CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202324Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA #/Product Name: NDA 202324/Inlyta (axitinib) Tablets

PMR/PMC Description: Provide the analytical methods and method validation for testing of (b) (4) and (b) (4) in the final drug substance

PMR/PMC Schedule Milestones:

Final Protocol Submission:	NA
Study/Trial Completion:	NA
Final Report Submission:	04/22/2012
Other:	NA

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

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

The sponsor proposal included testing on (b) (4) the drug substance which was fund to be unacceptable. Minor changes and validation to the method is needed for its use on the final drug substance. This has been identified as a low risk and should require minimal resource.

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

The sponsor proposal included testing on (b) (4) the drug substance which was fund to be unacceptable. Minor changes and validation to the method is needed for its use on the final drug substance.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Method validation report and analytical procedure for testing (b) (4) and (b) (4) in the final drug substance

Required

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

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

_____
(signature line for BLAs)

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/s/

DON L HENRY
01/24/2012

RICHARD T LOSTRITTO
01/24/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion

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

Memorandum

Date: January 4, 2012

To: Lisa Skarupa – Regulatory Project Manager
Division of Oncology Products 1 (DOP 1)
Office of Hematology Oncology Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

Subject: Comments on draft labeling for INLYTA (axitinib) tablets for oral administration (Inlyta), NDA 202324

This review is in response to DOP 1's consult request dated April 25, 2011, for OPDP review of the proposed Package Insert (PI) and proposed Patient Package Insert (PPI) for Inlyta.

Reference is made to OPDP's review of the proposed PI dated December 21, 2011. Reference is also made to the Division of Medical Policy Program's (DMPP) review of the proposed PPI on January 3, 2012. Both reviews utilized the substantially complete version of the proposed PI dated December 20, 2011.

DDTCP has reviewed DMPP's comments on the proposed PPI, and has no further comments from a promotional perspective at this time.

Thank you for your consult.

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/s/

MICHELLE L SAFARIK
01/04/2012

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

PATIENT LABELING REVIEW

Date:	January 3, 2012
To:	Robert Justice, MD, Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Patient Package Insert)
Drug Name (established name):	INLYTA (axitinib)
Dosage Form and Route:	tablets for oral administration
Application Type/Number:	NDA 202324
Applicant:	Pfizer, Inc
OSE RCM #:	2011-1289

1 INTRODUCTION

This review is written in response to a request by the Division of Oncology 1 (DOP 1) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for Inlyta (axitinib) tablets for oral administration.

On April 14, 2011, Pfizer, Inc. submitted original New Drug Application (NDA), 202324 for Inlyta (axitinib) tablets for oral administration. The purpose of the Applicant's submission is to seek approval for the proposed indication of the treatment of patients with advanced renal cell carcinoma.

2 MATERIAL REVIEWED

- Draft Inlyta (axitinib) tablets for oral administration Patient Package Insert received April 14, 2011, and revised by the review division throughout the current review cycle and received by DMPP on December 20, 2011.
- Draft Inlyta (axitinib) tablets for oral administration Prescribing Information (PI) received April 14, 2011, and revised by the review division throughout the current review cycle and received by DMPP on December 20, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI, meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/

LATONIA M FORD
01/03/2012

BARBARA A FULLER
01/03/2012

LASHAWN M GRIFFITHS
01/03/2012

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

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

Memorandum

Date: December 21, 2011

To: Lisa Skarupa, RPM, DOP1

CC: Karen Rulli, Professional Review Group II Leader, OPDP
Amy Toscano, DTC Review Group IV Leader, OPDP
Michelle Safarik, Regulatory Review Officer

From: Marybeth Toscano, Regulatory Reviewer Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Promotion (DPP)

Subject: Comments on draft labeling (Package Insert) for axitinib tablets for oral administration, NDA 202324

In response to your consult request dated April 25, 2011, we have reviewed the draft version of the Package Insert for axitinib tablets. OPDP's comments have been addressed during labeling meetings. We have no additional comments on the proposed draft version of the PI.

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/s/

MARYBETH TOSCANO
12/21/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 20, 2011

TO: Amy McKee, Reviewing Medical Officer
John Johnson, Clinical Team Leader
Lisa Skarupa, RHPM
Division of Oncology Products I

FROM: Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202324
APPLICANT: Pfizer Inc.
10646 Science Center Drive
San Diego, CA 92121
DRUG: axitinib (Inlyta)
NME: Yes
THERAPEUTIC CLASSIFICATION: standard

INDICATION: treatment of advanced renal cell carcinoma

CONSULTATION REQUEST DATE: 17 May 2011
DIVISION ACTION GOAL DATE: 14 Feb 2012
PDUFA DATE: 14 Feb 2012

I. BACKGROUND:

Pfizer, Inc. submitted this application for the use of axitinib as second line treatment of metastatic renal cell carcinoma (RCC). About 80% of renal cell carcinomas are clear cell RCC and frequently have an allelic loss on chromosome 3p or mutational inactivation of the von Hippel-Lindau tumor suppression gene. The latter is characterized by vascularity of and the production of high levels of vascular endothelial growth factor (VEGF) by the tumor. Axitinib is a potent selective tyrosine kinase inhibitor of several VEGF receptors.

The adequate and well controlled study supporting this application was Protocol A4061032 entitled " Axitinib [AG-013736] as Second-Line Therapy for Metastatic Renal Cell Cancer: Axis Trial", a randomized, open label, multicenter study of axitinib starting at 5 mg twice daily v sorafenib starting at a dose of 400 mg twice daily in subjects that had failed one prior first line drug: sunitinib, bevacizumab plus IFN-alpha, temsirolimus or cytokines(s). The study continued until disease progression, intolerable toxicity or patient withdrawal. Disease status was followed first at 6 week intervals and then at 8 week intervals by tumor imaging.

The adverse reactions reported in the proposed package insert include: hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of hemoglobin or hematocrit, hemorrhage, gastrointestinal perforation, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, and animal abnormal fetal development.

The study was conducted at 175 sites in 22 countries and 723 subjects were randomized. Only a quarter of the subjects were from the US. Four clinical investigator sites, two foreign and two domestic were selected for inspection based on high enrollment.

II. RESULTS (by Site):

Name of CI	Protocol and # of Subjects	Inspection Date	Final Classification
Bernard Escudier Institut Gustave Roussy Service d'Immunotherapie 39 53 rue Camille Desmoulins VILLEJUIF CEDEX 94805 FRANCE	A4061032/ 19	October 3-7, 2011	Pending (Preliminary classification VAI)
Sergey A. Ivanov (Note: Original Investigator at site was Andrey Kaprin) Radiology Department 86 Profsoyusnaya str. Moscow 117997 RUSSIAN FEDERATION	A4061032/ 22	October 10-14, 2011	NAI
Robert John Motzer Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10065	A4061032/ 15	September 13-19, 2011	NAI
Marc Dror Michaelson Massachusetts General Hospital Cancer Center 55 Fruit Street Boston, MA 02114	A4061032/ 15	August 3-10, 2011	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Bernard Escudier**
Institut Gustave Roussy, Service d'Immunotherapie, 39 53 rue Camille Desmoulins
VILLEJUIF CEDEX, 94805 FRANCE

Note: Observations noted are based on a preliminary review of the Establishment Inspection Report (EIR); an inspection summary addendum will be generated if conclusions change upon full review of the EIR.

a. **What was inspected:** At this site 29 subjects were screened and 19 were enrolled into the study. The case histories of 15 enrolled subjects were reviewed. Visits were made to the radiology department and pharmacy.

b. **General observations/commentary:** The records appeared to be in good order. Based on preliminary information, the study appears to have been conducted adequately, except that nine subjects failed to sign an addendum to the informed consent form that updated information on side effects of the test article. This observation was the subject of a Form FDA 483 issued to the clinical investigator.

c. **Assessment of data integrity:** The data generated at this site appears to be acceptable/reliable in support of the pending application. The major objectionable finding relates to the documentation of updated consent and not to data integrity.

2. **Sergey Ivanov**
Radiology Department, 86 Profsoyusnaya str.
Moscow 117997, RUSSIAN FEDERATION

a. **What was inspected:** At this site 25 subjects were screened, and of which 22 subjects were entered into the trial. The case histories of ten subjects were reviewed.

b. **General observations/commentary:** There was no evidence of under reporting of adverse events. No significant regulatory violations were found and a Form FDA 483 was not issued.

c. **Assessment of data integrity:** The data generated at this site appears to be acceptable/reliable in support of the pending application.

3. **Robert Motzer**
Memorial Sloan-Kettering Cancer Center, 1275 York Avenue
New York, NY 10065

a. **What was inspected:** A total of 22 subjects were screened and of which 15 were entered into the study. The case histories of ten subjects were reviewed.

b. **General observations/commentary:** There was no evidence of under reporting of adverse events. No significant regulatory violations were found and a Form FDA 483 was not issued.

c. **Assessment of data integrity:** The data generated at this site appears to be acceptable/reliable in support of the pending application.

4. **Marc Mitchaelson**
Massachusetts General Hospital Cancer Center, 55 Fruit Street
Boston, MA 02114

a. **What was inspected:** At this site 15 subjects were screened, and of that number 14 were entered into the study.

b. **General observations/commentary:** No significant regulatory violations were found and a Form FDA 483 was not issued.

c. **Assessment of data integrity:** The data generated at this site appears to be acceptable/reliable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A total of four clinical sites were inspected for this application. For the clinical sites of Drs. Ivanov, Motzer, and Michaelson, there were no violations noted. For Dr. Escudier's site, the violations did not impact data integrity and the observations noted are based on a preliminary review of the EIR.

