CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202324Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW ADDENDUM Office of New Drugs Quality Assessment			
Application No.:	NDA 202-324	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Dates:	4/13/2011, 12/21/2012, 1/20/2012		
Division:	Division of Oncology Products	**Secondary Signature:** Sandra Suarez Sharp, Ph.D.	
Sponsor:	Pfizer	**Biopharmaceutics Lead:** Angelica Dorantes, Ph.D.	
Trade Name:	INLYTA®	**Date Assigned:**	4/13/2011
Generic Name:	Axitinib	**Date of Review:**	1/25/2012
Indication:	Treatment of advanced renal cell carcinoma (RCC)	**Type of Submission:** Original New Drug Application	
Formulation/strengths:	Immediate Release (IR) Film-Coated Tablet/1 mg and 5 mg		
Route of Administration:	Oral		

SUMMARY:

This addendum incorporates the agreements in terms of pending issues not resolved at the time the original Biopharmaceutics review was entered into DARRTS on December 12, 2011 by this reviewer.

During the review cycle, the review team had concerns with the coating weight gain because there was no data (i.e., dissolution data) supporting the proposed specifications. The Applicant proposed a coating weight gain of (b) (4). The ONDQA review team communicated to the Applicant that the dissolution data do not support a film coating specification (b) (4) and recommended to adopt an upper limit for coating weight based on the provided dissolution data. In later communications, the Applicant provided dissolution data that support (b) (4) coating weight gain for the 5 mg strength. Although the dissolution data provided do not directly support the same specification for the 1 mg strength, the review team considers that coating weight gain (b) (4) is acceptable for both strengths based on the following information:

1. In vivo data showing that both strengths are bioequivalent; and
2. Formulation characteristics and in vitro dissolution performance of the drug product.

Additionally, the review team had concerns that the proposed (b) (4) design space would provide adequate dissolution of axitinib and communicated this to the Applicant during the review cycle. The Applicant responded that (b) (4) However, the ONDQA review team later on communicated to the Applicant that their proposed design space (b) (4) was not acceptable and advised the Applicant to establish target values for the process parameters to ensure the formation of axitinib (b) (4). The Applicant revised their design space; however, there was a concern about the (b) (4), as allowed by the specification, could have. Therefore, the Applicant was requested to provide data/justification that undetected (b) (4) drug substance polymorphs will not affect the bioavailability of the drug product. On a teleconference dated January 19, 2012, the Biopharmaceutics review team communicated to the Applicant that based on the information provided on December 21, 2011 and on an internal analysis of the exposure-response data for the drug product, the FDA considers that the presence of drug substance polymorphs (b) (4) will not likely affect the clinical performance of the drug product.

RECOMMENDATION:

1. The proposed film coat weight gain [redacted] (b) (4) is acceptable for the 1 mg and 5 mg tablet.
    - This specification is supported by the information received on December 21, 2011 and on the bioequivalency between both strengths, the formulation characteristics, and the in vitro dissolution performance.

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Office of New Drugs Quality Assessment

Sandra Suarez Sharp, PhD
Senior Biopharmaceutics Reviewer
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cc: Angelica Dorantes, Ph.D.

Drug Product Film Coating Weight

The Applicant proposed a film coat weight [redacted] (b) (4) to control the weight of film coating applied to tablets. However, there no data was submitted supporting this proposed film coat specification.

The following Biopharmaceutics comment related to film coating specification was made in the Information Request Letter dated September 26, 2011.

FDA Query 36
Indicate if [redacted] (b) (4) % of film coat has any impact on dissolution with supporting data, if available.

Sponsor Response

[redacted] (b) (4)

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/s/

KAREEN RIVIERE
01/25/2012

SANDRA SUAREZ
01/25/2012

Clinical Pharmacology Review

NDA	202324
Submission Date:	April 14, 2011
Brand Name:	Inlyta®
Generic Name:	Axitinib
Formulation:	1 mg and 5 mg tablets
OCP Reviewer:	Sarah Schrieber, PharmD
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OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Pfizer
Submission Type; Code:	NME/0000/1
Dosing regimen:	Axitinib 5 mg orally twice daily without regards to food.
Indication:	Axitinib in patients with advanced renal cell carcinoma (RCC).

OCP Briefing was held on December 12, 2011.

Table of Contents

1 Executive Summary 4
1.1 Recommendations 5
1.3 Summary of Clinical Pharmacology Findings 5
2 Question Based Review 6
2.1 General Attributes 6
2.2 General Clinical Pharmacology 8
2.3 Intrinsic Factors 24
2.4 Extrinsic Factors 30
2.5 General Biopharmaceutics 40
2.6 Analytical Section 44
3 Detailed Labeling Recommendations 50

4 Appendices 63
4.1 PHARMACOMETRICS REVIEW 63
4. 2 PHARMACOGEMOMICS Review 79
4.3 NDA Filing and Review Form 88

Index of Tables

Table 1. Progression free survival (PFS) in patients with advanced RCC (A4061032). 8

Table 2. Overview of Clinical Pharmacology Related Studies Submitted in NDA. 9

Table 3. Summary of Axitinib PK Parameters in Healthy Volunteers and Patients by Study and Treatment Group Following a Single 5 mg Oral Dose of Axitinib in the Fed State. 16

Table 4. Pharmacokinetic Parameters for Axitinib (b) (4) after Administration of single doses of 5 mg and multiple doses of 5 mg twice daily under Fed Conditions in Patients with Cancer. 17

Table 5. Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Axitinib (total and unbound) Comparing Healthy Volunteers with Mild or Moderate Hepatic Impairment to Volunteers without Hepatic Impairment in Study A4061036. 28

Table 6. Geometric mean (CV%) Pharmacokinetic Parameters for Axitinib (total and unbound) after Administration of 5 mg in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study A4061036. 29

Table 7. Geometric mean (CV%) Pharmacokinetic Parameters for Axitinib (unbound) after Administration of 5 mg in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study A4061036. 29

Table 8. Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Axitinib (unbound) Comparing Healthy Volunteers with Mild or Moderate Hepatic Impairment to Volunteers without Hepatic Impairment in Study A4061036. 29

Table 9. Ki values (μM) for axitinib inhibition of CYP activities in human liver microsomes (study PDM-020). 32

Table 10. Effect of increasing Axitinib (AG-013736) concentration on MDR1-MDCK permeability, efflux and inhibition. 33

Table 11. Digoxin Papp and net secretory flux values across Caco-2 cell monolayers in the presence of increasing concentrations of axitinib. 34

Table 12. Effect of increasing axitinib concentration on BCRP-MDCK permeability, efflux and inhibition. 35

Table 13. Effect of increasing axitinib concentration on OATP efflux. 35

Table 14. Geometric mean (95% CI) pharmacokinetic parameters of axitinib with and without multiple doses of ketoconazole 36

Table 15. Effect of multiple doses of ketoconazole on the pharmacokinetics of single dose of axitinib in Study A40601004. Test = AG-013736 (axitinib) 5 mg + ketoconazole 400 mg qd (N=28); Reference = axitinib 5 mg (AUC, N=31; Cmax: N=32). 36

Table 16. Geometric mean (CV%) pharmacokinetic parameters of axitinib with and without multiple doses of rifampin. 37

Table 17. Effect of multiple doses of rifampin (600 mg once daily) on the single-dose pharmacokinetic parameters of axitinib. Test = axitinib 5 mg + Rifampin 600 mg QD; Reference = axitinib 5 mg... 38

Table 18. Mean (CV%) every 3 week paclitaxel plasma pharmacokinetic parameters for Cohorts 1-3. Data from 2 subjects were excluded due to PK samples not being collected on Cycle 1 Day 1..... 39

