2. PK metric (predicted AUC, observed steady state Ctrough, observed Ctrough nearest to event , predicted steady state Ctrough [one column for each PK metric])
 3. Discontinuation due to AE (yes/no)
 4. Time to discontinuation due to AEs
 5. Corresponding censoring variable for time-to-event analysis for discontinuation due to AEs
 6. Dose reduction due to AEs (y/n)
 7. Time to first dose reduction due to AEs
 8. Corresponding censoring variable for time-to-event analysis for dose reduction due to AEs
 9. Safety population flag (yes/no)
 10. Planned treatment group
 11. Actual treatment group
 12. Study
 13. All demographics variable [one variable per column] including gender, body weight, race, body weight category (<65 or >=65), renal function status, creatinine clearance, age etc. Include any other stratification factor used in the study design
 14. All grade Diarrhea (yes/no)
 15. All grade Nausea (yes/no)
 16. All grade Vomiting (yes/no)
3. Provide the pooled dataset from studies 1190.30, 1190.32 and 1190.34 with the following variables for ER analysis for efficacy. There should be one record for each unique ID.
 1. Unique subject ID
 2. PK metric (predicted AUC, observed steady state Ctrough, observed Ctrough nearest to event, predicted steady state Ctrough [one column for each PK metric])
 3. Annual rate of FVC decline
 4. Absolute change from baseline in FVC at 52 weeks
 5. Exacerbation (yes/no)
 6. Time to first acute exacerbation (days) over 52 weeks
 7. Corresponding censoring variable for time-to-event analysis for above

8. Change from baseline in SGRQ total score at 52 weeks
9. Mortality (yes/no)
10. Time to all-cause mortality
11. Corresponding censoring variable for time-to-event analysis for above
12. 5% FVC responder (yes/no)
13. 10% FVC responder (yes/no)
14. TS flag (yes/no)
15. Planned treatment group
16. Actual treatment group
17. Study
18. All demographics variable [one variable per column] including gender, body weight, race, body weight category (<65 or >=65), renal function status, creatinine clearance, age etc. Include any other stratification factor used in the study design

Provide your responses to points 2 and 3 by the close of business, July 2, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: JLee/June 27, 2014

Initialed by: LJafari/June 27, 2014

Finalized by: JLee/June 27, 2014

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/s/

JESSICA K LEE
06/27/2014



NDA 205,832

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director
Regulatory Affairs

Dear Ms. Cherian:

Please refer to your New Drug Application (NDA) dated May 2, 2014, received May 2, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Nintedanib Capsules.

We also refer to your amendments dated May 30, June 6, 11, and 17, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is January 2, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 4, 2014. In addition, the planned date for our internal mid-cycle review meeting is August 4, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

We request that you submit the following information:

You propose to perform (b) (4) testing for the Microbial Limits test for drug product release. (b) (4) testing for drug products is not allowed by regulation (21 CFR 211.165 (a) and (b).) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points:

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
 - a. Define the maximum processing time for the (b) (4).
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.
4. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced. If you choose to test every batch, provide data from studies demonstrating suitability of use of the Microbial Limits tests with the drug product. Submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

Please respond only to the above requests for information by July 1, 2014. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
06/25/2014

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following requests for information:

Clinical Pharmacology/Pharmacometric:

In addition to the exposure-response analysis that was specified in the Information Request dated, June 2, 2014, we request the following additional analyses:

1. Conduct exposure-response analyses for efficacy endpoint(s) including annual rate of decline in FVC and safety endpoints including GI and liver toxicities using pooled data from pivotal phase III studies 1199.32 & 1199.34 and **phase II study 1199.30** using both population PK model derived and observed pre-dose plasma concentrations as PK exposures. Conduct both univariate and multivariate analysis. For multivariate analysis, include all possible covariates that are likely to influence response.

Provide data and associated codes that were used for the analysis. Please refer to the following pharmacometric data and models submission guidelines for your submission:

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>).

Statistics:

2. Provide the program codes for the efficacy analyses in the study 1199.30 report.

Provide your responses by June 30, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: JLee/June 23, 2014

Initialed by: LJafari/June 23, 2014

Finalized by: JLee/June 23, 2014

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/s/

JESSICA K LEE
06/23/2014

Liu, Youbang

From: ann.cherian@boehringer-ingenelheim.com
Sent: Wednesday, June 18, 2014 10:22 AM
To: Liu, Youbang
Cc: shohreh.shabrang@boehringer-ingenelheim.com; Lee, Jessica K (ODEII/DPARP)
Subject: RE: Information Request for NDA 205832, Nintedanib Capsules

Dear Dr. Liu,

Confirming receipt of your email below.

I have copied m colleague from CMC Reg Affairs, Shoreh, who will follow-up with you on submission timeline.

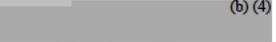
Thank you.
Regards
Ann

From: Liu, Youbang [<mailto:Youbang.Liu@fda.hhs.gov>]
Sent: Wednesday, June 18, 2014 9:25 AM
To: Cherian,Ann (DRA) BIP-US-R
Subject: Information Request for NDA 205832, Nintedanib Capsules

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Cherian
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Ms. Cherian:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205832, Nintedanib Capsules, received May 2, 2014. We have the following comments and information requests:

1.  (b) (4)
2. The stability data provided from three registration batches are not adequate to demonstrate that their levels have always been well below , which is the safety threshold, and therefore justify not controlling them in the drug substance. Control  in the drug substance unless additional data are provided to justify not doing so. Additionally, provide level of  (b) (4)
3. Since the highest observed concentration of  in BIBF 1120  is  and there is no data to support that any higher concentration of this impurity can be effectively purged in the drug substance to

less than (b) (4) it is recommended to tighten the acceptance criterion for (b) (4) in BIBF 1120 (b) (4) from NMT (b) (4) to NMT (b) (4)

4. Provide batch data to demonstrate that the proposed individual acceptance criterion of NMT (b) (4) of (b) (4) (b) (4) in BIBF 1120 (b) (4) will ensure its final level in the API is less than (b) (4)

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

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/s/

YOUBANG LIU
06/18/2014

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following requests for information:

Chemistry, Manufacturing, and Controls (CMC):

1. Provide information regarding a possible reaction [REDACTED] (b) (4) in the drug product [REDACTED] (b) (4) which may be mutagenic.
2. If this [REDACTED] (b) (4) can be detected upon storage of the drug product, provide information regarding its control strategy.
3. Provide the acceptance testing for receipt of the compendial excipients e.g., identity testing plus a supplier CoA or complete compendial testing.
4. Explain the difference between “monitoring” and “controlling” in Table 2 in 3.2.P.2. (Document ID q00204489-02).
5. Specify the heating parameters [REDACTED] (b) (4)

Submit CMC responses to the NDA by Thursday, June 26, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA.