There were no significant regulatory findings relating to data integrity from any of the four sites inspected. The data may be used in the evaluation of this application. An inspection summary addendum will be generated if conclusions change upon full review of the EIR for Dr. Escudier's site.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROBERT S K YOUNG
12/20/2011

SUSAN LEIBENHAUT
12/20/2011

TEJASHRI S PUROHIT-SHETH
12/20/2011

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

Label and Labeling Review

Date	November 8, 2011
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strengths	Inlyta (Axitinib) Tablets, 1 mg and 5 mg
Application Type/Number	NDA 202324
Applicant	Pfizer, Inc.
OSE RCM #	2011-1316

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

1 INTRODUCTION

This review evaluates the container labels (b) (4) and insert labeling for Inlyta (Axitinib) Tablets for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Axitinib is the established name for the proposed proprietary name, Inlyta, which was found acceptable by DMEPA (OSE Review # 2011-1314 dated July 7, 2011).

1.2 PRODUCT INFORMATION

Inlyta (axitinib) tablets is a tyrosine kinase inhibitor which will be indicated for the treatment of metastatic renal cell carcinoma after disease progression on prior systemic therapy. The product will be available in 1 mg and 5 mg tablets. The intended starting dose for Inlyta will be 5 mg (one tablet) taken orally twice a day. The dose may be adjusted upward based on patient tolerance or downward based upon adverse drug effects to Inlyta. The other possible doses of Inlyta include 2 mg (2 x 1 mg tablets), 3 mg (3 x 1 mg tablets), 7 mg (2 x 1 mg and 1 x 5 mg tablets) or 10 mg (2 x 5 mg tablets) taken twice daily. Inlyta will be available in bottles containing 60 or 180 tablets which will be stored at room temperature (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 14, 2011 (see Appendix A)
- (b) (4)
- Insert Labeling submitted April 14, 2011 (no image)

(b) (4)

3 RESULTS AND DISCUSSION

The following sections describe DMEPA's evaluation of the proposed labels and labeling for Inlyta.

3.1 GENERAL COMMENT

The storage temperature is stated as (b) (4) and cites USP Controlled Room Temperature to support this statement. However, this temperature statement is not consistent with the definition of Controlled Room Temperature per USP.

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

3.2 CONTAINER LABEL [redacted]

A. Although the established name is at least half the size of the proprietary name, the proprietary name is presented in thick, black font whereas the established name is presented in thin black font and lacks prominence.

B. The dosage form, 'tablets' appears after the statement of strength which is not the traditional sequence for identifying drug products.

C. The logo, 'Pfizer' is presented in the same color scheme as the statement of strength and is located just above the proprietary name giving it more prominence than the important information used to identify the drug product.

D. The proprietary name is presented in upper case letters making this information difficult to read.

E. There is a blue banner containing the manufacturer's name which is located vertically across the container labels for both strengths. This presentation minimizes the impact of the color differentiation between the strengths and makes the container labels appear similar. This presentation may contribute to selection errors.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label [redacted] introduce vulnerability that can lead to medication errors. We recommend the following:

A. GENERAL COMMENTS

Revise the statement, [redacted] on the label and labeling to read "Store at 20°C to 25°C (68°F to 77°F)" to be in accordance with the USP definition of Controlled Room Temperature (see USP 10.30.60 *Controlled Room Temperature*).

B. CONTAINER LABELS (1 MG AND 5 MG)

1. We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name should also " . . . have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features". Therefore, we request you revise the established name accordingly.

2. The established name includes the active ingredient and the finished dosage form. We request you relocate the dosage form, 'tablets', to appear after axitinib.

3. Relocate the logo, ‘Pfizer’ which appears above the proprietary name, to the lower third of the label/labeling. Additionally, remove the name from the color block.

4. The proprietary name is presented in upper case letters (INLYTA). To increase its readability, revise the proprietary name so that it is presented in title case (Inlyta).

5. Increase the prominence of the four middle numbers in the NDC number as this information is how the pharmacist identifies the correct strength for drug products. For example, NDC 0069-0151-11 should be revised to read 0069-**0151**-11 for the 5 mg strength.

6. The blue banner containing the manufacturer name and logo that appears vertically across both the 1 mg and 5 mg labels minimizes the impact of the color differentiation between the strengths. To avoid selection errors, remove this banner.

7. Relocate the ‘Rx only’ statement to the bottom of the principal display panel.

(b) (4)

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/s/

DENISE V BAUGH
11/08/2011

LUBNA A MERCHANT
11/08/2011

CAROL A HOLQUIST
11/08/2011

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

NDA	202324
Generic Name	AG-013736 (Axitinib)
Sponsor	Pfizer Inc.
Indication	Advanced Renal Cell Carcinoma (RCC)
Dosage Form	Tablets
Drug Class	Kinase inhibitor of VEGF (vascular endothelial growth factor) receptors 1, 2, and 3
Therapeutic Dosing Regimen	5 mg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Submission Number and Date	SDN 001 14 Apr 2011
Review Division	DDOP / HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QTc intervals (i.e., >20 ms) were detected in the first 3 hours post-dose (i.e., up to the median T_{max} of axitinib) following a single dose of 5 mg axitinib in the absence and presence of 400 mg ketoconazole. The largest upper bounds of the 2-sided 90% confidence intervals (CI) for the mean changes from placebo (baseline-adjusted) were 5.2 and 8.4 ms in the absence and presence of 400 ketoconazole, respectively. However, due to study design limitations (e.g., lack of positive control), small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out.

This is a randomized, single-blinded, 2-way crossover ketoconazole drug-drug interaction study in 35 healthy subjects. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Axitinib in the Absence and Presence of 400 mg Ketocoanzole (FDA Analysis)

Treatment	Time* (hour)	ΔΔQTcS (ms)	90% CI (ms)
Axitinib 5 mg single dose	1	0.4	(-1.9, 5.2)
Axitinib 5 mg single dose + 400 mg Ketoconazole	2	-1.7	(3.7, 8.4)

*: ECGs were only collected up to 3 hours post-dose.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- No ketoconaozole-alone arm was included in the study. Ketoconazole is known to increase QT interval in a concentration-dependant manner. So the QT effect observed in ketoconazole + axitinib arm overestimates the QT effect of axitinib at boosted exposure level. No large changes in mean QTc interval (i.e., >20 ms) observed in the ketoconazole + axitinib arm provides additional assurance that at regular 5 mg dose level, there is no substantially elevated proarrythmic risk during the first 3 hours of dosing.
- The review division may request additional QT assessment as part of the PMR. For the objective of QT evaluation, there are several limitations of the current trial.
    - ECGs were collected up to 3 hours post-dose. Any potentially delayed QT effect was not investigated.
    - Axitinib exposure tested in the trial does not represent the maximum therapeutic exposure. With the coadministration of ketoconazole, the tested axitinib exposure is sufficient to represent the steady state axitinib exposure following a treatment of 5 mg axitinib twice daily. However, per the current label, axitinib can be dosed up to 10 mg b.i.d. The tested axitinib exposure is 50% lower than the steady state exposure using the maximum therapeutic dose.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert.

"12.2 Pharmacodynamics

(b) (4)

2.2 QT-IRT PROPOSED LABEL

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

The effect of a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole on QTc interval was evaluated in a randomized, single-blinded, 2-way cross over study in 35 healthy subjects. No large changes in mean QTc interval (i.e., >20 ms) from placebo were detected up to 3 hours post-dose (i.e., median T_{max} of axitinib). Because of study design limitations, small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out. The tested maximum axitinib exposure in the axitinib and ketoconazole group is 50% lower than the steady state maximum exposure following a dosing of 10 mg twice daily.

3 BACKGROUND

Also see previous QT-IRT reviews under IND 63662 dated July 8, 2010.

3.1 PRODUCT INFORMATION

Axitinib (AG-013736) is an oral, potent and selective inhibitor of VEGF (vascular endothelial growth factor) receptors 1, 2, and 3. The proposed indication for AG-013736 is for the treatment of patients with advanced renal cell carcinoma.

3.2 MARKET APPROVAL STATUS

Axitinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Please refer to QT-IRT review dated 8 July 2010.

Reviewer's comments: No meaningful effect of the study drug was seen either on the hERG assay or in the in vivo cardiovascular function study. However, only one concentration of the study drug was tested in the hERG assay and the study was not validated.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

"The safety of axitinib was investigated in 3655 subjects treated in 41 clinical studies (31 completed and 10 ongoing studies [including the continued access Study A4061008]). Of the 3655 subjects (excluding 29 subjects in continued access Study A4061008), 2507 received at least one dose of axitinib either as a single agent or as a component of combination therapy, 994 received a comparator, and 154 are being reported as blinded therapy. A total of 699 subjects received single-agent axitinib at a 5 mg b.i.d. starting dose in completed single-agent studies, including 537 (76.8%) subjects who received single-agent axitinib in the 4 completed advanced RCC studies (pivotal Phase 3 Study A4061032, and supportive Phase 2 Studies A4061012, A4061023, and A4061035).

"As a part of subject safety evaluation in clinical studies of axitinib, ECGs were recorded to assess the potential of axitinib to affect cardiac repolarization, as indicated by QT interval prolongation. Methods of analysis for ECGs are described in Section 2.7.4.1.1.2 of this summary.

Completed Single-Agent Studies with Triplicate ECG Measurements

"Triplicate ECG measurements were recorded in 3 completed single-agent studies (Studies A4061032 [pivotal Phase 3 RCC study; first 86 axitinib-treated subjects], A4061035 [Phase 2 RCC study in Japanese subjects; 64 subjects] and A4061044 [Phase 1 study in Japanese subjects with advanced solid tumors; 6 subjects]). A total of 152 axitinib-treated subjects in Studies A4061032, A4061035 and A4061044 had post-baseline triplicate QT measurements on Cycle 1/Day 15 (requested per protocol to be collected at expected time of peak concentration); 40 subjects had measurements performed at end of treatment; and 6 subjects had unplanned measurements. All subjects received a continuous axitinib starting dose of 5 mg b.i.d. As shown in Table 2, most subjects had QTcF and QTcB intervals <450 ms and/or changes from baseline that were less than 30 ms. Subjects who had a postbaseline absolute value >500 ms and/or a change from baseline >60 ms are listed in Appendix 1 Table 10.2.2.1. All 4 subjects were from the pivotal Phase 3 RCC Study A4060132. Two of the subjects had Grade ≥3 QTc prolongation (absolute QTc >500 ms) at Cycle 1 Day 15.