Table 19. Mean (CV%) weekly paclitaxel plasma pharmacokinetic parameters for Cohort 4. Data from 1 subject excluded due to PK samples not being collected on Cycle 2 Day 1. 39

Table 20. Comparison of Plasma Pharmacokinetics of axitinib in the presence and absence of rabeprazole. 40

Table 21. Solubility of Axitinib in Aqueous Media as a Function of pH at 20°C for at least 24 Hours..... 41

Table 22. Solubility of Axitinib in Organic Solvents after Equilibration for at least 24 hours at 20°C. 41

Table 23. Composition of Axitinib Film-Coated Immediate Release 1 mg and 5 mg Tablets. 42

Table 24. Descriptive Summary of Pharmacokinetic Parameters of Axitinib 5 mg Administration under Fasting Conditions, after administration with a Standardized Moderate-fat Meal, or a High-fat Meal in Study A4061053..... 43

Table 25. Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Axitinib Comparing Administration of 5 mg under Fasting Conditions Versus Administration with Standardized Moderate-fat or High-fat Meals in Study A4061053. 43

Table 26. Summary of Bioanalytical Methods Used in Clinical Studies for Pharmacokinetic Measurements of Axitinib. 46

Index of Figures

Figure 1. Structural Formula of axitinib. 7

Figure 2. Exposure dependent increase in hypertension (left) and proteinuria (right). Reduction of Dose from 5 to 3 mg bid will reduce the risk of hypertension and proteinuria. 13

Figure 3. Occurrence of Diarrhea and Fatigue Increases with Axitinib Exposures. 13

Figure 4. Dose Titration Based on Tolerability Reduces Variability in Axitinib Exposures..... 14

Figure 5. No effect of healthy vs. patients on the clearance of axitinib. 18

Figure 6. Median Cumulative Percent of Radioactive Dose Recovered in Urine and Feces at Specified Intervals after a Single 5 mg (100 µCi) Oral Dose of [^{14}C]-axitinib to Healthy Male Subjects in Study A4061003 (N=6). 20

Figure 7. Proposed *In Vivo* Axitinib Metabolic Schema..... 21

Figure 8. Single dose Log AUCinf (ng*h/mL) vs. Log of Dose (mg) in the Dose Proportionality Studies (A4060010, A4061044, and A4061050) in the Dose Range of 2 to 30 mg. 23

Figure 9. Steady-state Log AUC0-24 (ng*h/mL) vs. Log of the Total Daily Dose (mg) in the Dose Proportionality Studies (A4060010 and A4061019) in the Dose Range of 1 to 20 mg Twice Daily. 23

Figure 10. No effect of gender on the clearance of axitinib..... 24

Figure 11. Axitinib clearance in Japanese vs. non-Japanese patients from the popPK model. 25

Figure 12. No effect of weight on the clearance of axitinib..... 25

Figure 13. Axitinib clearance in <60 and >60 year subjects. 26

Figure 14. No effect of UGT1A1*28 (left) and CYP2C19 (right) genotype on axitinib clearance. 26

Figure 15. No effect of CrCL in axitinib clearance (left) and individual observed and median with 25th - 75th percentile range Axitinib Clearance (L/h) after Administration of 5 mg in Healthy Volunteers and/or Patients with Normal (N=381), Mild (N=139), Moderate (N=64), Severe (N=5), or End-stage (N=1) Renal Impairment (right). 27

Figure 16. Individual and Geometric mean with 95% CI Axitinib (total and unbound) AUC_{last} (ng*h/ml) after Administration of 5 mg in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study A4061036. 28

Figure 17. Axitinib clearance in non-smokers, active-smokers and ex-smokers. 31

Figure 18. The median time-concentration profiles of axitinib in healthy subjects on a semi-log scale, following a single 5 mg oral axitinib dose alone (N=31) or coadministered with 400 mg ketoconazole once daily (N=28) in a 2-treatment, 2-period, 2-sequence crossover design. 37

Figure 19. The median time-concentration profiles of axitinib in healthy subjects on a semi-log scale, following a single 5 mg oral axitinib dose alone (N=40) or coadministered with 600 mg rifampin once daily (N=39) in a 2-treatment, 2-period, 2-sequence crossover design. 38

1 Executive Summary

Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR)-1, -2, and -3. The current submission is the original NDA for axitinib for the treatment of advanced renal cell carcinoma (RCC).

To support the efficacy in advanced renal cell carcinoma, the sponsor conducted one randomized, controlled phase 3 trial. Patients in the phase 3 trial were randomized to receive axitinib tablets 5 mg twice daily or sorafenib 400 mg twice daily. Progression free survival (PFS) was the primary endpoint. The median PFS for the axitinib treatment arm was 6.7 months compared to 4.7 months for patients receiving sorafenib.

Exposure-safety analysis demonstrated that there was exposure dependent increase in hypertension, proteinuria, fatigue, and diarrhea. The proposed dose reduction strategy (5 to 3 to 2 mg bid) to manage hypertension and proteinuria is acceptable. Additionally, the dose titration scheme, which is the same as that used in the phase 3 trial (5 to 7 to 10 mg based on tolerability), is reasonable and can reduce variability in axitinib exposures based on observed pharmacokinetic data.

The pharmacokinetics of axitinib has been evaluated in twenty studies in healthy volunteers and cancer patients. Following oral administration, the median axitinib plasma T_{max} ranges between 2.5 – 4.1 hours and the mean half-life ranges between 2.5 – 6.1 hours. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%. A clinically significant effect of food was not observed; axitinib may be administered with or without food.

The results of the hepatic impairment study support the labeling recommendations of reducing the axitinib dose by half for patients with moderate hepatic impairment. No dose adjustment is warranted for patients with mild hepatic impairment. Patients with severe hepatic impairment have not been studied. Based on the population pharmacokinetic analysis, no adjustment to the starting dose is needed for patients with pre-existing mild, moderate, or severe renal impairment. As only one subject was enrolled with end-stage renal impairment, a definitive conclusion

regarding the effect of end-stage renal impairment on axitinib exposure cannot be made.

In vitro data indicate that axitinib is primarily metabolized by CYP3A4/5. In drug-drug interaction studies, ketoconazole (a strong CYP3A4/5 inhibitor) increased axitinib exposure by 106%, while rifampin (a strong CYP3A4/5 inducer) decreased axitinib exposure by 80%. Therefore, concomitant use of strong inhibitors or inducers of CYP3A4/5 should be avoided. However, if a strong CYP3A4/5 inhibitor must be co-administered, the axitinib dose should be reduced by half.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology 5, Pharmacometrics, and Pharmacogenomics have reviewed the information contained in NDA 202324. This NDA is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 Phase IV Requirements

None.

1.3 Summary of Clinical Pharmacology Findings

Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR)-1, -2, and -3. Axitinib is being developed for oral use in the treatment of advanced renal cell carcinoma (RCC).

The applicant has conducted twenty studies in healthy volunteers, and patients with cancer to evaluate the safety and pharmacokinetics of axitinib. The T_{max} of axitinib typically occurs 2.5-4.1 hours following oral administration, and the concentrations of axitinib decreased over time with a half-life of approximately 2.5-6.1 hours after a single 5 mg axitinib oral dose in the fed state. No major deviation from dose proportionality was observed following multiple dosing in the dose range of 1 to 20 mg twice daily. There are no significant differences between the pharmacokinetics in healthy volunteers and patients with cancer. A moderate-fat meal decreased the AUC of axitinib by 10%, while a high-fat increased the AUC of axitinib by 19%.