Clinical and Statistics:

6. We note an increase in the number of malignancy adverse events in the nintedanib treatment group compared to placebo. Provide a descriptive analysis of all malignancy adverse events in your clinical development program, including ongoing, open-label, long-term extension studies. For each identified malignancy, include a narrative which includes the following information:
 - Trial
 - Patient number
 - Age/Gender
 - Treatment groups (all)(all treatment doses)
 - Treatment start (for each treatment group) (for each treatment dose)
 - Treatment end (for each treatment group) (for each treatment dose)
 - Total treatment duration (for each treatment group) (for each treatment dose)
 - First sign/symptoms date
 - Event onset date
 - Number of days from treatment start to first sign/symptom
 - Number of days from treatment start to event onset date
 - Outcome (e.g., fatal, early d/c)
 - Smoking status

- Personal malignancy history
 - Weight decrease prior to event onset date (yes/no and quantitative data)
7. In addition to the requested narratives for malignancy adverse events, provide a brief summary of any additional information relevant to the malignancy imbalance, e.g., non-clinical information, biologic plausibility, interpretation of malignancy data from the clinical program, etc.
 8. Provide safety analyses as included in the Summary of Clinical Safety for an additional safety grouping, which pools Studies 1199.32, 1199.34, and 1199.30 (treatment arms of nintedanib 150mg BID and Placebo).
 9. Provide a pooled analysis on mortality from studies 1199.30, 1199.32, and 1199.34 with stratification for the studies, as previously provided for studies 1199.32 and 1199.34 (Table 3.2.1.5:1 in Summary of Clinical Efficacy). Provide a description of statistical models for the analyses requested and program codes used with appropriate documentation.
 10. Clarify the location of the efficacy datasets in SAS transport format for study 1199.30. Provide the data if not already included in the submission.
 11. Clarify the location of the list of investigators who are sponsor employees (including both full-time and part-time). Provide the list if not already included in the submission.

Nonclinical:

12. Provide assessments of exposures of patients to nintedanib impurities and degradants using the recommended human daily dose of 300-mg nintedanib. Conduct safety evaluations of these compounds in nintedanib capsules using the revised numbers. Your current estimates of exposures of patients to the impurities were based on a 250-mg nintedanib dose. Assessments made using this dose underestimate the exposure of patients to the impurities.

Submit Clinical and Statistics, and Non-clinical responses to the NDA by Monday, July 7, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: AShaw/June 12, 2014
MPaterniti/June 12, 2014
LPei/June 12, 2014

Initialed by: CBertha/June 13, 2014
BKarimi-Shah/June 12, 2014
MWood/June 12, 2014
LJafari/June 12 and June 13, 2014

Finalized by: JLee/June 13, 2014

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/s/

JESSICA K LEE
06/13/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205832

**ACKNOWLEDGE -
BREAKTHROUGH THERAPY REQUEST**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director
Regulatory Affairs

Dear Ms. Cherian:

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

We acknowledge receipt on May 28, 2014, of your May 28, 2014, request for Breakthrough Therapy designation submitted under section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) for Idiopathic Pulmonary Fibrosis (IPF). We are reviewing your request and will respond to you within 60 days of the receipt date. We will contact you if we have any questions or require additional information.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JESSICA K LEE
06/09/2014

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following request for information:

Non-Clinical:

1. The submission contained study reports DDB0007: BIBF 1120: Carcinogenicity Study by Oral Gavage Administration to Han Wistar Rats for 104 Weeks and DDB0006: BIBF 1120: Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice for 104 Weeks. Provide the SAS XPORT Transport Files for the study data for both the mouse and rat studies to allow a complete statistical evaluation of study findings. These files are described in the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications" and the document "*Study Data Specifications*." The guidance documents can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf> and <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>

Provide the non-clinical files by COB Monday, June 9, 2014.

Clinical Pharmacology/Pharmacometric:

2. The following comment pertains to your Clinical Study Reports 1199.32 and 1199.34. You indicated that a population pharmacokinetic analysis will be performed on nintedanib and BIBF 1202 plasma concentrations (in combination with other IPF studies). Submit the integrated population PK analysis results by incorporating all PK data available. Justification should be made if certain studies are excluded from the analysis.
3. The following comment pertains to your Clinical Overview. Treatment-dependent differences for safety were observed in the subgroups for gender, race (Asian vs. White), and body weight (<65 kg vs. ≥65 kg). Based on your current population PK analysis results, these factors were also identified as significant covariates for PK exposure. Conduct PK exposure-response analyses for both efficacy endpoint(s) including annual rate of decline in FVC and safety endpoints including GI and liver toxicities for your pivotal phase III studies 1199.32 & 1199.34, using both population PK model derived and observed pre-dose plasma concentrations as PK exposures.

Submit your analyses by June 30th, 2014. The updated population PK analysis, exposure-response analyses with observed pre-dose plasma concentrations, and exposure-response analyses with model derived PK exposures, can be submitted separately as soon as possible. Provide data, NONMEM control streams, and scripts used to generate analyses

for the final population PK and exposure-response models. Submit data files as SAS transport files with *.xpt format (eg. Data1.xpt) and other files be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_out.txt).”

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 205832

Drafted by: LZhao/May 30, 2014
CGalvis/June 2, 2014
JLee/June 2, 2014

Initialed by: LJafari/June 2, 2014

Finalized by: JLee/June 2, 2014

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/s/

JESSICA K LEE
06/02/2014

MEMORANDUM

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

DATE: June 5, 2014

APPLICATION/DRUG: NDA 205832/nintedanib

The “Table 1. Highlights of Clinical Pharmacology and Cardiac Safety” attachment was inadvertently omitted from NDA 205832 Information Request dated June 4, 2014, which was sent to Boehringer Ingelheim via electronic mail on June 4, 2014. The omitted attachment (“Table 1. Highlights of Clinical Pharmacology and Cardiac Safety”), was sent to the applicant on June 5, 2014 as part of the below email.

Lee, Jessica K (ODEII/DPARP)

From: Lee, Jessica K (ODEII/DPARP)
Sent: Thursday, June 05, 2014 11:24 AM
To: ann.cherian@boehringer-ingenelheim.com
Subject: RE: Information Request
Attachments: NDA 205832_Highlights_ClinPharm_and_Cardiac_Safety.pdf

Hi Ann,

Please find attached the Attachment referenced in Question 7. Additionally, the request for additional data is related only to study report 1199-0029 and its interim report 411-2411-01. Let me know if you have any further questions.

Best regards,
Jessica

From: ann.cherian@boehringer-ingenelheim.com [<mailto:ann.cherian@boehringer-ingenelheim.com>]
Sent: Thursday, June 05, 2014 6:48 AM
To: Lee, Jessica K (ODEII/DPARP)
Subject: RE: Information Request

Good morning Jessica,

We realized this morning that the attached FDA correspondence sent yesterday was missing an attachment as referred to in Questions 7:

7. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (attached)

Please provide the attachment at your earliest convenience.