Table 2: QTc Outlier Results for Axitinib-Treated Subjects with Triplicate ECG Measurements in Studies A4061032, A4061035, and A4061044

Cycle 1/Day 15	QTcF n (%)	QTcB n (%)
Postbaseline QTc value, N	152	152
≥450 msec	9 (5.9)	16 (10.5)
≥480 msec	3 (2.0)	3 (2.0)
>500 msec	1 (0.7)	2 (1.3)
Change from baseline, N	152	152
≥30 msec	9 (5.9)	8 (5.3)
≥60 msec	4 (2.6)	2 (1.3)
End of Treatment		
Postbaseline QTc value, N	40	40
≥450 msec	1 (2.5)	6 (15.0)
≥480 msec	0	0
>500 msec	0	0
Change from baseline, N	40	40
≥30 msec	3 (7.5)	2 (5.0)
≥60 msec	0	0
Postbaseline QTc value, N		
Unplanned	6	6
≥450 msec	1 (16.7)	2 (33.3)
≥480 msec	0	0
>500 msec	0	0
Change from baseline, N	6	6
≥30 msec	0	0
≥60 msec	0	0

Source: Appendix 1 Table 10.2.1.1
N=Number of subjects; n = number of subjects meeting prespecified criteria; QTcB=Bazett's correction; QTcF=Fridericia's correction

Source: 2.7.4., Table 45, page 182.

"Two additional subjects had on-treatment increase in QTc greater than 60 ms; both of these subjects had sinus bradycardia at baseline.

Adverse Events Potentially Associated with an Effect on QT Interval - Completed Single-Agent Studies

"The incidences of AEs (serious and non-serious) that could reflect the clinical manifestation of a drug effect on QT interval are summarized, by event, in Table 3 for completed single-agent studies.

Table 3: Incidence of Adverse Events (All Causalities) Potentially Associated with an Effect on QT Interval - Completed Single Agent Studies

Event (Preferred Term)	Axitinib, (N=699) n (%)
Arrhythmia	2 (0.3)
Cardiac arrest	1 (0.1)
Convulsion	7 (1.0)
Syncope	10 (1.4)
Sudden death	0
Torsade de pointes	0
Ventricular fibrillation	0
Ventricular flutter	0
Ventricular tachycardia	0

Source: Appendix 1 Table 4.3.2.1
Includes Studies: A4060010, A4061011, A4061012, A4061014, A4061015, A4061022, A4061023, A4061032, A4061035, A4061044
N = number of subjects, n = number of subjects meeting prespecified criteria,

Source: eCTD, table 46, page 185

Combination Studies with Triplicate ECG Measurements

"Phase 3 Study A4061028 compared the combination treatment of axitinib + gemcitabine to placebo + gemcitabine in subjects with advanced pancreatic cancer. ECGs were performed at screening, on Day 15, Cycle 1, and at 28-day follow-up for the first 100 subjects randomized. Mean QTc results (QTcF and QTcB) and changes from baseline were similar for both treatment groups (A4061028 CSR, Section 9.5.2). There was 1 subject in the axitinib+gemcitabine treatment group with a clinically significant mean QTcF result (≥Grade 3) observed at the Follow-up visit, 21 days after the last dose of axitinib, when the subject was also experiencing severe hypokalemia (serum potassium 2.7 mmol/L).

Pooled Healthy Volunteer Studies with Single ECG Measurements

"Single ECG measurements were collected in completed healthy volunteer (Studies A4061003, A4061004, A4061006, A4061018, A4061021, A4061026, A4061033, A4061037, A4061047, A4061050, A4061052, A4061053 and A4061063). A total of 490 axitinib-treated subjects had available postbaseline QT measurements. The maximum post-dose QTc value in each subject was used for the summary tables and results described here. Most subjects had a QTcF interval of <450 ms: 23 subjects (4.7%) had a QTcF interval of ≥450 ms, 3 subjects (0.6%) had a QTcF interval of ≥480, and none had a QTcF interval ≥500 ms; 26 subjects (5.3%) had a change from baseline in QTcF interval ≥30 ms, and 1 subject (0.2%) had a change from baseline ≥60 ms. Seventeen subjects (3.5%) had a QTcB interval of ≥450 ms, and none had a QTcB interval of ≥480 ms; 29 subjects (5.9%) had a change from baseline in QTcB interval ≥30 ms, and 1 subject (0.2%) had a change from baseline ≥60 ms. The 2 subjects with a change from baseline of≥60 ms are listed in Appendix 1 Table 10.2.2.3. Summary statistics are provided in Appendix 1 Table 10.2.5.3. Subject A4061026 10011011 (Study A4061026) had a QTcB change of 61 ms from baseline (baseline 403 ms) following 8 days of rifampin dosing that was not considered clinically significant by the investigator. In

addition, Subject 10011056 (Study A4061018) had a QTcF change of 71 ms 2 hours after a single-dose of axitinib (baseline 412 ms). The QTcF value recovered to 414 ms 24 hours after dosing, this was not noted as clinically significant by the investigator.
"Of the 484 subjects who had normal (Grade 0 severity) QTcF results at baseline (≥450 ms), 465 (94.9%) remained at Grade 0, 17 (3.5%) had a postbaseline shift to Grade 1 (>450-470 ms), and 2 (0.4%) had a shift to Grade 2 (>470-500 ms or increase from baseline ≥60 ms) (Appendix 1 Table 10.2.3.3). Of the 6 subjects who had Grade 1 severity QTcF results at baseline, 1 (0.2%) remained at Grade 1, 2 (0.4%) had a postbaseline shift to Grade 2, and 3 (0.6%) had a postbaseline shift to Grade 0. No subjects experienced a result of Grade 3/4 severity. Similar results were seen using QTcB. Of 271 subjects with abnormal post-baseline ECG results, only 1 subject (0.2%) had an ECG result that was considered clinically significant based on investigator assessment (Appendix 1 Table 10.2.6.3)."

Reviewer's comments: In study A4061018, a healthy subject had a QTcF change from baseline of 71 ms 2 hours after a single dose of axitinib and returned to normal 24 hours after dosing.
In study A4060132, a single agent RCC study, four subjects had an increase in QTcF >60 ms and two of these subjects had a QTcF >500 ms. Events were ruled by the investigator as linked to study drug.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of AG-013736 clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the QT assessment plan in a Pre-NDA package under IND 63662, but did not review the study protocol. The sponsor submitted the study report PMAR-0074 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Population Pharmacokinetic/Pharmacodynamic Evaluation of the Effect of AG-013736 Alone, and in Combination with Ketoconazole, on QT Intervals in Healthy Volunteers

4.2.2 Protocol Number

A4061004

4.2.3 Study Dates

Start: 23-June-2004 / End: 14-August-2004

4.2.4 Objectives

The objective of this pharmacokinetic/pharmacodynamic (PK/PD) analysis was to characterize the effect of AG-013736, alone and in combination with ketoconazole, a potent cytochrome P450 (CYP) 3A4 inhibitor on the heart rate corrected QT interval length (QTc) when a single dose of AG-013736 is co-administered with repeated dosing of ketoconazole to healthy subjects using mixed-effects modeling

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, 2-way crossover study with at least 14-day washout between treatment periods. Prior to the start of the first treatment period, there were lead-in baseline (no medications administered) and placebo (administration of placebo at same time as AG-013736 dosing on subsequent days) days. Subjects were randomly assigned to receive two separate treatments (A=AG-013736, 5 mg p.o. on Day 1; and B= ketoconazole, 400 mg p.o. on Days 1-7 with a single AG-013736 5-mg p.o. dose on Day 4) in a crossover design. In both treatments, AG-013736 was dosed in the morning after an overnight fast of at least 8 hours. There was a washout period of at least 14 days between the 2 treatments.

4.2.5.2 Controls

There was no moxifloxacin used in this study. No ketoconazole-alone arm was included in the study.
Reviewer's comment: Ketoconazole is known to increase QT interval in a concentration-dependant manner. So the QT effect observed in ketoconazole + axitinib arm overestimates the QT effect of axitinib at boosted exposure level. No large changes in mean QTc interval (i.e., >20 ms) observed in the ketoconazole + axitinib arm provides additional assurance that at regular 5 mg dose level, there is no substantially elevated proarrythmic risk during the first 3 hours of dosing.

4.2.5.3 Blinding

This study was blinded only to subjects, not to study personnel or sponsor.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

32 subjects were randomly assigned to receive two separate treatments (A=AG-013736, 5 mg p.o. on Day 1; and B=ketoconazole, 400 mg p.o. on Days 1-7 with a single AG-013736, 5-mg p.o. dose on day 4) in a crossover design. There was a washout period of at least 14 days between the 2 treatments (Table 4).

Table 4: Treatment Groups and Regimens

Treatment Period	Drug	Form	Route	Regimen	Lot Number/FID Number
Placebo	Placebo[a]	Tablet, white oval	Oral	Single 0-mg AM dose on Day –1	598.122/F-AG013736-005.1
A	AG-013736	Tablet, white oval	Oral	Single 5-mg AM dose on Day 1 (Treatment A) and Day 4 (Treatment B)	SDM03001LJ/F-AG013736-008.0
B	Ketoconazole[b] (Nizoral, Janssen)	Tablet	Oral	Single 400-mg AM dose on Days 1-7	93P0241E/NA
	AG013736	Tablet, white oval	Oral	Single 5-mg AM dose on Day 4	SDM03001LJ/F-AG013736-008.0

Data source: Appendix A1; source documents.
Note: NA = not available (study site supplied ketoconazole)
[a] Placebo tablets matched the AG-013736 tablets.
[b] Ketoconazole was supplied by the study site as commercially available tablets containing 200 mg of ketoconazole.

(Source: Sponsor's Study Report A4061004, Table 3. on Page 36)

Reviewer's Comment: The mean elimination half-life after single-dose oral administration of 5 mg AG-013736 is ~3 hours. A washout period of 14 days was sufficient in order to avoid carry-over effects of AG-013736*/ketoconazole.*

4.2.6.2 Sponsor's Justification for Doses

The sponsor did not provide clear justification for dose in the study report.