After administration of radio-labeled axitinib in healthy subjects, approximately 41% of the radioactivity was recovered in feces and approximately 23% was recovered in urine. Unchanged axitinib was not detected in urine, but was the major component identified in feces (12% of the dose). In plasma, unchanged axitinib accounted for approximately 20% of the circulating radioactivity. Two metabolites of axitinib have been detected in human blood and these metabolites showed ≥400-times less activity than axitinib itself. A hepatic impairment study in subjects with moderate hepatic impairment showed that the average AUC was 2-fold higher that found in subjects with normal hepatic function. A dose reduction by 50% for patients with

moderate hepatic impairment is recommended.

Axitinib is a substrate of CYP3A4/5, P-glycoprotein, and UGT1A1. Drug-drug interaction studies indicate a 106% increase in axitinib exposure (AUC) when administered with ketoconazole and an 80% reduction in axitinib AUC when administered with rifampin. Axitinib inhibited CYP2C8 (I/Ki=0.15) and 1A2 (I/Ki=0.11) *in vitro*; however, *in vivo*, co-administration of axitinib did not increase paclitaxel plasma concentrations, indicating a lack of CYP2C8 inhibition. Axitinib was not found to induce any cytochrome P-450 enzymes *in vitro*. The aqueous solubility of axitinib is pH dependent. Drug-drug interaction studies indicate a 15% decrease in axitinib AUC and 42% decrease in axitinib Cmax when administered rabeprazole.

Exposure-safety analysis was conducted by pooling data from three phase 2 and one phase 3 trial. There was exposure dependent increase in hypertension, proteinuria, fatigue, and diarrhea. The proposed dose reduction strategy (5 to 3 to 2 mg bid) to manage hypertension and proteinuria is acceptable since these adverse events are exposure related. Additionally, the dose titration scheme proposed by the sponsor, which is the same as that used in the phase 3 trial (5 to 7 to 10 mg based on tolerability), is reasonable and would reduce variability in axitinib exposures.

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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

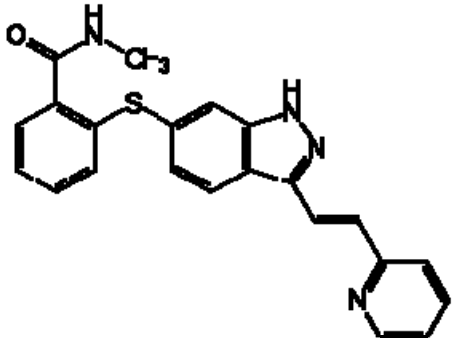
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Axitinib has been developed as 1 mg and 5 mg film-coated tablets for oral administration. The 1 mg tablet is a red oval shaped tablet debossed with “Pfizer” on one side and “1 XNB” on the other. The 5 mg tablet is a red triangular shaped tablet debossed with “Pfizer” on one side and “5 XNB” on the other.

Physical-chemical properties

1. **Structural formula:**

Figure 1. Structural Formula of axitinib.



2. **Established names:** Axitinib, AG-013736
3. **Molecular Weight:** 386.5 Daltons
4. **Molecular Formula:** $C_{22}H_{18}N_4OS$
5. **Partition coefficient (log P):** 3.5
6. **Dissociation Constant (pKa):** 4.8
7. **Chemical Name:** *N*-Methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide
8. **Melting Point:** 225°C
9. **Solubility:** Axitinib solubility in aqueous media decreases with increasing pH. It is soluble in excess of 0.2 µg/mL in aqueous media over the range pH 1.1 to pH 7.8. See section 2.5.1.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR)-1, -2, and -3. These receptors are implicated in pathologic angiogenesis, tumor growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumor vasculature that expressed the target *in vivo* and produced tumor growth delay, regression, and inhibition of metastases in many experimental models of cancer.

The proposed indication is for axitinib in patients with advanced renal cell carcinoma (RCC).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes a dosing regimen of 5 mg of oral axitinib administered twice daily without regard to food. Patients who tolerate 5 mg twice daily may have the dose increased to 7 mg bid, and further to a maximum of 10 mg twice daily if they meet the following criteria:

- No Adverse drug reactions >Grade 2 for two consecutive weeks
- Normotensive
- Not receiving anti-hypertension medication

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A single pivotal trial in patients with advanced renal cell carcinoma (RCC) was conducted to support the efficacy claim.

Pivotal Phase 3 Trial in Patients with advanced RCC (A4061032)
The pivotal trial was a phase 3 multi-center, 2-arm, randomized, open-label study of axitinib (5 mg twice daily with food) or sorafenib (400 mg twice daily) in patients with advanced RCC whose disease had progressed on or after treatment with one prior systemic first-line therapy, including: sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens. This study randomized 723 patients 1:1 to receive axitinib or sorafenib. During the study, the dose of axitinib was allowed to be escalated from 5 mg twice daily to 7 mg twice daily and 10 mg twice daily based on patient safety and tolerability.

The primary efficacy endpoint was progression free survival (PFS) and Table 1 below shows a summary of the sponsors results based on this primary endpoint.

Table 1. Progression free survival (PFS) in patients with advanced RCC (A4061032).

	Axitinib (n=361)	Sorafenib (N=362)
Median PFS in Months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)
p-value	< 0.0001	
Hazard Ratio (95% CI)	0.67 (0.54, 0.81)	

CI, confidence interval

The secondary efficacy endpoints were overall response rate (ORR), overall survival (OS), and duration of response (DR).

A total of 19 completed studies and 1 ongoing study were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA (Table 2).

Healthy subject studies:

- Nine Phase 1 studies - Dose proportionality (A4061050), bioavailability. (A4061007), relative bioavailability / bioequivalence (A4061021, A4061033, A4061052, A4061063), food effect (A4061006, A4061053) and mass balance (A4061003)
- One organ impairment study - Hepatic (A4061036)
- Two drug interaction studies - CYP3A4/5 inhibitor (A4061004), 3A4/5 inducer (A4061026)
    - QT study – substudy of A4061004.

Cancer patient studies:

- Three Phase 1 studies - Advanced solid tumor; Dose escalation (A4060010, A4060019, A4061044)
- Four Phase 2 studies - Advanced RCC (A4061046 [ongoing], A4061012, A4061023, A4061035)
- One Phase 3 study – Advanced RCC (A4061032)

Clinical Pharmacology Reports of data from more than one study:

The axitinib plasma concentration data from several studies were used to develop a population pharmacokinetic (popPK) model (reports PMAR-00075, PMAR-00079) to investigate the potential influence of covariates that contribute significantly to between-patient variability in pharmacokinetic parameters of axitinib. The model was also used to characterize the exposure-safety relationships for select adverse events (population PK/PD).

Table 2. Overview of Clinical Pharmacology Related Studies Submitted in NDA.