Many thanks
Regards
Ann

From: Lee, Jessica K (ODEII/DPARP) [<mailto:Jessica.Lee@fda.hhs.gov>]
Sent: Wednesday, June 04, 2014 1:27 PM
To: Cherian,Ann (DRA) BIP-US-R
Subject: Information Request

Dear Ann,

You will find attached an Information Request for NDA 205832. Please confirm receipt of this email and the attached document.

Best Regards,
Jessica
(301) 796-3769

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

JESSICA K LEE
06/05/2014

June 5, 2014

The below correspondence was sent to the applicant without the table referenced in item 7 on its second page. The missing table was sent in a separate e-mail on June 5, 2014. It was entered into DARRTS as a COR-NDAIR-01 (Information Request) and finalized on June 5, 2014.

Dear Ms. Cherian:

Your submission dated, May 2, 2014, to NDA 205832, is currently under review. We have the following request for information:

1. A data definition file which describes the contents of the electronic data sets
2. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
3. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
4. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
5. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
6. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
7. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (attached)

Submit responses to the NDA by Tuesday, June 10, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
06/04/2014

MEMORANDUM

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

DATE: May 23, 2014

SUBJECT: Breakthrough Therapy Designation

APPLICATION/DRUG: NDA 205832/nintedanib

In a telephone conversation, on May 22, 2014, Ann Cherian from Boehringer Ingelheim (BI) and Jessica Lee from DPARP discussed whether BI had considered Breakthrough Therapy Designation for BI's product, nintedanib. BI will consider the suggestion of requesting Breakthrough Therapy Designation for nintedanib to the NDA.

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/s/

JESSICA K LEE
05/23/2014



NDA 205832

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director
Regulatory Affairs

Dear Ms. Cherian:

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

Name of Drug Product: Nintedanib 100 mg and 150 mg capsules

Date of Application: May 2, 2014

Date of Receipt: May 2, 2014

Our Reference Number: NDA 205832

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 1, 2014, in accordance with 21 CFR 314.101(a).

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

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JESSICA K LEE
05/15/2014



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Meeting Type: Type B Meeting
Meeting Category: Face-to-face EOP2 Meeting
Meeting Date and Time: December 01, 2010 at 1:00 P.M.
Meeting Location: Conference Room 1417
Application Number: IND 74683
Product Name: BIBF 1120
Received Briefing Package October 19, 2010
Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Requestor: Amy Van Anandel, DVM, MPH
Associated Director
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Meeting Recorder: Sadaf Nabavian, Pharm.D.
Regulatory Management Officer
Meeting Attendees:

FDA Attendees

Division of Pulmonary, Allergy, and Rheumatology Products

Badrul A. Chowdhury, M.D, Ph.D., Director
Robert Temple, M.D., Deputy Center Director for Clinical Sciences
Sally Seymour, M.D., Deputy Director for Safety
Banu Karimi-Shah, M.D., Clinical Reviewer
Wang Ying, Ph.D., CMC Reviewer
Kathleen Young, Ph.D., Pharmacologist/Toxicology Reviewer
Molly Topper, Ph.D., Pharmacologist/Toxicologist Supervisor
Joan Buenconsejo, Ph.D., Acting Statistical Team Leader
Feng Zhou, M.S., Statistical Reviewer
Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer
Yun Xu, Ph.D., Clinical Pharmacology Acting Team Leader
Sadaf Nabavian, Pharm.D., Regulatory Project Manager

Sponsor Attendees

Jeff Snyder, Executive Director, US Drug Regulatory Affairs
Amy Van Anandel, DVM, MPH, Associate Director, US Drug Regulatory Affairs
Bernd Disse, MD, PhD, Therapeutic Area Head, Pulmonary
Matthias Klueglich, MD, Team Member Medicine, Clinical Research
Nolwenn Juhel, MSC, Project Statistician, Biometry
Doreen Luedtke, PhD, Project Pharmacokinetics, DMPK

Michele Brun, Trial Clinical Monitor
Florian Colbatzky, DVM, PhD, Project Toxicologist, Nonclinical Drug Safety
Bernd Krist, PhD, R&D Project Leader, Dept. R&D project Management
Michael Lutzenburg, PhD International Project Leader, CDept, International
Project Management
Joanne Palmisano, MD, FACP, Vice President, US Drug Regulatory Affairs
Rainer Palluk, PhD, Global Regulatory Affairs

1.0 BACKGROUND

Boehringer Ingelheim submitted a meeting request dated September 14, 2010, for a Type B, End-of-Phase 2 Meeting to obtain feedback from the Division on the proposed trial design for their Phase 3 program and to discuss the overall clinical development program in support of BIBF 1120 in patients with idiopathic pulmonary fibrosis (IPF). A briefing package for this meeting was submitted on October 19, 2010. Upon review of the briefing package, the Division responded to BI's questions via fax on November 29, 2010. The content of that fax is printed below. BI further responded to Division's response by providing clarifying comments to Ms. Nabavian via email. The responses from BI are provided under the relevant original responses followed by any discussion that took place at the meeting. BI's questions are in *bold italics*; FDA's responses are in *Italics*; BI's clarifying comments and any discussion that took place with the FDA are in normal font.

2.0 DISCUSSION

Clinical

Question 1:

Does the Agency agree that the proposed clinical development program will provide adequate clinical experience to support an NDA for BIBF 1120 in patients with IPF and the proposed indication for 'slowing the decline of lung function in the long-term maintenance treatment of idiopathic pulmonary fibrosis'?

Division Response:

The proposed clinical development program appears to provide for adequate clinical experience to support an NDA submission for BIBF 1120 in patients with IPF. The final labeled indication for BIBF 1120 will depend on what the data show. Refer to our additional comments on your development plan in the responses below.

Discussion:

No discussion occurred.

Question 2.1:

Does the Agency agree with the major elements of trial design, including the proposed study population, sample size, dose, posology and treatment duration, efficacy endpoints, safety monitoring the statistical analysis plan of the Phase 3 trials (1199.32 and 1199.34) in patients with IPF?

Division Response:

Overall, the major elements of trial design, including dose, dosing frequency, and duration of treatment appear reasonable. Based on the information you have provided, we have the following comments regarding the study population, efficacy endpoints, and statistical analysis plan:

A) Study Population

- 1. The inclusion criteria with respect to IPF diagnosis and lung function appear reasonable. However, it is unclear from the information provided where you plan to conduct your clinical trials. With regards to non-US study sites, you should address to what extent the study population will represent U.S. patients with IPF.*

BI Clarifying Comment:

BI plans to conduct the clinical trials world wide and to optimize US enrollment to the extent possible. To our knowledge, no evidence exists for any regional differences in IPF. In the clinical trials, a common standard of diagnosis will be ensured by the inclusion criteria including the use of a central reading for pulmonary function and CT.