Reviewer's Comment: The studied 5-mg dose is the to-be-marketed starting dose. However, the exposure at the single dose is expected to be lower than that at steady state at 5 mg b.i.d. (with geometric mean accumulation ratio of 1.4). Moreover, for patients who can tolerate the starting 5-mg b.i.d. dose well, they may have their dose increased to a maximum of 10 mg b.i.d. which may result in exposure at steady state could be ~3-fold that at 5 mg.
The current single dose with ketoconazole scenario resulted in 100% higher AUC and 50% fold higher C_{max} compared to that at a single dose of AG-013736 alone. Therefore, the scenario studied in the current QT study provided an exposure which might be 50% lower than that at 10 mg b.i.d. at steady state without CYP3A4/5 inhibitors.

4.2.6.3 Instructions with Regard to Meals

AG-013736 or placebo dose was administered in the morning after an overnight fast of at least 8 hours. Food and beverages were permitted 4 hours after AG-013736 or placebo dosing. Water could have been consumed *ad libitum*. Ketoconazole doses in Treatment B were administered with breakfast once daily in the morning, except on Day 4. On Day 4 of Treatment B, ketoconazole was administered simultaneously with AG-013736 after an overnight fast of at least 8 hours. All study medications (placebo, AG-013736 and ketoconazole) were administered with 240 mL ambient temperature water. In order to standardize conditions, all subjects were required to refrain from lying down (except for blood pressure, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

Reviewer's Comment: The effect of food on PK was not substantial. Axitinib 5 mg commercial tablets with a high-fat, high-calorie meal were associated with 19% higher AUC (90% CI 1.06-1.34) and 11% higher C_{max} (90% CI 0.95 - 1.30) compared to overnight fasting. Therefore the instructions regarding to meals appear to be acceptable.

4.2.6.4 ECG and PK Assessments

PK Assessment:

During Treatment A, blood samples for PK were collected on Day 1 at 0 (predose), 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours; on Day 2 at 24 and 36 hours; and on Day 3at 48 hours after AG-013736 dosing.

During Treatment B, blood samples were collected on Day 4 at 0 hours (predose) and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours after dosing; on Day 5 at 24 and 36 hours after dosing; on Day 6 at 48 hours after dosing; on Day 7 at 72 hours after dosing; and on Day 8 at 96 hours after dosing.

ECG Assessment:

Time-matched, triplicate, 12-lead ECGs were performed at 1, 2, and 3 hours after dosing at baseline (Day -2) and on specific days during Placebo (Day -1) and Treatment Periods A (Day 1) and B (Day 4).

Reviewer's Comment:

*The ECG/PK sampling schedule is able to cover the T_{max} in the current study (median [range] is 1.5 [1.0, 3.0] hours for*AG-013736 alone and 2.00 [1.00, 4.13] hours for AG-013736 + ketoconazole *based on the current study report). However, it may not be able to cover the potential delayed effect.*

4.2.6.5 Baseline

The sponsor used time-matched baseline in the primary analysis.

4.2.7 ECG Collection

Time-matched ECGs, in triplicate, were obtained at 1, 2, and 3 hours after dosing of axitinib alone (5-mg single-dose), corresponding placebo, matching time-matched baseline, ketoconazole alone (steady-state dose of 400 mg once daily [q.d.]), or axitinib (5-mg single-dose) in combination with ketoconazole (steady-state dose of 400 mg q.d.). A fully automated approach was used for the ECG collections. A centralized ECG collection system, a service provided by a third party vendor, (b) (4) , was utilized for this study. Standardized machines with consistent algorithms and software were provided by (b) (4) to the clinical site, and ECGs were transmitted electronically to (b) (4) on a daily basis. Machine-read ECGs were used for the analysis provided and potential bias due to differences in readers (using manual over-read) were avoided.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Baseline demographic data for the study subjects in Groups A and B are provided in Table 5.

Table 5: Demographics and Baseline Characteristics

Demographics and Baseline Status	Group A→B n = 20	Group B→A n = 15	Total N = 35
Sex, n (%)			
Male	18 (90.0)	14 (93.3)	32 (91.4)
Female	2 (10.0)	1 (6.7)	3 (8.6)
Race, n (%)			
Asian	0	1 (6.7)	1 (2.9)
Black	2 (10.0)	2 (13.3)	4 (11.4)
Caucasian	10 (50.0)	9 (60.0)	19 (54.3)
Hispanic/Latino	7 (35.0)	3 (20.0)	10 (28.6)
Other	1 (5.0)	0	1 (2.9)
Age (y)			
n	20	15	35
Mean	35.1	34.9	35.0
Standard deviation	11.5	11.0	11.1
Median	33.5	32.0	32.0
Minimum	19	21	19
Maximum	54	53	54
Systolic Blood Pressure (mm Hg)			
n	20	15	35
Mean	114.8	113.7	114.3
Standard deviation	9.6	8.1	8.9
Median	114.0	112.0	114.0
Minimum	96	98	96
Maximum	135	135	135
Diastolic Blood Pressure			
n	20	15	35
Mean	69.8	71.9	70.7
Standard deviation	8.4	5.9	7.4
Median	67.5	72.0	70.0
Minimum	58	62	58
Maximum	86	83	86

Data source: Clinical Study Report; Protocol A4061004.
Note: LS means estimates come from a mixed model using treatment, period, and treatment sequence as explanatory variables, with random effects for treatment sequence within subject.
n = number of subjects in a specified subpopulation; N = number of subjects in the total population. Group A→B = Treatment A followed by Treatment B; Group B→A = Treatment B followed by Treatment A. (Subjects in Treatment A received a 5-mg dose of AG-013736 in the morning of Day 1 followed by a 14-day washout. Subjects in Treatment B received 400 mg of ketoconazole in the morning for 7 consecutive days with a single 5-mg dose of AG-013736 administered with the ketoconazole on Day 4.)

Source: CSR, Table 1, page 13.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

A study-specific QT correction (QTcS) was used to analyze the data. No substantial QTc interval prolongation for any of the treatment groups was detected (Table 6).

Table 6: Summary of the Highest Mean Placebo-Corrected Change from Baseline

Correction	Value	Highest mean placebo-corrected change from baseline* (90% Confidence Interval)		
		AG-013736 alone	Ketoconazole alone	AG-013736 with keto
Fridericia's (QTcF)	0.33	6.1 (1.8 – 10.5)	-5.7 (-8.7 – -2.7)	9.1 (6.7 – 11.5)
Bazett's (QTcB)	0.50	-0.7 (-4.2 – 2.8)	4.2 (1.3 – 7.1)	4.4 (1.9 – 6.9)
Study-Specific (QTcS)	0.44	2.2 (-1.9 – 5.4)	0.7 (-2.2 – 3.5)	6.1 (3.7 – 8.4)_

* highest value reported at 1, 2, or 3 hrs post dose

(Source: Sponsor's Study Report pmar-00074, Table 4. on Page 21)

Reviewer's Comments: Sponsor's conclusions are reasonable. The reviewer performed independent analyses in section 5.2.

4.2.8.2.2 Categorical Analysis

The categorical evaluation of the maximum absolute QTcF and QTcB intervals indicated that none of the male or female subjects had values >450 or >470 ms across all treatments, respectively. Similarly, the maximum QTcF and QTcB change from baseline did not exceed the clinically significant category of 60 ms for any subject across all treatments.

4.2.8.3 Safety Analysis

The sponsor did not report safety data.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 7 and Figure 1. AG-013736 exposure was increased in the presence of ketoconazole, as shown by the geometric mean ratios for $AUC_{0-\infty}$ and C_{max} of 2.06 (90% CI: 1.84, 2.30) and 1.50 (90% CI: 1.33, 1.70), respectively.

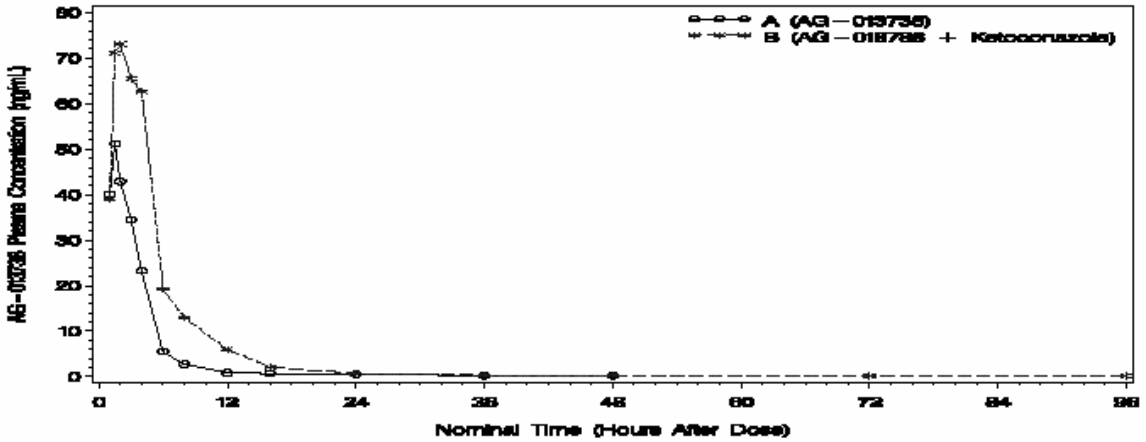
Table 7: Summary of Plasma Pharmacokinetic Parameters of AG-013736

PK Parameter (unit)	Geometric LS Mean (95% CI)		Statistical Comparison ([AG-013736 + ketoconazole]/ [AG-013736])	
	AG-013736 (n=31)	AG-013736 + Ketoconazole (n=28)	Geometric LS Mean Ratio	90% CI
$AUC_{0-\infty}$ (ng*h/mL)	196.7 (162.0, 238.8)	404.8 (332.3, 493.2)	2.06	1.84, 2.30
AUC_{last} (ng*h/mL)	193.8 (159.9, 234.9)	401.9 (330.1, 489.3)	2.07	1.86, 2.31
C_{max} (ng/mL)	51.03 (43.91, 59.30)	76.72 (65.59, 89.74)	1.50	1.33, 1.70

Source: Summary Tables 13.5.1.1.3, 13.5.1.2.3, 13.5.1.3.3, and 13.5.1.4.
LS = least squares; CI = confidence interval; ng = nanogram(s); h = hour(s); mL = milliliter(s).