Study Number Start/End Date	**Study Description/Design**	**Subjects Evaluated Sex M/F Age (yr): Mean (SD) Race (W/B/His/As/Other)**	**Treatment Regimen/ Duration Route of Administration Batch Number**
Bioavailability Studies			
A4061007 02 Aug 2005/ 19 Aug 2005	Phase 1, randomized, open-label, single-dose, 3-treatment, 2-way crossover study designed to determine the absolute bioavailability of axitinib tablets vs. IV solution formulation in healthy subjects.	**Subjects:** 16 **Sex:** 14 M / 2 F **Age (yr):** 37.4 (14.9) **Race (W/B/Ot):** 12/3/1	Axitinib 5 mg po with a 7-day washout between each dosing period. Subjects were randomized to 1 of 2 treatments sequences (ABC or BAC). Treatment Groups: A: 1 mg axitinib IV fasted B: 5 mg axitinib po fasted C: 5 mg axitinib po fed Formulation: (b) (4) solution for IV administration
Comparative Bioavailability and Bioequivalence Studies			
A4061021 06 Jul 2006/ 15 Aug 2006	Phase 1, open-label, randomized, single-dose, 2-sequence, 3-period crossover trial designed to determine the relative bioavailability of 5 mg (b) (4) in fed healthy subjects.	**Subjects**: 40 **Sex:** 38 M / 2 F **Age (yr)**: 33.4 (13.3) **Race (W/B/As/Ot)**: 29/5/3/3	Axitinib 5 mg was administered under fed conditions according to the treatment sequence (ABB or BAA) with a 7 to 10-day washout period between each single dose treatment. Treatment Groups: A: 5 mg axitinib (b) (4), fed (Reference) B: 5 mg axitinib (b) (4), fed Formulations: (b) (4)
A4061033 02 Jan 2008/ 21 Feb 2008	Phase 1, open-label, single-dose, randomized, 4-sequence, 4-period, crossover study to determine the relative bioavailability of 5 mg (b) (4) in fed healthy male subjects.	**Subjects**: 56 M **Age (yr)**: 34.6 (10.3) **Race (W/B/As/Ot)**: 27/2/25/2	Axitinib 5 mg was administered under fed conditions according to the treatment sequence (ABCD, BDAC, CADB, or DCBA) with a 7-day washout period between each single dose treatment. Treatment Groups: A: 5 mg axitinib (b) (4) particle size, fed (Reference) B: 5 mg axitinib (b) (4) particle size, fed C: 5 mg axitinib (b) (4) particle size, fed D: 5 mg axitinib (b) (4), fed Formulations: (b) (4)
A4061052 13 Jul 2009/ 02 Sep 2009	Phase 1, open-label, randomized, single-dose, 2-sequence, 4-period crossover to establish the bioequivalence of test 5 x1 mg axitinib tablet to reference 1 x 5 mg axitinib tablet in fasted healthy male subjects.	**Subjects**: 60 M **Age (yr)**: 30.6 (7.0) **Race (As)**: 60	Axitinib 5 mg was administered under fasted conditions according to the treatment sequence (BABA or ABAB) with a 7-day washout period between each single dose treatment. Treatment Groups: A: 5 mg x 1 axitinib (b) (4), fasted (Reference) B: 1 mg x 5 axitinib (b) (4) fasted, Formulation: (b) (4)
A4061053 01 Jul 2009/ 18 Jul 2009	Phase 1, open-label, randomized, single-dose, 6-sequence, 3-period crossover to assess the effect of food vs. fasting on Form XLI axitinib pharmacokinetics in healthy male subjects.	**Subjects**: 30 M **Age (yr)**: 37.2 (9.5) **Race (W/B)**: 29/1	Axitinib 5 mg was administered under fasted and fed conditions according to the treatment sequence (ABC, ACB, BCA, BAC, CAB, or CBA) with a 7-day washout period between each single dose treatment. Treatment Groups:

			A: 5 mg axitinib, fasted (Reference) B: 5 mg axitinib, fed, high-fat, high-calorie C: 5 mg axitinib, fed, moderate-fat, moderate calorie Formulation: (b) (4)
A4061063 06 Jan 2010/ 26 Feb 2010	Phase 1, open-label, randomized, single-dose, 2-sequence, 4-period, replicate, cross-over to establish the bioequivalence of test 5-mg commercial tablets of axitinib Form XLI to reference 5-mg tablets of axitinib Form IV in fed healthy male subjects.	**Subjects**: 42 M **Age (yr)**: 29.9 (6.1) **Race (As/Ot)**: 41/1	Axitinib 5 mg was administered under fed conditions according to the treatment sequence (AB) with a 7-day washout period between each single dose treatment. Treatment Groups: A: 5 mg axitinib, Form IV, fed (Reference) B: 5 mg axitinib, Form XLI, fed Formulations: (b) (4)
Healthy Subject Pharmacokinetic and Initial Tolerability Studies			
A4061050 05 Aug 2009/ 28 Aug 2009	Phase 1, open-label, single dose, fixed sequence study designed to evaluate PK of single oral doses of 5 mg, 7 mg, and 10 mg of axitinib in Chinese healthy subjects	**Subjects:** 14 M **Age (yr):** 28.9 (5.7) **Race (As):** 14	Single dose of 5, 7, and 10 mg axitinib orally; administered in the fed state. Formulation: (b) (4)
A4061006 07 Dec 2004/ 14 Jan 2005	Phase 1, open-label, single dose, 3-treatment period, cross-over study to assess the effect of a high-fat, high-calorie meal and fasting on axitinib PK in healthy volunteers.	**Subjects:** 42 **Sex:** 34 M; 8 F **Age (yr):** 31.1 (13.3) **Race (W/B/His/As):** 33/5/2/2	Axitinib 5 mg po with a 5-day washout between each dosing period. Treatment Groups: A: 5 mg axitinib overnight fast and fast 4 hours post dose B: 5 mg axitinib, fed C: 5 mg axitinib, fast 2 hours pre-dose, fast 2 hours post–dose, D: 5 mg axitinib, fast 1 hour pre- dose, fast 1 hour post-dose Formulation: (b) (4)
A4061003 10 Dec 2003/ 22 Dec 2003	Phase 1, open-label, single dose, mass balance study of ^{14}C labeled axitinib in healthy male subjects.	**Subjects:** 8 M **Age (yr):** 35.4 (8.4) **Race (W/B):** 6/2	Each subject received 5 mg containing 100 µCi ^{14}C-axitinib Formulation: (b) (4)
A4061050 05 Aug 2009/ 28 Aug 2009	Phase 1, open-label, single dose, fixed sequence study to evaluate the plasma pharmacokinetics of single oral doses of 5 mg, 7 mg, and 10 mg of axitinib in healthy, male Chinese subjects.	**Subjects:** 14 M **Age (yr):** 28.9 (5.7) **Race (As):** 14	Three single doses of axitinib at 5 mg, 7 mg (2x1 mg + 1x5mg tablets), and 10 mg (2x5 mg tablets) orally with a 7-day washout between each dosing period. Formulation: (b) (4)
Patient Pharmacokinetic and Initial Tolerability Studies			
A4060010 03 Nov 2002/ 02 Nov 2003	Phase 1, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) and plasma pharmacokinetics of axitinib, as well as assessing the drug-drug interaction potential with in fasted patients with advanced solid tumors.	**Subjects:** 36 **Sex:** 16 M / 20 F **Age (yr):** 56.9 (8.5) **Race (W/B/His/As):** 30/1/2/3	Treatment Groups: 1: axitinib 10 mg qd, 10, 20, or 30 mg bid, fed 2: axitinib 20 mg bid, fed 3: axitinib 5 mg bid, fed 4: axitinib 15 mg qd, fed 5: axitinib 5 mg bid, fasted 6: axitinib 2 mg bid on the Day 1, then 5 mg bid, fasted Formulation: (b) (4)
A4060019 13 Dec 2005/ 31 Aug 2009	Phase 1, open-label, dose-finding study to determine the MTD of axitinib in combination with paclitaxel + carboplatin or weekly paclitaxel, as well as evaluate the plasma PK of axitinib, paclitaxel and carboplatin or weekly paclitaxel when given in combination to patients with advanced solid tumors.	**Subjects:** 35 **Sex:** 25 M / 10 F **Age (yr):** 37 – 75 **Race (W/B/As):** 32/2/1	Treatment Group: 1-3: axitinib po 1, 3, and 5 mg bid, fed + paclitaxel IV 200 mg/m^2 + carboplatin IV (AUC=6), fed 4: axitinib po 5 bid, fed + paclitaxel IV 90 mg/m^2 qwk Formulation: (b) (4)
A4061044 29 Jul 2008/ 26 Apr 2010	Phase 1, open-label, non-randomized study to evaluate plasma pharmacokinetics of axitinib following single doses of 5, 7, and 10 mg in fed Japanese patients with advanced solid tumors.	**Subjects:** 6 **Sex:** 3 M / 3 F **Age (yr):** 53.8 (15.8) **Race (As):** 6	Single doses of 5 mg, followed by 7 mg, and subsequently 10 mg. After the single dose at each dose level, subjects were monitored for at least 48 hours (no additional dosing during this time). Following the single doses, 5 mg bid was administered, fed. Formulation: (b) (4)
Intrinsic Factor Pharmacokinetic Studies			