Considering the variable use of certain concomitant medications in different regions, BI will conduct sensitivity analyses based on subgroups of concomitant treatment to assure the results obtained in Phase 3 can be applied to the US IPF population.

Discussion:

No discussion occurred.

B) Efficacy Endpoints

- 1. Your proposed primary endpoint of annual rate of decline of FVC and key secondary endpoints of time to first IPF exacerbation and mean change of SGRQ total score over the 52 weeks appear to be reasonable.*
- 2. Mortality is an important clinical endpoint and will be evaluated regardless of the results of the analyses of the primary and secondary efficacy endpoints. The lack of non-clinical support for BIBF 1120 further elevates the importance of the mortality outcome.*
- 3. Specify criteria for how you plan to address lung transplant or listing for transplant into your efficacy analysis.*

BI Clarifying Comment:

The detailed procedure for how we plan to address lung transplant or listing for transplant will be outlined in our IND submission. All patients will be included in all analyses, unless actually elected for transplantation. In this case they will be counted as “discontinued” patients at the time they are admitted for the procedure. Subsequent assessments for transplant patients will not be included in the primary efficacy analysis, in contrast to other discontinued patients. Follow-up for all discontinued patients will include FVC measures throughout the duration of the trial. As with all discontinued patients, transplant patients will be followed for the trial duration and detailed information about their vital status outcome and any emergent post-treatment events will be documented.

Discussion:

The Division stated that the intent of the comment regarding lung transplant patients was to remind BI to collect pertinent data as to which patients receive a lung transplant or are listed for transplant during the course of the study, and to consider how this information should be included in the analyses and to pre-specify in the protocol. BI accepted the Division's recommendation.

C) Statistical Analysis Plan

- 1. Based on our understanding, the order of your proposed testing sequence is 1) the annual rate of decline in FVC; 2) the time to first exacerbation; 3) the mean change from baseline of total SGRQ score over the 52 weeks. The proposed sequential hierarchical procedure is acceptable.*
- 2. You propose to apply a random coefficient regression (random slopes and intercepts) model to evaluate the annual rate of decline in FVC between treatment groups. Specify the covariance structure you plan to use in the analysis.*

BI Clarifying Comment:

A variance components structure will be used.

In addition, this approach assumes missing data to be missing at random (MAR). Dropouts observed in the Phase 2 study appears mostly to be due to adverse events and therefore is most likely treatment-related. Therefore it may be difficult to justify the assumption of MAR. We recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in different direction from the result of the primary analysis. Of note, this comment also applies to the key secondary endpoints (i.e. exacerbation and total SGRQ).

BI Clarifying Comment:

The primary analysis, random coefficients regression model, will be supplemented to provide pattern-mixture models (e.g. Hedeker & Gibbons 1997) which will investigate the effects of missing data. Depending on the pattern of the missingness in the data, multiple imputation methods may also be considered. In addition, Kaplan-Meier graphs will be used to compare the drop out pattern between the two treatment arms. Further details will be given in the Trial Statistical Analysis Plan.

We also recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,'

'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned.

- 3. The sample size calculation is reasonable. However, we note your powering based upon a difference of 100mL. The Division's assessment of efficacy will evaluate the statistical significance and clinical meaningfulness of the treatment effect.*

Discussion:

The Division replied that we are concerned with the proposed statistical model (i.e. random coefficient regression model) because this model does not capture within-subject variability. The Division reiterated that before initiating the trial, BI needs to understand the applicability of the assumptions to the data and to provide a rationale (if any) in the protocol. The Division recommended that BI submit their protocol for review, including a detailed description of the primary endpoint and the analysis plan. BI agreed to submit a protocol and will consider the points that were discussed during the meeting.

Post-Meeting Notes: The Division would like to correct that the currently proposed model does not capture within-subject correlation, and not within-subject variability.

Question 2.2:

Does the Agency agree with the primary endpoint of annual rate of decline of FVC and its proposed analysis?

Division Response:

See our Response to your Question 2.1.

Discussion:

See the Discussion section under Clinical Response 2.1 (3)(C).

Question 2.3:

Regarding secondary endpoints, does the Agency agree:

- That we have identified the appropriate secondary efficacy endpoints?*

Division Response:

The chosen secondary efficacy endpoints are acceptable. For specific comments regarding these endpoints, refer to our Response to Question 2.1.

Discussion:

No discussion occurred.

- *With the definition of an IPF exacerbation?*

Division Response:

The proposed definition of an IPF exacerbation is acceptable.

Discussion:

No Discussion occurred.

- *Our approach to mortality?*

Discussion:

No Discussion occurred.

Division Response:

See our Response to your Question 2.1.

- *Our approach to the SGRQ?*

Division Response:

Elevating the SGRQ total score to a key secondary endpoint is at your discretion. Currently, there is no literature to support the use of SGRQ in evaluating patients with IPF. The extent to which the results of the key secondary endpoints, including SGRQ, will be described in the product label will be a review issue based on the study results.

Discussion:

No Discussion occurred.

- *The proposed different key secondary endpoints and hierarchical procedures for EU and US registrations?*

Division Response:

See our Response to your Question 2.1.

Discussion:

No Discussion occurred.

Question 2.4:

Does the agency agree that the data from the Phase 2 trial adequately support the selection of the 150 mg bid dose, with optional step down to 100 mg bid, for Phase 3?

Division Response:

Based on the information provided from study 1199.30, the dose you have selected to move forward into Phase 3 appears reasonable.

Discussion:

No Discussion occurred.

Question 2.5:

Does the Agency agree that the safety assessments and evaluation plan in Phase 3 are adequate to support the safety profile of BIBF 1120 in patients with IPF?

Division Response:

The proposed safety assessments and evaluation plan in Phase 3 appear adequate based on the information available to date from the Phase 2 IPF and ongoing oncology development programs. However, if new safety signals are demonstrated during the development program, further assessments may be required.

Discussion:

No Discussion occurred.

Question 3:

Does the Agency agree that the planned exposure in the target IPF population will be adequate to support the review of the NDA and provide adequate information to establish the safety and efficacy of BIBF 1120 in patients with IPF?

Division Response:

While the overall number of patients may be adequate, if new safety signals are demonstrated during the development program, a larger safety database may be required.

A summary of the safety data from the oncology development programs should be provided with the NDA submission.

Discussion:

No Discussion occurred

Clinical Pharmacokinetic

Question 4.1:

Does the Agency agree that for population pharmacokinetic analysis the PK data from cancer and IPF patients can be combined; and, that no PK sampling is necessary during Phase 3 in IPF patients?