(Source: Sponsor's Study Report A4061004, Table 13. on Page 56)

Figure 1: Median AG-013736 Plasma Concentrations Versus Nominal Time For the Axitinib and Axitinib + Ketoconazole Treatments

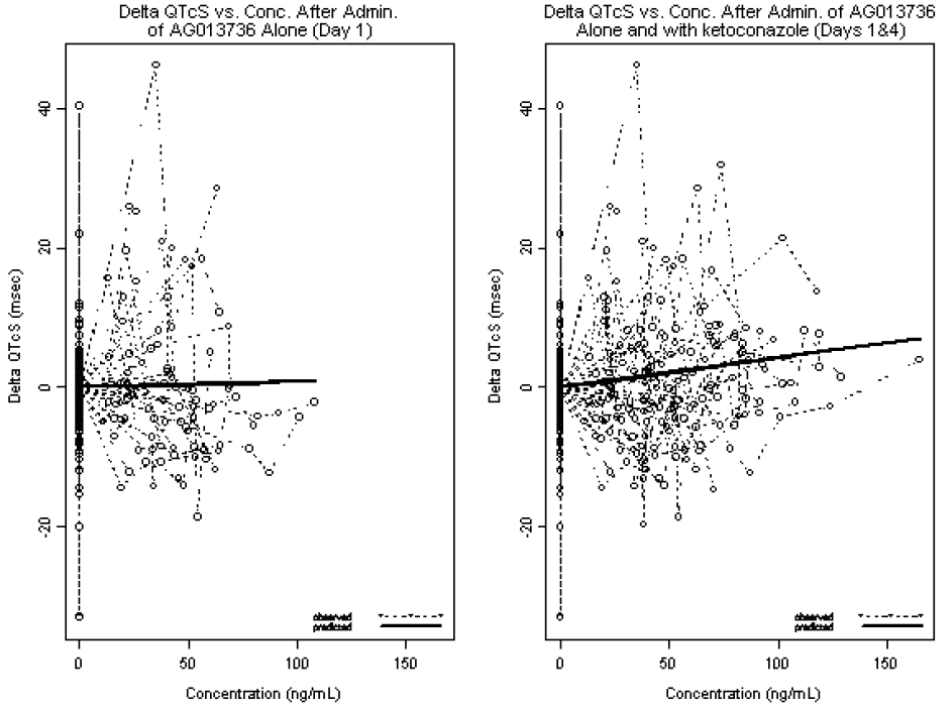


(Source: Sponsor's Study Report A4061004, Figure 1. on Page 55)

4.2.8.4.2 Exposure-Response Analysis

The concentration-ΔQTc analysis results show the relationship between the change from baseline in QTcS and AG-013736 concentrations is relative flat without ketoconazole (Figure 2).

Figure 2: Changes (ms) from Baseline in QTcS versus AG-013736 Concentrations



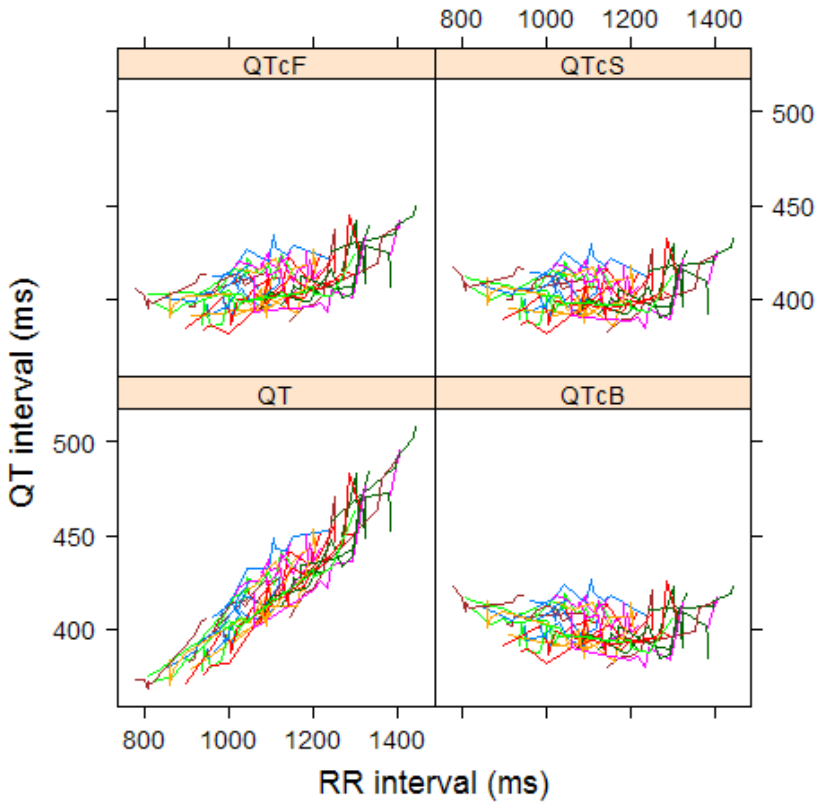
(Source: Sponsor's Study Report pmar-00074, Figure 4. on Page 24)

Reviewer's Analysis: The reviewer performed independent analyses to explore the relationship between AG-013736 concentration and ΔΔQTc (see section 5.3). Consistent with the sponsor's results, the slope of the concentration-response relationship is relatively flat and non-significant from zero.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

Figure 3: QT, QTcB, QTcF, and QTcS vs. RR (Each Subject's Data Points are Connected with a Line)



The Study-Specific correction displayed the most horizontal pattern, indicating that it was the best correction for heart rate effect (Figure 3). Therefore, the primary analysis used the Study-Specific correction method.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for AG-013736

The reviewer used mixed model to analyze the ΔΔQTcS effect. The analysis results are listed in Table 8 and Table 9. The largest upper bound of the two-sided 90% CI for

ΔΔQTcS is 8.4 ms. There was no moxifloxacin arm in the study so the assay sensitivity can not be established.

Table 8: Analysis Results of ΔQTcS and ΔΔQTcS for Treatment Group = Axitinib 5 mg

	Axitinib 5 mgQD ΔQTcS	Placebo ΔQTcS	ΔΔQTcS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	0.4	-1.3	1.7	(-1.9, 5.2)
2	0.0	-1.7	1.7	(-1.4, 4.8)
3	-0.2	-0.4	0.2	(-3.2, 3.6)

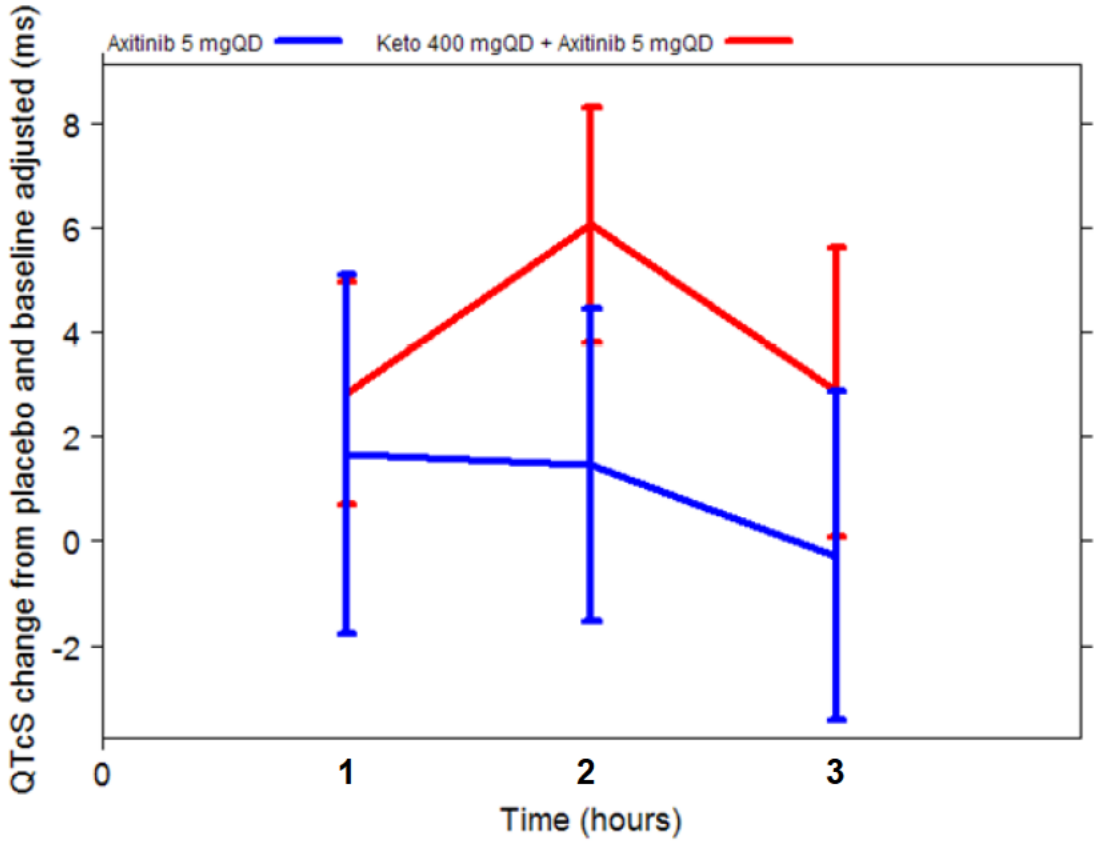
Table 9: Analysis Results of ΔQTcS and ΔΔQTcS for Treatment Group = Keto 400 mg QD + Axitinib 5 mg

	Keto 400 mgQD + Axitinib 5 mgQD ΔQTcF	Placebo ΔQTcF	ΔΔQTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	1.6	-1.3	2.8	(0.4, 5.2)
2	4.3	-1.7	6.1	(3.7, 8.4)
3	1.6	-0.4	1.9	(-2.2, 6.1)

5.2.1.2 Graph of ΔΔQTcS Over Time

Figure 4 displays the time profile of ΔΔ QTcS for different treatment groups.