A4061036 16 May 2008/ 26 Oct 2008	Phase 1, open-label, single-dose, parallel group study to evaluate the effects of mild and moderate hepatic impairment on the single-dose pharmacokinetics of axitinib in healthy subjects.	**Subjects:** 24 **Sex:** 20 M / 4 F **Age (yr):** 39 – 60 **Race (W/B):** 21/3	Single dose of 5 mg axitinib, fed Formulation: (b) (4)
Extrinsic Factor Pharmacokinetic Studies			
A4061004 23 Jun 2004/ 14 Aug 2004	Phase 1 randomized, blinded, 2-way, cross-over study to characterize the potential change in axitinib plasma pharmacokinetics when a single dose of axitinib is co-administered with repeated dosing of ketoconazole and to characterize the effects of axitinib on QTc and blood pressure when given alone and when coadministered with ketoconazole in healthy subjects.	**Subjects:** 24 **Sex:** 32 M / 3 F **Age (yr):** 35.5 (11.1) **Race (W/B/His/As/Ot):** 9/4/10/1/1	Before the start of the 1st treatment period, there was a 1 day lead-in baseline day and 1 day placebo dose day. Axitinib 5 mg was administered according to the treatment sequence (AB or BA) with a 14-day washout period between each single dose treatment. Treatment Groups: A: axitinib 5 mg, fasted B: ketoconazole 400 mg qd x 7 + axitinib 5 mg on Day 4, fasted Formulation: (b) (4)
A4061026 18 Sep 2006/ 04 Feb 2007	Phase 1, open-label, 2-period, 2-treatment crossover study to estimate the potential for pharmacokinetic interaction between axitinib and rifampin. in Caucasian and Japanese healthy male subjects.	**Subjects:** 40 M **Age (yr):** 29.0 (7.6) **Race (W/As):** 20/20	Axitinib 5 mg was administered according to the treatment sequence (AB or BA) with a 7 day washout between Day 1 of Treatment A and Day 1 of Treatment B for sequence 1 (AB), and at least a 21 day washout between Day 9 of Treatment B and Day 1 of Treatment A for sequence 2 (BA). Treatment Groups: A: axitinib 5-mg, fasted B: rifampin 600 mg qd x 9 + axitinib 5 mg on Day 8 , fasted Formulation: (b) (4)
Efficacy and Safety Controlled Clinical Studies			
A4061032 15 Sep 2008/ 31 Aug 2010	Phase 3, 2-arm, randomized, open-label study to compare the Progression-Free Survival (PFS) of patients with advanced RCC receiving axitinib vs. sorafenib following failure of one prior systemic 1st-line regimen containing ≥1 of the following: sunitinib, bevacizumab + IFN α, temsirolimus, or cytokine(s).	**Randomized (ITT):** 723 **(Control Arm:** 362) **Axitinib Arm:** 361 **Sex:** 265 M / 96 F **Age (yr):** 59.7 (10.5) **Race (W/B/As/Ot):** 278/1/77/5	Treatment Groups: A: Axitinib 5 mg bid as starting dose, fed B: Sorafenib 400 mg bid, fasted Formulation: (b) (4)
A4061046 Ongoing (01 July 2010 cutoff for interim PK reporting)	Phase 2, randomized, double-blind, placebo-controlled, study to compare the ORR in patients with mRCC receiving axitinib with or without dose titration.	To be randomized: ~70 Control Arm: 35 Axitinib Arm: 25	4 week lead-in period with axitinib 5 mg bid dosing, fed **Treatment Groups:** Randomized 1:1 to A: Axitinib 5 mg bid + dose titration, fed B: Axitinib 5 mg bid, fed + placebo dose titration C: Axitinib 5 mg bid, fed; no dose titration Formulation: (b) (4)
Efficacy and Safety Uncontrolled Clinical Studies			
A4061012 05 Nov 2002/ 01 Feb 2007	Phase 2, open-label study to determine the activity of axitinib in patients with advanced RCC who have received 1 prior cytokine-based therapy.	**Subjects:** 52 **Sex:** 40 M / 12 F **Age (yr):** 58.8 (11.3) **Race (W/As/Ot):** 50/1/1	Axitinib 5 mg BID, fasted Formulation: (b) (4)
A4061023 08 Mar 2006/ 16 Jan 2009	Phase 2, open-label study to determine the activity of axitinib in patients with advanced and refractory RCC as measured by overall objective response rate.	**Subjects:** 62 **Sex:** 42 M / 20 F **Age (yr):** 57.9 (9.4) **Race (W/As/Ot):** 64/1/1	Axitinib 5 mg bid as starting dose, fed Formulation: (b) (4)
A4061035 12 Dec 2007/ 26 Feb 2010	Phase 2, open-label, non-randomized study to investigate objective tumor response of axitinib in Japanese patients with advanced RCC.	**Subjects:** 64 **Sex:** 44 M / 20 F **Age (yr):** 61.8 (10.8) **Race (As):** 64	Axitinib 5 mg bid as starting dose, fed Formulation: (b) (4)

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the phase 3 protocol (A4061032) was progression free survival (PFS). The secondary efficacy endpoints were:

- Overall survival
- Objective response rate
- Duration of response

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, all the submitted clinical pharmacology related studies analyzed plasma samples for the parent compound axitinib.

In the mass balance study (A4061003), the mean plasma Cmax and AUC values were ~3.0 and ~6.6-fold higher for total radioactivity in plasma (mean Cmax 103 ng-eq/mL; AUC 997 ng-eq•h/mL) than for axitinib alone (mean Cmax 34 ng/mL; mean AUC 150 ng•h/mL), respectively. These results indicate the presence of other circulating metabolic product(s) in plasma after administration of [^{14}C]-labeled axitinib. In the pooled plasma samples used for metabolic profiling (study PDM-043), circulating radioactivity was assessed from pre-dose through 12 hours post-dose. During this time period, the glucuronide M7 represented the predominant metabolite, accounting for ~50% of the circulating radioactivity. The sulfoxide M12 and unchanged parent axitinib accounted for ~16% and ~22% of the circulating radioactivity, respectively. The M7 and M12 metabolites show ≥400-fold less *in vitro* potency against VEGFR-2 compared to axitinib. See section 2.2.12.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The applicant did an exploratory exposure-response analysis for PFS, the primary endpoint in the pivotal phase 3 trial A4061032. There were insufficient exposure data collected in trial A4061032 to support evidence of exposure-response for PFS. Pharmacokinetic data were available for only 55/359 (15%) of the patients in trial A4061032. The applicant also conducted exposure-efficacy analysis separately for the three phase 2 trials (cytokine refractory patients or patients who failed prior treatment to sorafenib) which indicated that higher exposures were related to partial response and associated with longer PFS. However, this exposure-efficacy analysis from phase 2 trials was not reviewed since it does not contain sunitinib refractory patients, which comprised of ~53% of the pivotal trial population.