Division Response:

In principle, we agree that for population pharmacokinetic analysis the PK data from cancer and IPF patients can be combined. We encourage you to collect PK samples in Phase 3 trials planned to conduct in IPF patients to allow exposure-response analysis in this population.

BI Clarifying Comment:

BI will be collecting at least one pre-dose sample at steady-state from all IPF patients enrolled in Phase 3 studies. We believe this will provide a robust basis for the population PK analyses, including the renally impaired subgroup. In the event that there is insufficient data in renally impaired patients in Phase 3, BI will provide a proposal to conduct additional work, to the Division for review.

Discussion:

In general, the Division agreed with BI's proposal to conduct population PK analyses in IPF patients. However, the adequacy of the data and whether a dedicated renal impairment study is required will be a review issue. The Division recommended that BI consider including a wider range of renally impaired patients so that the results can be more informative of how the PK changes over the spectrum of severity of renal impairment. In addition, the Division recommended that renal function be considered as one of the covariates when conducting a population PK analysis, if appropriate.

Question 4.2:

Does the Agency agree that the hepatic impairment studies conducted within the BIBF 1120 oncology program are sufficient and no additional study in patients with hepatic impairment is necessary?

Division Response:

No, we do not agree. It is important that impaired hepatic function be the cause of alterations in the Child-Pugh components in the hepatic impairment study. In patients with metastatic cancer, hypoalbuminemia, encephalopathy, and ascites may be related to cancer cachexia or cancer metastatic to the brain or peritoneal surfaces rather than impaired hepatic function. Therefore, we recommend that you conduct the hepatic impairment study in patients without HCC or non-cancer patients. We refer you to "Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, May 2003". (b) (4)

the labeling should indicate that the impact of severe hepatic impairment was not studied.

BI Clarifying Comment and Question:

(b) (4)

(b) (4)

Does the FDA have additional comments/concerns with this proposal?

Discussion:

The Division reiterated that BI should consider non-cancer patients when conducting a hepatic impairment study, to minimize the effect of cancer on the Child-Pugh scoring.

BI asked whether the Division would be willing to review the results from currently on-going hepatic impairment study in hepatocellular carcinoma patients in the near future. The Division agreed to review the study to determine the adequacy of the data. BI stated that the current studies are on-going and that the data will be available in April 2011.

The Division reminded the sponsor to submit the hepatic impairment study results to the IND related to IPF indication.

Question 4.3:

Does the Agency agree that the PK of IPF patients with renal impairment is adequately addressed in the proposed clinical development program?

BI Clarifying Comment:

Refer to comment provided to question 4.1.

Division Response:

In principle, we agree that you may use population PK analysis to explore the PK of BIBF 1120 in IPF patients with reduced renal function. You need to be sure that the database includes a wide range of renal function and the data collected is robust.

We encourage you to conduct a dedicated renal impairment study. Current knowledge suggests that drugs with the following properties may be waived for dedicated renal studies: Gaseous or volatile drug and active metabolites that are primarily eliminated via the lungs; drugs intended only for single-dose administration, and monoclonal antibodies.

Your proposed product does not fall into any of the above three categories. We refer you to "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, September 2009 draft".

Discussion:

Refer to the Discussion section under Clinical Pharmacology Response 4.1.

Preclinical**Overall nonclinical program****Question 1:**

Does the Agency agree that the outlined toxicological data and characterization are adequate to support conducting the Phase 3 trials in the US and for a NDA submission for BIBF 1120 in IPF?

Division Response:

Based on the summary data, your justifications for nonclinical issues identified at the previous Pre-IND meeting held in August 2006, and the summarized completed clinical Phase 2 program in IPF patients, it appears that you have sufficiently characterized the chronic toxicity of BIBF 1120 in rats and monkeys. However, completion of an adequate

GLP reproductive program is needed (see our response to question 2). Specifically, female fertility and two GLP embryo-fetal development studies (1 rat and 1 rabbit) should be completed prior to initiating Phase 3 studies. Alternatively, inclusion of two methods of birth control in the Phase 3 studies is an acceptable path forward while completing the reproductive toxicology program. If feasible to conduct such a study, the peri-/post-natal study may be conducted in parallel to the Phase 3 program. In general, the approach of initiating toxicity studies in multiple species (rat, dog, minipig, Cynomolgus monkey and then Rhesus monkey) and selecting the species that can tolerate the product for the longest duration at adequate doses is not an acceptable nonclinical toxicology assessment strategy. Selection of the most sensitive species to a drug's toxicity and then titrating the drug down to levels where a No Observed Adverse Effect Level (NOAEL) can be identified is the appropriate process for drug characterization. From the NOAEL, appropriate safety margins are used to determine the safe clinical dose and consideration of those adverse effects for clinical monitorability may allow for dosing beyond the supported NOAEL.

Upon submitting your IND for IPF, provide a rationale with supportive data for selection of the Rhesus monkey rather than the Cynomolgus monkey for the non-rodent species chronic toxicity study. A detailed review of the nonclinical toxicology data and of the clinical Phase 2 study completed in IPF patients is needed prior to confirming that your proposed Phase 3 studies are supported.

BI Clarifying Comment:

The IND submission will include reports for completed chronic toxicology studies and an expanded rationale for the selection of the animal species used in the toxicology studies, including the rationale for selection of the Rhesus monkey instead of the previously used Cynomolgus monkey.

Discussion:

BI further discussed the development of their toxicology program with regard to species selection. The Sponsor's preliminary studies in Rhesus and Cynomolgus monkeys showed severe hepatic toxicity in the Cynomolgus monkey. The results of further investigation suggested to BI that the Rhesus monkey may be the more sensitive species. The Division requested that BI provide the final study reports for the evaluations in Rhesus and Cynomolgus monkeys and the expanded rationale for species selection which will be taken into consideration during review of the IND submission.

Reproductive toxicology studies

Question 2:

Does the Agency agree with BI's approach to reproductive toxicology?

Division Response:

Based on the summary data you provided, additional reproductive studies are needed to complete your reproductive toxicology program. Completion of the fertility study battery (fertility study in females) is recommended prior to initiating Phase 3 clinical studies. Additionally, completion of two GLP teratogenicity studies (1 rat and 1 rabbit) is needed. Although the pilot teratogenicity study in rats showed a positive signal, dose reduction in this study may allow for longer exposure and better characterization of the potential teratogenic effects. Additionally, the rabbit teratogenicity study may reveal different findings. Lastly, if the teratogenicity studies in rat can be completed at lower BIBF 1120 doses, then completion of the peri/post-natal studies is expected. Consideration of the GLP rat teratogenicity study results will be taken to determine the feasibility of conducting a pre- and post-natal development study in this species.