Figure 4: Mean and 90% CI ΔΔQTcS Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.3 Categorical Analysis

In this study, there is no subject's QTcS was above 450 ms. Table 10 lists the categorical analysis results for ΔQTcS. No subject's change from baseline was above 60 ms.

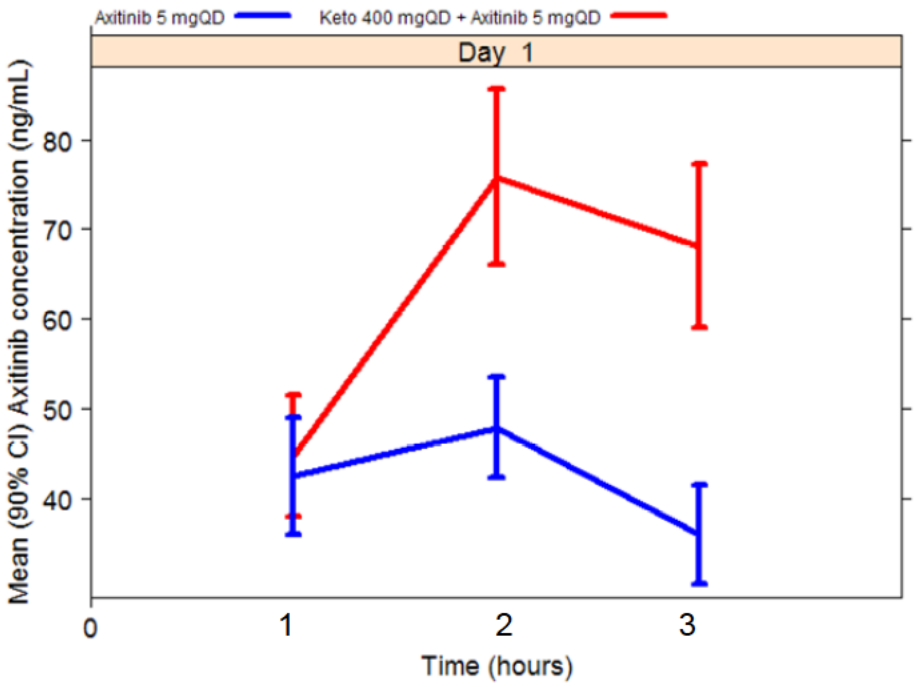
Table 10: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	35	105	34 (97%)	104 (99%)	1 (2.9%)	1 (1%)
Axitinib 5 mg	32	96	31 (97%)	95 (99%)	1 (3.1%)	1 (1%)
Keto 400 mg QD + Axitinib 5 mg	28	84	27 (96%)	83 (99%)	1 (3.6%)	1 (1.2%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 5.

Figure 5: Mean Concentration-time Profiles for Axitinib 5 mg (Blue Line) And Ketoconazole 400 mg QD + Axitinib 5 mg (Red Line)



The relationship between ΔΔQTcS and AG-013736 concentrations is visualized in Figure 6 with no significant exposure-response relationship after adjusting ketoconazole QT effect (β_1= 0.055 with p-value: 0.07).

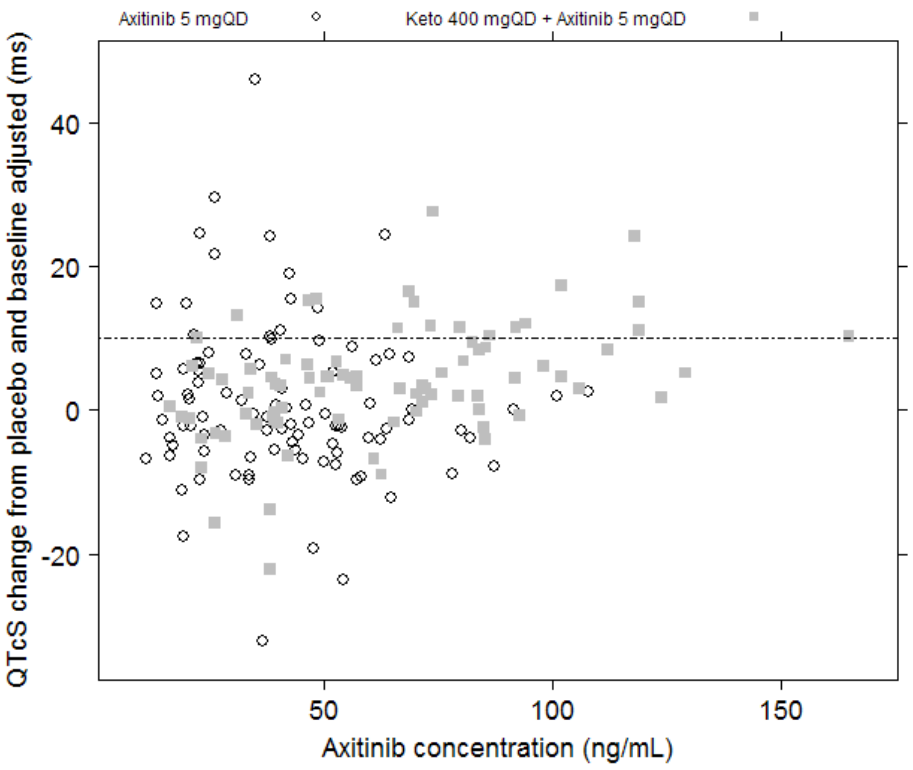
The structural model for concentration-QT analysis is shown in Equation 1.

$\Delta\Delta QTcS = \beta_0 + \beta_1 \times Conc + \beta_2 \times TrT$ (Equation 1)

(Trt = 1, when ECGs were collected from ketoconazole + AG013736. Otherwise Trt = 0)

Where β_0 is the intercept, β_1 is the concentration-QT slope for AG-013736, and β_2 represents the mean QT effect for ketoconazole. Trt is a dichotomous variable with the value of 1 when ECGs were collected from ketoconazole +AG-013736 group.

Figure 6: ΔΔ QTcS vs. AG-013736 Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Sponsor did not report safety data.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR Interval

Five subjects had a PR >200 ms, in all cases increase in PR was ≤ 10% over baseline and none had a PR >216 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The recommended starting dose for axitinib in all patients (pts) is 5 mg twice daily (BID). Dose increase or reduction is recommended based on individual safety and tolerability. In the subset of patients (pts) (~ 30%) who are able to tolerate study drug, the dose may be increased incrementally from 5 mg BID to 7 mg BID and subsequently to a maximum of 10 mg BID	
Maximum tolerated dose	5 mg BID oral dose	
Principal adverse events	According to the latest (August 2009) Investigator Brochure, for single-agent axitinib, the most common adverse events reported from 364 cancer pts regardless of causality included fatigue (227 pts, 62.4%), diarrhea (pts, 54.1%), hypertension (173 pts, 47.5%), anorexia (15 pts, 41.2%), nausea (139 pts, 38.2%), dysphonia (129 pts, 35.4%), headache (104 pts, 28.6%), palmar-plantar erythrodysaesthesia syndrome (104 pts, 28.6%), weight decreased (100 pts, 27.5%), cough (89 pts, 24.5%), dyspnoea (88 pts, 24.2%), constipation (86 pts, 23.6%), arthralgia (83 pts, 22.8%), vomiting (77 pts, 21.2%), stomatitis (76 pts 20.9%), and pain in extremity (73 pts, 20.1%). Additionally, proteinuria was reported as an adverse event in 72 pts (19.8%). Grade 3+ events occurred most frequently for hypertension (68 pts, 18.7%) and fatigue (52 pts, 14.3%).	
Maximum dose tested	**Single Dose**	30 mg [n=6 pts with various solid tumors, First In Human (FIH) study A4060010]
	Multiple Dose	30 mg BID [n=1 pt with solid tumor (who was subsequently dose-reduced to 10 mg BID); FIH study A4060010]
Exposures Achieved at Maximum Tested Dose	**Single Dose**	Geometric mean C_{max} (CV%) = 314 (66%) ng/mL Geometric mean AUC_{inf} (CV%) = 2049 (52%) ng h/mL [n=6, 30 mg single-dose, Study A4060010]
	Multiple Dose	Cmax = 117 ng/mL AUC_{0-12} = 918 ng h/mL [n=1, 30 mg BID, Day 15, Study A4060010)
Range of linear PK	PK linear between 5-10 mg following single-dosing [n=6 pts in study A4061044 and n=14 healthy volunteers (HV) in study A4061050]	
Accumulation at steady state	Geometric mean accumulation ratio on day 15 versus day 1, at 5 mg BID = 1.40 (CV 26%) [n=6 pts, Study A4061044]	
Metabolites	The major circulating metabolites in human plasma are an N-glucuronide (M7) and a sulfoxide (M12). M7 and M12 are inactive (approximately 8000-fold and 400-fold less in vitro potency, respectively, against VEGFR-2 compared to axitinib).	
Absorption	**Absolute/Relative Bioavailability**	Absolute oral bioavailability 58% (CV 45%) [n=16 HVs, study A4061007]
	Tmax	• Median 3.0 hr (range 2.0 – 6.0 hr) in fed state [n=30 HVs, 5 mg single dose, study A4061053] • Metabolites (inactive) not monitored clinically
Distribution	**Vd/F or Vd**	Geometric mean Vz=68L (CV 23%); [n=16 HV receiving intravenous dosing, Study A4061007]
	% bound	Geometric mean fraction unbound, fu = 0.00405 (CV 25%) [n=8 HVs, 5 mg single dose study A4061036]
Elimination	**Route**	• Hepatobiliary elimination: metabolized primarily by CYP3A4/5 and to a lesser extent, CYP1A2, CYP2C19 and UGT1A1. Following oral administration of a 5 mg radioactive dose of