2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Exposure-safety analysis was conducted for four adverse events of interest: hypertension, proteinuria, fatigue, and diarrhea. To support exposure-response, data from three phase 2 trials (A4061012 and A4061045 (N=116), A4061023 (N=62)) and the pivotal phase 3 trial (A4061032 (N=55)) were pooled. Logistic regression analysis was conducted to explore relationship between exposures (AUC before the adverse event occurred) with hypertension, proteinuria, fatigue, and diarrhea (Figure 2, Figure 3). There was significant exposure-response observed for all of the above mentioned adverse events. Sponsor proposes a dose reduction from 5 to 3 to 2 mg bid for hypertension and proteinuria which is acceptable since these adverse events are exposure driven. For a typical patient, reduction of dose from 5 mg bid to 3 mg bid will reduce the risk of hypertension from 55% to 41%. Similar dose reduction for a patient experiencing proteinuria would reduce the risk of proteinuria from 16% to 12%. The actual reduction in these adverse events will vary depending on where the exposure of a patient lies on the exposure-response curve.

Figure 2. Exposure dependent increase in hypertension (left) and proteinuria (right). Reduction of Dose from 5 to 3 mg bid will reduce the risk of hypertension and proteinuria.

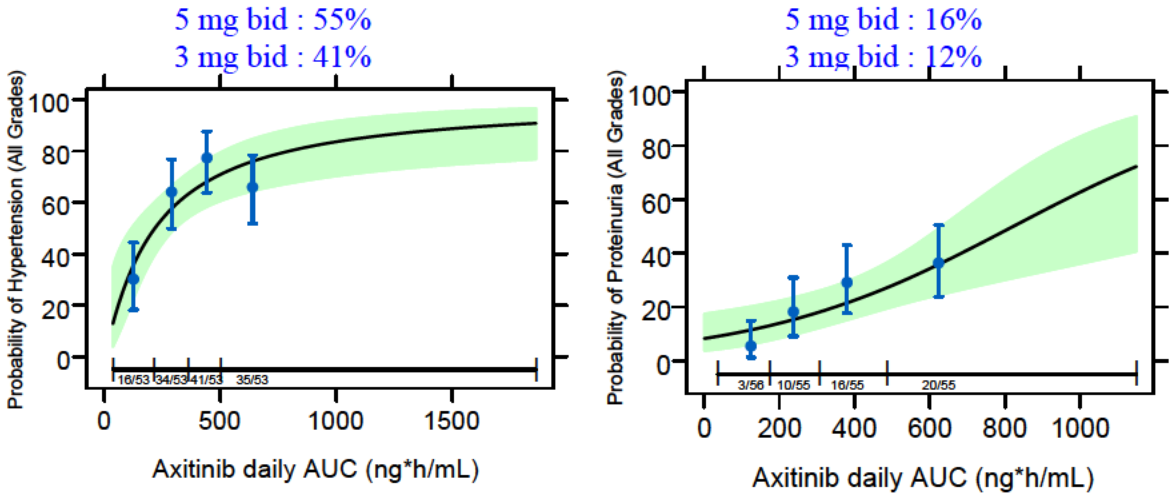
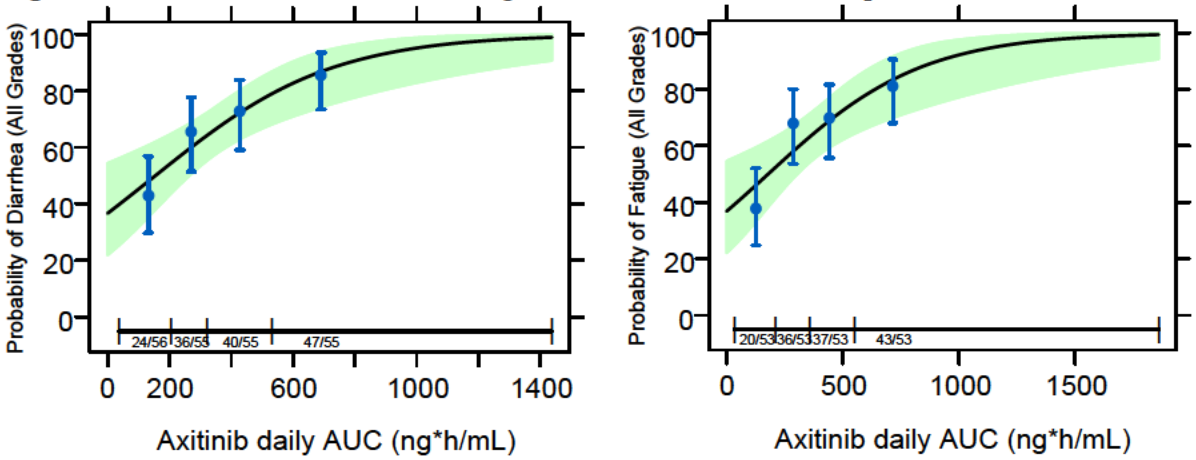


Figure 3. Occurrence of Diarrhea and Fatigue Increases with Axitinib Exposures.



2.2.6 Is it appropriate to titrate up to 10 mg twice daily based on tolerability?

Yes, the dose titration scheme proposed by the sponsor based on tolerability is reasonable and would reduce variability in axitinib exposures.

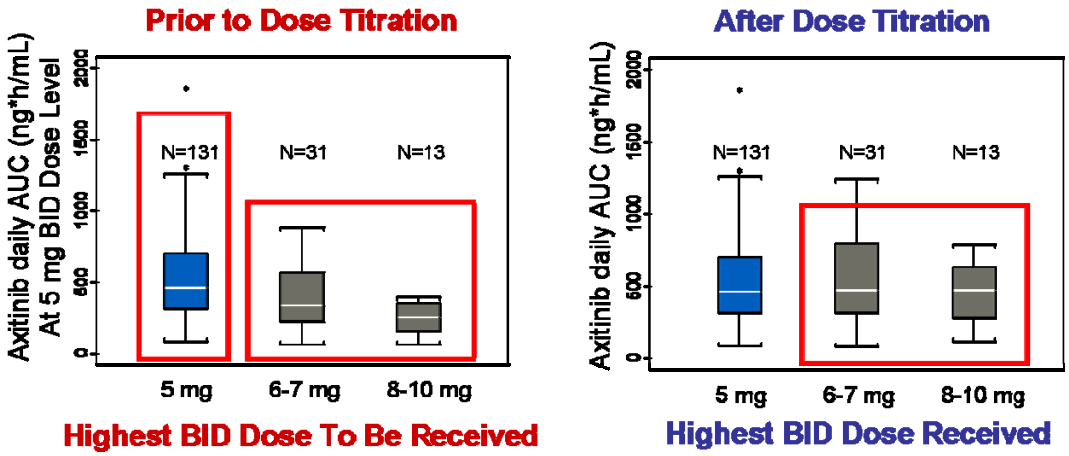
- There is considerable intersubject variability (~70%) in exposures following axitinib dose of 5 mg bid which provides an opportunity to individualize the dose.
- It was observed that patients who were able to tolerate axitinib and required upward dose titration had lower initial exposures. This was consistent with our previous finding that adverse events were exposure driven and patients with lower exposures are likely to have lower adverse events.