BI Clarifying Comment and Question:

BI acknowledges the reproductive toxicology liabilities of BIBF 1120 at doses resulting in exposure well below the therapeutic range, and assumes respective restrictions in the use of BIBF 1120 including requiring two methods of birth control for WoCBP in the Phase 3 studies.

We would like to understand more fully the objective of the FDA for conducting additional reproductive toxicology studies using lower doses.

Would the Division provide clarification for the rationale around the suggestions for completion of the reproductive toxicology battery?

Discussion:

The Division informed BI that for IPF patients a full reproductive toxicity battery is expected (completion of the fertility, embryo-fetal development, and peri- and post-natal studies) prior to Phase 3 with two teratogenicity studies, particularly since there was a strong signal in the preliminary teratogenicity study. The study results should be submitted with the IND, although since two forms of birth control are required the Phase 3 studies may be initiated. The Division further acknowledged the feasibility limitations to performing the complete reproductive toxicity study battery, noting that other species may be considered (i.e., rabbit). The Division indicated that a NOAEL was not identified in the preliminary teratogenicity study in rats and adequate safety margins for their findings need to be provided. The Division recommended that BI choose a dose level that is high enough to characterize the toxicity by BIBF 1120, as well as a dose level that is low enough to determine a NOAEL so that the risk/benefit ratio can be determined. BI stated that they were surprised that the teratogenic effects were observed early on in the reproductive toxicology program, and further concluded that the value of additional studies may be very limited. The Division replied that BI still needs to submit the data to support their conclusions and that the findings in the pilot teratogenicity study in rats do not eliminate the need to conduct the standard fertility study in female rats and teratogenicity studies in rats and rabbits. If it is found to be unfeasible to complete the

full reproductive study battery, a thorough justification should be provided for consideration during the formal review. BI agreed to further investigate the feasibility of additional reproductive toxicology studies and repeated that they will require two methods of birth control in their clinical trials. The Division responded that all available information regarding the toxicology/safety studies should be submitted.

The Division commented that BI should provide safety information from the clinical studies conducted with BIBF1120 as that information will be critical to determine the safety of the proposed clinical trials.

Carcinogenicity studies

Question 3:

Can the Agency provide further guidance regarding the materials required and the process for making a final determination of the timing for submission of the carcinogenicity studies?

Division Response:

The material required to make a final determination regarding the timing of the submission of the carcinogenicity studies include submission and detailed review of the chronic toxicity studies and genetic toxicity studies. Information from the completed clinical studies is also taken into consideration. Provided that chronic studies do not reveal a safety signal that would require completion and submission of the carcinogenicity studies at the time of your NDA submission for the IPF population, then it will be acceptable to submit the results of the carcinogenicity studies in both the mouse and the rat species (final study reports) as soon as the results are available and analyzed, as a Phase 4 Commitment.

Discussion:

The timing of the carcinogenicity final study report submissions to the NDA will be a review issue.

CMC

Question 1:

Does the Agency concur with BI's proposal that a cross-reference of CMC information to IND (b) (4) is adequate to support the conduct of the phase 3 trials in the US?

Division Response:

Yes. It is acceptable to cross-reference the CMC information in IND (b) (4) to support your phase 3 trial. We also recommend that you provide CMC specific questions at your future pre-NDA meeting.

Discussion:

No discussion occurred.

ADDITIONAL COMMENTS**Clinical Pharmacology**

- You indicated your product is a substrate for both P-gp and CYP3A4, we recommend that you conduct Drug-Drug Interaction (DDI) study(ies) in human to evaluate the effect of P-gp and CYP3A4 precipitators on the PK profile of your product. Clarify if you have conducted any study to evaluate the effect of your product on P-gp activity. Also clarify if you have evaluated the DDI potential of your circulating metabolites. We refer you to “Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling, September 2006”.

BI Clarifying Comment and Question:

The BIBF 1120 information package for IPF did not explicitly summarize the data available on BIBF 1120 and its main metabolites, BIBF 1202 and BIBF 1202 glucuronide, as P-gp and CYP3A4 substrates / inhibitors. The information package (pp 54 – 55), however, referenced data summaries from the End-of-Phase 2 second-line NSCLC information package submitted to IND (b) (4) on December 20, 2007 (Serial Number 0136) and the information package of the first-line OC submitted to IND (b) (4) on December 10, 2008 (Serial Number 0166).

The data available on BIBF 1120 and its main metabolites, BIBF 1202 and BIBF 1202 glucuronide, as P-gp and CYP3A4 substrates / inhibitors as summarized in the above mentioned documents are provided below. Citations for the references included below were provided in the BIBF 1120 information package for IPF.

Based on this information, BI does not propose to conduct DDI studies in human to evaluate the effect of P-gp and CYP3A4 precipitators on BIBF 1120 and its metabolites.

Would the Division please advise if this information does not adequately address the underlying issues that prompted the recommendation to conduct additional studies?

BIBF 1120 as a P-gp inhibitor

In an in vitro transcellular transport study using transfected LLC-PK1 cells, BIBF 1120 inhibited MDR1(P-gp)- mediated vectorial transport of digoxin. However, the inhibition was not found to occur in a concentration-dependent manner. A minor reduction of digoxin transport by 17% was seen at a concentration of 3 μ M but this minor effect was diminished at the highest concentration of BIBF 1120 ES (30 μ M) when the digoxin transport was nearly back at the level of the control experiments in the absence of inhibitors. Therefore, an IC₅₀ could not be estimated and prediction of interaction potential was not attempted. The IC₅₀ must be clearly above > 3 μ M and is expected to be > 30 μ M, qualifying BIBF 1120 as a moderate to weak P-gp inhibitor (U05-3076). Even the highest individual BIBF 1120 maximum plasma concentration found so far in a 250 mg BIBF 1120 BID dose group (264 ng/ml corresponding to 0.49 μ M) under treatment with 250 mg bid doses to cancer patients would be far below a possible threshold needed for a significant clinical interaction.

BIBF 1120 was also administered to cancer patients in combination with other P-gp substrates (e.g. docetaxel or paclitaxel in trials 1199.4, 1199.5 and 1199.6). Neither in trial 1199.4, 1199.5 or 1199.6 clinically relevant interaction of BIBF 1120 was found on the pharmacokinetic characteristics of paclitaxel or docetaxel or vice versa.

Preliminary combination therapy data of BIBF 1120 with another investigational drug (BIBW 2992 – also a P-gp substrate with an expected K_m between 10 to 30 μ M: U04-1771) displayed no influence of BIBF 1120 on the PK of BIBW 2992 in a concomitant administration setting (trial 1239.1) BIBF 1120 was administered twice daily (150 mg bid) together with a once daily dosing schedule for BIBW 2992 (10 mg) in patients with advanced cancers.