		axitinib, 30-60% of radioactivity recovered in feces • No renal elimination of unchanged drug; 23% of administered radioactivity recovered in urine [n=8 HVs, 5-mg single dose, study A4061003]
	Terminal t½	Geometric mean t½ = 2.97 hr (CV 41%) [n=29 HVs, 5 mg single dose, study A4061053].
	CL/F or CL	Geometric mean CL=21 (CV 44%) [n=16 HV receiving intravenous dosing, Study A4061007]
Intrinsic Factors	**Age**	Pending final pooled population PK analysis
	Sex	Pending final pooled population PK analysis
	Race	Pending final pooled population PK analysis. Similar PK observed in Chinese, Japanese and Caucasian subjects.
	Hepatic & Renal Impairment	AUC and Cmax in subjects with mild (Child-Pugh Class A; n=8) hepatic impairment comparable to those with normal hepatic function (n=8). AUC and Cmax 1.95-fold and 1.28 fold higher, respectively, in subjects with moderate (Child-Pugh Class B; n=8) hepatic impairment compared to those with normal hepatic function. [n=24 total subjects, study A4061036] Axitinib not renally eliminated. Results from pooled final population PK analysis pending.
Extrinsic Factors	**Drug interactions**	Ketoconazole (potent CYP3A4/5 inhibitor), 400 mg once daily (QD) for 7 days, increased the mean axitinib AUC 2-fold (90%CI 1.84-2.30) and Cmax 1.5-fold (90% CI 1.33-1.70) [5-mg single dose, n=32 HVs, study A4061004] Rifampin (potent CYP3A4/5 inducer), 600 mg QD for 9 days, reduced the mean axitinib AUC by 80% (90% CI 0.18-0.24) and Cmax by 70% (90% CI 0.24-0.35) [5-mg single dose, n=40 HVs, study A4061026].
	Food Effects	Axitinib 5-mg commercial tablets with a high-fat, high-calorie meal were associated with 19% higher AUC (90% CI 1.06-1.34) and 11% higher Cmax (90% CI 0.95 - 1.30) compared to overnight fasting. With a moderate-fat, standard-calorie meal axitinib AUC was decreased by 10% (90% CI 0.796 – 1.006) and Cmax was decreased by 16% (90% CI 0.78-0.99) compared to overnight fasting [n=30 HVs, study A4061053].
Expected High Clinical Exposure Scenario	The worst-case scenario would be when axitinib is administered with potent CYP3A4/5 inhibitors, which would result in 2-fold higher (supra-therapeutic) AUC and 1.5 fold higher Cmax (based on ketoconazole DDI study A4061004 in HVs). Potent CYP3A4/5 inhibitors are not permitted in ongoing studies In the proposed draft US package insert, selection of an alternate concomitant medication with no or minimal enzyme inhibition potential will be recommended. If alternative treatment cannot be administered, an axitinib dose adjustment will be recommended.	

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

/s/

HAO ZHU
07/21/2011

JIANG LIU
07/21/2011

MONICA L FISZMAN
07/21/2011

NORMAN L STOCKBRIDGE
07/21/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 202324 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Inlyta Established/Proper Name: axitinib Dosage Form: tablet Strengths: 1 mg and 5 mg		
Applicant: Pfizer Inc. Agent for Applicant (if applicable):		
Date of Application: April 14, 2011 Date of Receipt: April 14, 2011 Date clock started after UN:		
PDUFA Goal Date: February 14, 2012	Action Goal Date (if different):	
Filing Date: Day 74 = June 27, 2011	Date of Filing Meeting: May 13, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1= NME		
Proposed indication(s)/Proposed change(s): Kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma.		

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

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 063662	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	Y			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	Y			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	Y			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	**X**			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

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

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

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			Yes, attached to the form.
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	**X**			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***				All via eDR.

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	**X**			

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

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	**X**			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	**X**			Submitted 4/14/2011, DARRTS category correct
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***	**X**			Called Pharmacovigilance Plan-Risk Minimization plan
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ (b) (4) ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	**X**			
Is the PI submitted in PLR format?[4]	**X**			

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

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

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, (b) (4) and immediate container labels) consulted to DDMAC?	**X**			Consult sent 4/25/2011
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	**X**			Consult sent 4/25/2011
(b) (4) immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	**X**			Consult sent 4/25/2011
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	**X**			QT-IRT consult sent 4/21/2011
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 5/17/2007 6/19/2008 = CMC EOP2 ***If yes, distribute minutes before filing meeting***	**X**			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 2/3/2009; 1/27/2010, 7/14/2010, 2/28/2011 ***If yes, distribute minutes before filing meeting***	**X**			
Any Special Protocol Assessments (SPAs)? **Date(s):** Renal Cell Ca 4/17/2008 ***If yes, distribute letter and/or relevant minutes before filing meeting***	**X**			

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 13, 2011

BLA/NDA/Supp #: NDA 202324

PROPRIETARY NAME: INLYTA

ESTABLISHED/PROPER NAME: axitinib

DOSAGE FORM/STRENGTH: tablet; (b) (4) 1 mg and 5 mg

APPLICANT: Pfizer Inc., 10646 Science Center Drive, San Diego, CA 92121

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
Kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma.

BACKGROUND: Axitinib is a selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor VEGFR-1, VEGFR-2, and VEGFR-3. Axitinib inhibited the phosphorylation of VEGFR-2 in xenografts tumor vasculature that expressed the target in vivo and produced tumor growth delay, regression, and inhibit metastases in many experimental models of cancer. The NDA submitted on April 14, 2011 includes data from Phase 3 RCC Study A4061032 and supportive Phase 2 RCC Studies A4061012, A4061023, and A4061035; the associated IND is 63662. The safety data is included for the above studies, cut-off date August 31, 2010. Other studies to support safety included monotherapy studies, axitinib plus chemotherapy combination studies and studies in healthy volunteers. Pfizer does agree to submit the 4-month safety update on August 1, 2011.
The drug substance manufacturing site identified for this NDA, is located in Ireland (Pfizer Ireland Pharmaceuticals); the drug product manufacturing site is located in Germany (Pfizer Manufacturing Deutschland GmbH).
Pfizer is proposing Pharmacovigilance Plan due to safety concerns for axitinib in advanced RCC. Pfizer identified the following known risks: arterial thromboembolic events, elevations of hemoglobin or hematocrit; gastrointestinal perforation, hemorrhage, hypertension, proteinuria, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, venous thromboembolic events and the 'potential' risks: hepatic disorders and wound healing complications. These events are typical of the other anti-VEGF for advanced RCC. Pfizer also outlines the various drug-drug interactions.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Yes
	CPMS/TL:	Alice Kacuba	No
Cross-Discipline Team Leader (CDTL)	John Johnson		Yes
Clinical	Reviewer:	Amy McKee	Yes
	TL:	John Johnson Amna Ibrahim (Deputy DD)	Yes Yes
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sarah Schrieber	Yes
	TL:	Qi Liu	No
Biostatistics	Reviewer:	Somesh Chattopadhyay	Yes
	TL:	Shenghui Tang	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Anwar Goheer	Yes
	TL:	Whitney Helms	No
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Amit Mitra and Jean Tang	No
	TL:	Hari Sarker	Yes
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Latonia Ford	No
	TL:	Barbara Fuller	No
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	PharmacoGenomics: Rosane Charlab Orbach; TL= Issam Zineh		No
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☒ YES Date if known: December 2011 ☐ NO ☐ To be determined Reason: NME, unusual toxicity,

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office, Dr. Pazdur

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

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

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

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

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/s/

LISA M SKARUPA
06/21/2011

DSI CONSULT: Request for Clinical Inspections

Date: May 17, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Robert Young, M.D., CDER/OC/DSI/GCPBII
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Amy McKee, M.D./Clinical Reviewer/Division of Drug Oncology Products*
John Johnson, M.D./Clinical Team Leader/DDOP

From: *Lisa Skarupa, Regulatory Health Project Manager/DDOP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 202-324
Applicant/ Applicant contact information (to include phone/email): Pfizer
Drug Proprietary Name: Axitinib (AG-013736)
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Renal Cell Carcinoma

PDUFA: 2/14/2012
Action Goal Date: 2/14/2012
Inspection Summary Goal Date: 12/2011

II. Protocol/Site Identification

DSI Consult
version: 5/08/2008

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 1106: Bernard Escudier Institut Gustave Roussy / Service d'Immunotherapie 39 53 rue Camille Desmoulins VILLEJUIF CEDEX 94805 FRANCE	A4061032	19	Second-Line Therapy for Metastatic Renal Cell Cancer
Site 1098: Dr. Piotr Tomczak Klinika Onkologii, Szpital Kliniczny Przemienienia Panskiego Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu ul. Lakowa 1/2 Poznan 61-878 POLAND OR Site 1062: Sergey A. Ivanov Radiology 86 Profsoyusnaya str. Moscow 117997 RUSSIAN FEDERATION	A4061032	26 22	Second-Line Therapy for Metastatic Renal Cell Cancer
Site 1024: Dr. Robert John Motzer Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York NY 10065	A4061032	15	Second-Line Therapy for Metastatic Renal Cell Cancer
Site 1087: Marc Dror Michaelson Massachusetts General Hospital Cancer Center 55 Fruit Street (Yawkey) Boston MA 02114	A4061032	15	Second-Line Therapy for Metastatic Renal Cell Cancer

III. Site Selection/Rationale

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

Rationale for DSI Audits

The three international sites were among the sites with the highest enrollment overall in the study, and we are requesting two international sites as only approximately 25% of the patients enrolled on the Phase 3 trial were from North America. We are requesting an audit of the site in France and either the site in Russia or Poland. The domestic sites were among the domestic sites with the highest enrollment.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects domestically
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections: NA

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): Enrollment of large numbers of study subjects. This would be the first approval of this new drug, and as most of the limited experience with this drug has been at foreign sites with only 25% of enrolled patients from North America, it would be desirable to include at least two foreign sites in the DSI inspections to verify the quality of conduct of the study.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

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

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Lisa Skarupa, RPM, at 301-796-2219 or Amy McKee, M.D., at 301-796-3909.