The axitinib clinical starting dose is 5 mg orally twice daily. Patients who tolerate 5 mg twice daily may have the dose increased to 7 mg bid, and further to a maximum of 10 mg twice daily if they meet the following criteria:

- No Adverse drug reactions >Grade 2 for two consecutive weeks
- Normotensive
- Not receiving anti-hypertension medication

It is important to note that this dose titration scheme was implemented in the clinical development program of axitinib, both in the phase 2 trials and the pivotal trial. The sponsor conducted a retrospective analysis to see the effect of dose titration on PK by pooling data from three phase 2 trials, A4061012, A4061023, and A4061035. Patients who were able to tolerate axitinib and required upward dose titrations appeared to have lower axitinib initial exposures at the initial 5 mg bid dose prior to the dose titration. Axitinib exposures in those subjects appeared to match those receiving a 5 mg bid dose following dose titrations to 6-7 mg (N=31) or 8-10 mg (N=13) twice daily (Figure 4).

Figure 4. Dose Titration Based on Tolerability Reduces Variability in Axitinib Exposures.



2.2.6 Does this drug prolong the QT or QTc interval?

Dedicated QT study (study A40610014, PMAR-0074)
The potential for QTc prolongation with axitinib was evaluated a randomized, single-blinded, 2-way crossover ketoconazole drug-drug interaction study in 35 healthy subjects. 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.

Please see IRT-QTc review by Dr. Hao Zhu for more information.

2.2.7 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The following support the selection of the 5 mg twice daily dose administered without regard to food:

- The maximum tolerated dose (MTD) was determined to be 5 mg twice daily (Study A40610010).
- The efficacy (i.e., PFS benefit) was demonstrated in the phase 3 trial (A4061032).
- The safety profile was considered manageable at the 5 mg dose level.
  - The exposure response analyses for safety conducted by the pharmacometrics reviewer support the selected dosage of axitinib. Despite the presence of an exposure response for hypertension and proteinuria with axitinib treatment, the starting dose is acceptable.
- There was no marked food effect observed (Study A4061053).

2.2.8 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.8.1 What are the single dose and multiple dose PK parameters?

The disposition of axitinib followed a biexponetial decline and included a lag time and first-order absorption constant. The lag time from dose administration to the beginning of the first-order absorption was estimated to be 0.454 hours. Based on the population PK model, the mean Cmax and AUC0-24 in subjects (b) (4) in the fed state are 21 ng/mL and 274 ng*h/mL, respectively, which is similar to what is obtained from the dedicated PK studies. The population apparent clearance (CL/F) and apparent volume of distribution (Vc/F) for axitinib was estimated to be 36.7 L/h and 119 L, respectively. Inter-individual variability (IIV) was estimated to be 60% for CL/F and 40% for Vc/F. Three covariates (age >60 years, smoking, and race) were found to be significant for explaining the inter-individual variability on clearance. However, after inclusion of the three covariates for clearance, the IIV for clearance reduced only by 4% (64% to

60%). The effect of these covariates and their relevance is discussed later in the sections 2.3 and 2.4.

The single 5 mg dose axitinib plasma PK in healthy subjects and patients with cancer is presented in Table 3. Based on a combined population pharmacokinetic analysis, the clearance of axitinib was similar between healthy volunteers and patients (Figure 5). The median axitinib plasma Tmax ranges between 2.5 – 4.1 hours post-dose and the mean half-life ranges between 2.5 – 6.1 hours.

The multiple 5 mg dose axitinib plasma PK in patients with cancer is presented in Table 4. The single and multiple dosing axitinib plasma PK are similar. A geomean accumulation ratio of ~1.4 was observed at steady-state (Table 4). Inter-subject variability was approximately 80% for both Cmax and AUC after multiple dosing, which was similar to the variability observed after a single dose. Also see section 2.2.15.

Table 3. Summary of Axitinib PK Parameters in Healthy Volunteers and Patients by Study and Treatment Group Following a Single 5 mg Oral Dose of Axitinib in the Fed State.

Parameters Mean (%CV)	Healthy Volunteer Studies (Fed)												Patient Studies (Fed)		
	A406 1006 High Fat (n=41)[c]	A406 1007 Mod Fat (n=15)[c]	A406 1033 Mod Fat (n=54)	A406 1036 Mod Fat (n=8)	A406 1037 Mod Fat (n=20)	A406 1063 Mod Fat (n=42)	A4061033 Mod Fat VMD 7 µ (n=54)	A4061033 Mod Fat VMD 16 µ (n=56)	A406 1050 Mod Fat (n=14)	A4061053 High Fat (n=30)	A4061053 Mod Fat (n=30)	A406 1063 Mod Fat (n=41)	A406 0010 Mod Fat (n=6)	A406 1022 Mod Fat (n=6)	A406 1044 Mod Fat (n=6)
Formulation															(b) (4)
C_{max} (ng/mL)	32.2 (29)	22.6 (52)	40.5 (47)	33.2 (42)	39.4 (27)	49.0 (28)	35.2 (47)	33.2 (43)	36.2 (36)	31.7 (40)	25.1 (51)	43.0 (33)	22.3 (42)	30.0 (33)	20.7 (70)
$AUC_{0-\infty}$ (ng.hr/mL)	160 (20)	136 (68)	189 (53)	177 (48)	185 (34)	246 (38)	163 (54)	159 (55)	171 (49)	179 (44)	144 (52)	220 (40)	99.8 (39)	210 (70)	180 (86)
AUC_{0-last} (ng.hr/mL)	158 (21)	134 (69)	186 (53)	171 (49)	182 (33)	242 (38)	160 (54)	155 (56)	167 (51)	171 (47)	131 (58)	216 (40)	--	204 (67)	
CL/F[e] (L/hr)	31.2 (20)	36.7 (68)	38.3 (81)	37.9 (72)	30.4 (38)	--	40.6 (59)	43.3 (60)	39.4 (71)	34.7 (55)	46.5 (60)	--	56.1 (34)	30.6 (43)	42.1 (57)
V_z/F (L)	275 (53)	325 (89)	134 (56)	187 (55)	119 (44)	--	156 (55)	160 (46)	119 (44)	138 (57)	195 (52)	--	188 (39)	208 (50)	305 (87)
$t_{1/2}$ (hr)	5.41 (28)	6.1 (53)	3.02 (51)	4.74 (80)	3.23 (78)	3.02 (33)	3.23 (59)	3.29 (63)	2.54 (52)	2.97 (41)	3.28 (43)	3.36 (33)	2.31 (28)	4.80 (24)	4.78 (59)
T_{max} (hr)[b]	--	--	2.50 (1.00-6.00)	3.50 (2.00-4.00)	3.00 (1.00-4.05)	3.00 (1.00-5.00)	3.00 (1.00-4.02)	3.00 (1.00-6.00)	2.50 (1.50-4.00)	3.00 (2.00-6.00)	2.75 (1.00-6.00)	3.25 (1.50-4.01)	4.00 (1.00-4.08)	4.00 (2.00-6.00)	4.1 (3.95-6.02)

Source: A4061003 CSR Tables 3, A4061004 CSR Table 13.5.2.3.1, A4061006 SCP Appendix 2 Table 2.1 and 2.2, A4061007 CSR Table 13.2.1.23, A4061018 SCP Appendix 2 Table 2.3 and 2.4, A4061021 CSR Table 13.5.2.2, A4061026 CSR Table 13.5.2.1, A4061033 CSR Table 13.5.2, A4061036 CSR Table 13.5.2.1, A4061037 CSR Table 13.5.2, A4061047 CSR Table 13.5.2.2, A4061050 CSR Table 13.5.2, A4061052 CSR Table 13.5.2.2, A4061053 CSR Table 13.5.2, A4061063 CSR Table 13.5.2.2, A4060010 CSR Table 30 and Section 2.7.2 Appendix 1 Table 1.9, A4061022 CSR Table 13.5.2.3, A4061044 CSR Table 13.5.2.1.1.