Based on this data and the draft FDA guideline “Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling” from Sept 2006 BI believes that it is not necessary to conduct distinct P-gp clinical drug-drug interaction trials with BIBF 1120 acting as a P-gp inhibitor.

BIBF 1120 as a P-gp substrate

The involvement of transporters in the efflux of BIBF 1120 was directly investigated using [¹⁴C] BIBF 1120. Asymmetric, apically-directed transport of BIBF 1120 in MDR1 (P-gp) transfectants suggested that BIBF 1120 may be excreted into bile by P-gp. This may occur only if BIBF 1120 remains intact in hepatocytes, which is unlikely given the rapid metabolism of BIBF 1120 in hepatocytes (U05-1001). Preliminary combination therapy data of BIBF 1120 with another investigational drug (BIBW 2992 – also a medium potent P-gp inhibitor with a K_i of 26 μ M (U04-1771) from trial 1239.1 displayed no influence of BIBW 2992 (10 mg) on the PK of BIBF 1120 (150 mg bid) in a concomitant administration setting. Therefore, an interaction on the intestinal absorption based on the potential inhibition of P-gp mediated intestinal efflux did not occur. Due to the analytical setting the K_m of BIBF 1120 to P-gp could not be determined and is presently unknown. However, based on the assumption that the K_m for BIBF 1120 would

be within the range of known P-gp substrates ($4\mu\text{M}$ – $213\mu\text{M}$), even the highest individual BIBF 1120 maximum plasma concentration found so far (264 ng/ml corresponding to $0.49\mu\text{M}$) under treatment with 250 mg bid doses to cancer patients would be far below a possible threshold needed for a significant clinical interaction. Based on this data and the draft FDA guideline “Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling” from Sept 2006 BI believes that it is not necessary to conduct distinct P-gp clinical drug-drug interaction trials with BIBF 1120 as a P-gp substrate.

Metabolites as P-gp as substrates/inhibitors

Based on *in vitro* data in human hepatocytes BIBF 1202 is neither a substrate nor an inhibitor of P-gp (U05-3076). For BIBF 1202-glucuronide the *in vitro* studies are still ongoing and therefore, no results are available yet.

BIBF 1120 as CYP 450 substrate/inhibitor/inducer

In human liver microsomes, the cleavage of [^{14}C] BIBF 1120 by esterase catalysed hydrolysis (formation of BIBF 1202) was the prevalent metabolic reaction (about 25% ester cleavage compared to about 5% CYP dependent metabolism). CYP 3A4 was the predominant enzyme involved in the oxidative metabolism of BIBF 1120 (U03-1355-01). In the human ADME study the oxidative N-demethylated BIBF 1120, which is catalysed by CYP 3A4 only around 3% were found in the urine (relative fraction of the total renal excretion after oral dosing) (U06-1950). Moreover, other Phase 1 metabolic reactions e.g. oxidation of the piperazine moiety which are catalysed by CYP 3A4 and CYP 2C8 (minor) only minor amounts were observed in the human urine around 1-3% (U06-1950). Due to the low prevalence of CYP-mediated metabolism drug-drug interactions due to inhibition or induction of cytochrome P450 enzymes by co-medications are considered as unlikely.

Inhibition of cytochrome P450-catalysed test reactions by BIBF 1120 was investigated in liver microsomes of humans. Minor inhibition of erythromycin N-demethylation was observed at a concentration of $70\mu\text{M}$, but no inhibition of three other CYP3A4 catalysed test reactions occurred at concentrations up to $100\mu\text{M}$. No pronounced inhibition of test reactions was observed for nine other human drug-metabolizing CYP enzymes by BIBF 1120. There was no indication of irreversible CYP 3A4 inhibition by BIBF 1120. Therefore, metabolic drug-drug interactions, based on inhibition of CYP enzymes by BIBF 1120, with other drugs that are substrates of CYP enzymes are unlikely to occur (U03-1386).

The oral administration of BIBF 1120 to rats caused no induction of CYP 2B and CYP 3A4 activities and also had no effect on liver to body weight ratios and total amount of microsomal protein. The changes observed in hepatic cytochrome P450, CYP 1A, CYP 2E1 and CYP 3A may not be considered biologically important. Therefore, induction of CYP enzymes to a biologically relevant extent may not occur during therapeutic use of BIBF 1120 (U04-2195).

Based on this data and the draft FDA Guidance entitled, "Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling (dated September 2006)," BI is not planning to perform any distinct CYP 450 based drug-drug interaction trials for BIBF 1120 as a CYP 450 substrate, inhibitor or inducer.

BIBF 1202/BIBF 1202-glucuronides as CYP 450 inhibitors

No pronounced inhibition of any of the following CYP P450 enzymes by BIBF 1202 and BIBF 1202-glucuronide (concentrations up to 100 μ M) was observed: CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11 (U08-1256, U09-1164). No indication of a mechanism based inhibition of CYP 3A4 was observed. Metabolic drug-drug interactions, based on inhibition of CYP enzymes by BIBF 1202 and by BIBF 1202-glucuronide are unlikely to occur.

Discussion:

The Division sought clarification on the product's metabolism since the meeting package indicated that ~25% of the product was metabolized by ester cleavage. BI commented that the product is metabolized mainly by glucoronidation and that CYP3A plays a very small role in its metabolism. The Division requested that BI submit this data to the IND for review. The need for further DDI studies to evaluate the effect of P-gp and CYP3A4 precipitators on BIBF 1120 and its metabolites will be a review issue.

CMC

- The following comments are directed towards your future NDA submission.
 1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
 2. It is expected that at least 12 months of real time data and 6 months of accelerated data be included in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
 3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
 4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.

5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

Discussion:

No discussion occurred.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ATTACHMENTS AND HANDOUTS

None provided

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Drafted: SNabavian/December 09, 2010

Initialed: KYoung/12.20.2010
MTopper/12.20.2010
BKarimi-Shah/12.21.2010
SSeymour/12/21/2010
JBuenconsejo/12/17/2010
EShang/12/28/2010
YXu/12/28/2010
BAChowdhury/12/29/2010

Finalized: SNabavian/12/30/2010

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/s/

SADAF NABAVIAN
12/30/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205832

LATE-CYCLE MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director, Regulatory Affairs

Dear Ms. Cherian:

Please refer to your New Drug Application (NDA) dated May 2, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ofev (nintedanib) Capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 11, 2014.