Concurrence: (as needed)
Robert Justice_____ OND Division Director

John Johnson _____ Medical Team Leader
Amy McKee _____ Medical Reviewer

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

/s/

LISA M SKARUPA
05/17/2011

AMY E MCKEE
05/17/2011

JOHN R JOHNSON
05/19/2011

ROBERT L JUSTICE
05/19/2011

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202324/000	**Action Goal:**	
S Date:	14-APR-2011	**District Goal:**	15-AUG-2011
Regulatory:	14-FEB-2012		
Applicant:	PFIZER	**Brand Name:**	INLYTA
	10646 SCIENCE CENTER DR	**Estab. Name:**	AXITINIB
	SAN DIEGO, CA 92121	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; TABLET; AXITINIB; 1MG 002; TABLET; AXITINIB; 5MG	

Application Comment: THIS APPLICANT CONTACT QBD ELEMENTS. THE ESTABLISHMENTS LISTED IN THIS APPLICATION ARE ALSO IDENTIFIED IN ANOTHER APPLICATION WITH THIS SPONSOR (NDA 202570 (b) (4) . THE INSPECTIONS CAN BE COORDINTATED TO ACCOMMODATE BOTH APPLICATIONS AT ONE TIME. (on 18-APR-2011 by D. HENRY () 301-796-4227)

WHEN SCHEDULING THE INSPECTION, CONTACT ONDQA FOR PARTICIPATION DURINNG THE INSPECTION. (on 19-APR-2011 by D. HENRY () 301-796-4227)

FDA Contacts:	D. HENRY	Project Manager		301-796-4227
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation:	ACCEPTABLE	on 04-DEC-2011	by M. STOCK	(HFD-320)	301-796-4753

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: (b) (4)

Establishment Comment:

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-APR-2011				HENRYD
SUBMITTED TO DO	21-APR-2011	**Product Specific**			SMITHDE
QBD ELEMENTS					
ASSIGNED INSPECTION TO IB	25-APR-2011	**Product Specific**			PHILPYE
INSPECTION PERFORMED	(b) (4)		(b) (4)		BRUCE.MCCULLOUGH

This was a drug CGMP and pre-approval inspection (b) (4), requested by HFD-325 and DFI (FACTS assignment ID # 5422798). Pre-approval coverage was for NDA 202324/000, Axitinib 1mg and 5mg Tablets (Applicant: Pfizer, Inc.).

(b) (4) facility is currently registered with CDER, for 2011. Operations at the facility are confined to (b) (4). This full-option inspection covered the Quality, Facilities & Equipment, Production, and Laboratory Controls Systems and Profile Class (b) (4) The inspection was conducted in accordance with Compliance Programs 7346.832, "Pre-proval Inspections" and 7356.002F, "Active Pharmaceutical Ingredients."

(b) (4)

I verified that the firm corrected those deficiencies.

At the start of the current inspection, I presented credentials to (b) (4) General Manager, who was the most responsible person at the facility. The current pre-approval inspectional coverage included all areas of concern listed in CDER's Knowledge Transfer Memo (KTM), which is attached to the EIR. The inspection revealed that the firm's qualifications, practices, procedures, controls, studies, and raw data in these KTM areas are acceptable. My inspection also found that general CGMP controls are acceptable. No FDA-483 was issued for the current inspection.

I submitted a recommendation to HFD-325 to approve NDA 202324/000.

I discussed one issue with management, regarding the proper way of documenting process data within executed batch records. Management agreed to implement my recommendation in future batch

INSPECTION SCHEDULED	(b) (4)		(b) (4)		PHILPYE
UNDER REVIEW	24-OCT-2011				STOCKM

Inspection was classified NAI, however some issues documented in the EIR but not on 483 are under review and must be resolved prior to DO/OC recommendation.

DO RECOMMENDATION	01-DEC-2011	ACCEPTABLE	BRYKMANR
INSPECTION PERFORMED ON 08/23-25/2011 WITH RESULT OF NAI WITH CENTER CONCURRENCE FOR (b) (4) PROFILE.		INSPECTION	
OC RECOMMENDATION	04-DEC-2011	ACCEPTABLE	STOCKM
		DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611504 **FEI:** 3002807097

PFIZER GMBH

MOOSWALDALLE 1
FREIBURG, , GERMANY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-APR-2011				HENRYD
SUBMITTED TO DO	19-APR-2011	Product Specific			SMITHDE
QBD ELEMENTS					
ASSIGNED INSPECTION TO IB	20-APR-2011	Product Specific			PHILPYE
POSSIBLE JOINT INSPECTION?					
INSPECTION SCHEDULED	06-JUN-2011		30-JUN-2011		IRIVERA
I CTION PERFORMED	30-JUN-2011		30-JUN-2011		MICHELE.PERRYWILLIA
See EIR					
UNDER REVIEW	06-SEP-2011				PHILPYE
VAI, under review, target date 9/26/2011					
DO RECOMMENDATION	01-DEC-2011			ACCEPTABLE	BRYKMANR
INSPECTION PERFORMED ON 06/24-30/2011 RESULTING IN VAI WITH CENTER CONCURRENCE FOR (b) (4) PROFILES.				INSPECTION	
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611880 **FEI:** 3003382089

PFIZER IRELAND PHARMACEUTICALS

LITTLE ISLAND
COUNTY CORK, , IRELAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Establishment Comment:

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-APR-2011				HENRYD
SUBMITTED TO DO	19-APR-2011	Product Specific			SMITHDE
QBD ELEMENTS					
ASSIGNED INSPECTION TO IB	20-APR-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	06-JUN-2011		17-JUN-2011		IRIVERA
INSPECTION PERFORMED	17-JUN-2011		17-JUN-2011		SIMONE.PITTS

This comprehensive pre-approval and GMP inspection of an active pharmaceutical ingredient manufacturer was conducted according to FACTS Assignment # 6886055, OP ID # 5390586 in accordance with CP 7356.002F Active Pharmaceutical Ingredient (API) Process Inspections and 7346.832 Pre-Approval Inspection/Method Validations. The inspection covered the manufacturing processes and included a review of the Quality, Production, Materials Management, Facilities & Equipment and Laboratory Systems for (b) (4) Crizotinib Drug Substance and NDA 202-324Axitinib Drug Substance under the profile class (b) (4).

The previous inspection conducted in September 2007 was classified as NAI and no FDA-483 was issued.

The current inspection continued to find the firm operating as an active pharmaceutical ingredient manufacturer. At the close of the inspection on June 17, 2011 a 5 item FDA-483, List of Inspectional Observations was issued citing the following deficiencies: (1) (b) (4) (2)The process validation protocol for Axinitib stated that lots A5A-00-0006, -0007, and -0008 would be used to validate the process. During the production of Lot A5A-00-0007, a failure in the (b) (4) specification was experienced (3)There should be documented procedures describing sampling, testing, approval, or rejection of materials, and recording and storage of laboratory data (4)Buildings used in the manufacture of intermediates of APIs were not properly maintained, repaired, and kept in a clean condition and (5)The suppliers of the regulatory starting materials (b) (4) have not been adequately qualified.

The FDA-483 items were discussed with management

DO RECOMMENDATION	17-OCT-2011	ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	17-OCT-2011	ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611016 **FEI:** 3002807852

PFIZER IRELAND PHARMACEUTICALS INC.

RINGASKIDDY API PLANT
RINGASKIDDY, COUNTY CORK, , IRELAND

DMF No: **AADA:**

Responsibilities: (b) (4)

Establishment Comment:

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-APR-2011				HENRYD
SUBMITTED TO DO	19-APR-2011	Product Specific			SMITHDE
QBD ELEMENTS					
ASSIGNED INSPECTION TO IB	20-APR-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	06-JUN-2011		24-JUN-2011		IRIVERA
INSPECTION PERFORMED	24-JUN-2011		24-JUN-2011		MINH.PHAN

This preapproval and GMP inspection (Trip #2011-122D) of an API manufacturer and control testing laboratory of human and veterinary drug substances was conducted per FACTS assignment #6286270 (CDER EES Request for Inspection Report) requesting the cover of (b) (4)

Axitinib 1 mg and 5 mg under NDA #202324/000. The applicant of (b) (4) NDA #202324/000 and NDA #202570/000 is Pfizer, an Diego, CA. The PAI and GMP inspection was conducted in accordance with CP 7356.002F (API) and CP 7346.832 (PAI). This inspection covered Quality, Facility & Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems. Profile class codes (b) (4) were covered. PAC codes 56002F and 46832 were covered.

(b) (4)

DO RECOMMENDATION	19-SEP-2011			ACCEPTABLE	STOCKM
				INSPECTION	
OC RECOMMENDATION	20-SEP-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 2623619 **FEI:** 3002173302

PFIZER PHARMACEUTICALS LLC

ROAD 689
VEGA BAJA, PR 00694

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

Establishment Comment:

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	19-APR-2011				HENRYD
SUBMITTED TO DO	19-APR-2011	10-Day Letter			SMITHDE
DO RECOMMENDATION	30-JUN-2011			ACCEPTABLE	RHERNAND
ACCETABLE RECOMMENDATION BASED ON INSPECTION RE-CLASSIFICATION BY COMPLIANCE BRANCH (SEE MEMO DATED JUNE, 8, 2011) AND REGULATORY MEETING HELD ON 6/30/2011. EI WAS INITIALLY CLASSIFIED OAI, HOWEVER AFTER FURTHER EVALUATION BY COMPLIANCE BRANCH THE SAME WAS RE-CLASSIFIED TO VAI.EI CONDUCTED ON 1/26/2011, PROFILES PLACED ACCEPTABLE ON 6/30/2011 BY CB				INSPECTION	
OC RECOMMENDATION	30-JUN-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	