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

If you have any questions, call Jessica Lee, Regulatory Project Manager at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Banu Karimi-Shah, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 11, 2014 at 2:00 PM

Meeting Location: via Teleconference

Application Number: NDA 205832

Product Name: Ofev (nintedanib) Capsules

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Banu Karimi-Shah, MD

Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Badrul A Chowdhury, MD, PhD, Director, DPARP

Lydia Gilbert McClain, MD, Deputy Director, DPARP

Sally Seymour, MD, Deputy Director for Safety, DPARP

Banu Karimi-Shah, MD, Clinical Team Leader, DPARP

Miya Paterniti, MD, Clinical Reviewer, DPARP

Marcie Wood, PhD, Supervisory Toxicology/Pharmacology, DPARP

Luqi Pei, PhD, Toxicology/Pharmacology, DPARP

Satjit Brar, PhD, Lead Clinical Pharmacologist, Division of Clinical Pharmacology II

Jianmeng Chen, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology II

Liang Zhao, PhD, Pharmacometrics Team Lead, Division of Pharmacometrics

Anshu Marathe, PhD, Pharmacometrics, Division of Pharmacometrics

Craig Bertha, PhD, Chemistry Team Lead, Division of New Drug Quality Assessment III

David Petullo, MS, Lead Mathematical Statistician, Division of Biometrics II

Yongman Kim, PhD, Mathematical Statistician, Division of Biometrics II

Jessica Lee, PharmD, Regulatory Project Manager, DPARP

Dipti Kalra, Safety Evaluator, Division of Pharmacovigilance I

Allen Brinker, MD, Lead Medical Officer, Division of Pharmacovigilance I

Nichelle Rashid, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)

Doris Auth, PharmD, Risk Management Analyst, Division of Risk Management

Teresa McMillan, PharmD, Safety Evaluator, DMEPA

Eileen Wu, PharmD, Safety Evaluator Team Leader, Division of Pharmacovigilance I

Tamara Meyer, PhD, Epidemiologist, Division of Epidemiology II

So Hyun Kim, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Tunde Otulana, MD, Sr. VP, Clinical Development & Medical Affairs, US

Joanne Palmisano, MD, VP, Drug Regulatory Affairs, US

Ellen Gold, MD, VP, Pharmacovigilance, US

Bernd Disse, MD, Therapeutic Area Head, Global Respiratory
Rozsa Schlenker-Herceg, MD, Global Team Member Medicine and Clinical Lead
Carl Coeck, MD, Global co-Team Member Medicine
Thomas Notter, MD, Global Pharmacovigilance
Craig Conoscenti, MD, Clinical Development and Medical Affairs, US
Bernd Krist, PhD, Team Member Research & Development
Florian Colbatzky, PhD, Toxicologist
Stefan-Lutz Wollin, PhD, Nonclinical Pharmacologist
Claudia Dallinger, PhD, Clinical Pharmacologist
Shoreh Shabrang, CMC Regulatory Affairs, US
Klaus-Helge Ibs, PhD, Global CMC Regulatory Affairs
Florence LeMaulf, Project Statistician
Inga Tschoepe, co-Project Statistician
Katy Pelling, co-Project Statistician
Kamila Sroka-Saidi, PhD, Project Medical Writer
Fee Alexandra Ruehmkorf, MD, International Project Leader
Christoph Hallman, MD, Global Medical Affairs, Respiratory
Daniel McBryan, MD, Medical Affairs, Respiratory, US
Jeff Snyder, Executive Director, Drug Regulatory Affairs, Respiratory, US
Gertrud Herzog, Global Regulatory Affairs
Ann Cherian, Drug Regulatory Affairs, US

1.0 BACKGROUND

NDA 205832 was submitted on May 2, 2014 for Ofev (nintedanib) Capsules.

Proposed indication: Idiopathic Pulmonary Fibrosis (IPF)

PDUFA goal date: January 2, 2015

FDA issued a Background Package in preparation for this meeting on August 29, 2014

2.0 DISCUSSION

1. Introductory Comments (RPM/CDTL)

Welcome, Introductions, Ground Rules, Objectives of the meeting

2. Information Requests

- No outstanding Information Requests at this time.

Discussion:

There were no outstanding Information Requests at the time the Late Cycle Meeting background package, dated August 29, 2014, was issued to Boehringer Ingelheim (BI). However, BI was informed at the September 2, 2014 labeling teleconference meeting between the Division and BI that an enhanced pharmacovigilance plan was a topic of internal discussion and would be sent to BI prior to the LCM. However, at the LCM, the decision had not yet been reached internally, and the Sponsor was informed that the plan may or may not be sent to BI.

3. Postmarketing Requirements/Postmarketing Commitments

Clinical Pharmacology:

- An on-going dedicated hepatic impairment study will be a post-marketing requirement. This may be discussed.

Discussion:

It was acknowledged that the hepatic impairment protocol, dated August 26, 2014, was received. BI clarified that the expected completion date of the hepatic impairment study will be 2015.

4. Major Labeling Issues

- Outstanding labeling topics identified during the pending labeling meeting on September 2, 2014 may be discussed.
- Recommendations regarding liver enzyme labeling may be discussed.

Discussion:

BI's submission of proposed labeling dated September 12, 2014 was discussed by each discipline: Clinical, Statistics, and Clinical Pharmacology. Each discipline requested changes to the proposed label. The FDA informed the Sponsor that the label, with FDA changes that were discussed during the Late Cycle Meeting, would be sent to BI in the next week or two.

Following the LCM, Clinical Pharmacology sent an email to BI with the following request:

Submit your simulation code and associated dataset for the calculation of effective half-life and accumulation ratio. Additionally submit a brief write-up on the methodology used for the simulation. Data files should be submitted as SAS transport files with *.xpt format (e.g. Data1.xpt) and other files be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_out.txt).”

5. Review Plans

Discussion:

It was discussed that NDA 205832 review is ongoing.

6. Wrap-up and Action Items

Discussion:

The Division will be sending out a further revised label in the next week or two.

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

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/s/

JESSICA K LEE
10/02/2014
Signing on behalf of CDTL



NDA 205832

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ann Cherian
Sr. Associate Director, Regulatory Affairs

Dear Ms. Cherian:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 11, 2014.
Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 11, 2014 at 2:00 PM – 3:00 PM
Meeting Location: Via teleconference as requested by Boehringer Ingelheim

Application Number: NDA 205832
Product Name: Ofev (nintedanib) capsules
Indication: Idiopathic Pulmonary Fibrosis (IPF)
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes (Jessica Lee/Dr. Karimi-Shah)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Information Requests
 - No outstanding Information Requests at this time.
3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
 - **Clinical Pharmacology:**
 - An on-going dedicated hepatic impairment study will be a post-marketing requirement. This may be discussed.
4. Major labeling issues – 10 minutes
 - Outstanding labeling topics identified during the pending labeling meeting on September 2, 2014 may be discussed.
 - Recommendations regarding liver enzyme labeling may be discussed.
5. Review Plans – 5 minutes
 - Completion of consults and tertiary reviews
 - Completion of inspections
 - Labeling discussions (as needed)
 - Review timeline
6. Wrap-up and Action Items – 5 minutes

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/s/

BADRUL A CHOWDHURY
08/29/2014