C_{max} = maximal plasma concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time profile from time 0 to infinity; AUC_{0-12}= area under the plasma concentration-time profile from 0 to 12 hours; AUC_{0-24}= area under the plasma concentration-time profile from 0 to 24 hours ; AUC_{0-last}= area under the plasma concentration-time profile from 0 to the time of last quantifiable concentration; CL/F= apparent oral clearance; V_z/F= apparent volume of distribution during the elimination phase; $t_{1/2}$= terminal half-life; T_{max} = time of maximal plasma concentration; (b) (4) (b) (4) Mod Fat=moderate fat; VMD=volume median diameter

[a] %CVcalculated as Standard Deviation/Mean for study A4061004. [b] T_{max} = median with range; [c] Geometric Least Squares Mean (Geometric %CV); [d] AUC_{0-12} is provided for study A4060010 in fasted state, since $AUC_{0-\infty}$ was not reported; [e] The mL/min units converted to L/hr for A4061033 and A4061036 studies.[Note: n represents the largest number of subjects for whom at least one pharmacokinetic parameter was estimated].

Table 4. Pharmacokinetic Parameters for Axitinib (b) (4) after Administration of single doses of 5 mg and multiple doses of 5 mg twice daily under Fed Conditions in Patients with Cancer.

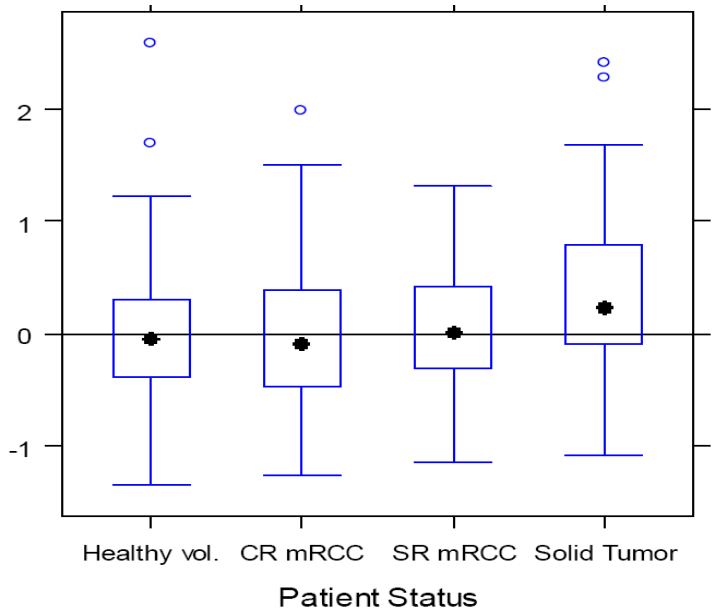
Patient Population	**Advanced Solid Tumor**		**Advanced RCC**
Study # (N)	**A4061044 Moderate fat (N=6)**		**A4061046 Moderate fat (N=20)**
PK Parameter	**C1D1**	**C1D15**	**C1D15**
Cmax (ng/mL) Geomean (CV%)	17.0 (70)	21.4 (84)	27.8 (79)

Cmax Rac Geomean (CV%) [90% CI]	1.26 (39) [0.87, 1.81]		n.a.
Tmax(h) Median (Range)	4.1 (4.0 – 6.0)	4.0 (3.9 – 7.7)	2.0 (1.0 – 2.5)
AUC (ng*h/mL)[a] Geomean (CV%)	100.4 (79)	137.6 (78)	265 (77)
AUC Rac Geomean[b] (CV%) [90% CI]	1.37 (28) [1.08, 1.74]		n.a
$T_{1/2}$ (h) Mean (CV%)	4.8 (59)	n.a.	4.1 (144)
CL/F (L/hr) Geomean (CV%)	35.2 (56.9)	36.3 (45)	37.8 (31.4)
Vd/F (L) Geomean (CV%)	206.4 (87.2)	n r.	160 (140)
Rac, accumulation ratio; n.r., not reported; n.a., not applicable [a] A4061044: AUC0-12; A4061046: AUC0-24			

2.2.8.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK of axitinib was similar between healthy volunteers and patients (Figure 5). Based on a combined population pharmacokinetic analysis, the clearance of axitinib was similar between healthy volunteers and patients. Furthermore, there was no effect of the patient population on clearance of axitinib. The median Tmax values were between 2.5 – 4.1 hours in the fed state (Table 3). High variability was observed in both the healthy subject and patient studies. See sections 2.2.8.1 and 2.2.16 for more information.

Figure 5. No effect of healthy vs. patients on the clearance of axitinib.
CR (cytokine refractory) and SR (sorafenib refractory)
(Source: Sponsor's pmar-00079 study report, Page 160)



2.2.9 What are the characteristics of drug absorption?

After oral dosing, axitinib is absorbed with a median Tmax occurring between 2.5 – 4.1 hours. The mean absolute bioavailability of a single dose of 5 mg oral axitinib is 58%. A single 1 mg dose of axitinib administered via intravenous infusion (Study A4061007) was used as the reference.

Compared to fasting conditions, a high-fat meal increased axitinib systemic exposure by ~19% but a moderate-fat meal decreased exposure by ~11% (Study A4061053). Axitinib may be taken with or without food. See section 2.5.4.

The aqueous solubility of axitinib is low over a wide range of pH values, and lower pH values result in higher solubility (section 2.5.1), which raises the question about the potential for gastric pH elevating agents (such as proton pump inhibitors (PPI), H2 blockers, or antacids) to alter the solubility of axitinib. The sponsor conducted a PK sub-study within Study A40610010 to evaluate the potential for drug-drug interactions with rabeprazole. In the presence of rabeprazole, a 42% decrease in axitinib Cmax (i.e., reduction in absorption rate) was observed. However, there were only a 15% decrease in AUC was observed, which is not considered clinical significant. There were no differences in Tmax or T½ with or without rabeprazole. Therefore, no axitinib dose adjustment is recommended. See section 2.4.8.

2.2.10 What are the characteristics of drug distribution?

Plasma Protein Binding

The mean binding of axitinib to proteins in human plasma was >99%, in a concentration-independent manner from 200 – 2000 ng/mL (Study AG13736-PDM-017).

Axitinib is highly bound to human serum albumin (HSA) in a concentration-independent manner from 10 – 300 ng/mL (mean [range] 99.0% [98.9 – 99.1%]) (Study 8216659).

A definitive value for the binding to α-1 acid-glycoprotein (AAG) could not be determined due to low recovery from the dialysis apparatus (≤ 46.1%) at the 10 – 100 ng/mL concentrations tested. The results, however, suggest that axitinib is moderately bound to AAG (mean 68.6%), with an unbound fraction between 0.291 – 0.342 (Study 8216659).

Protein binding analysis was conducted for plasma samples obtained from the hepatic impairment trial (A4061036). The geometric mean (CV%) unbound fraction (fu) of axitinib in the plasma of subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment was 0.0041 (25), 0.0030 (50), and 0.0041 (134), respectively (Table 8). The results of this analysis indicate that protein binding did not change based on mild and moderate hepatic impairment.

Blood to Plasma Ratio

Axitinib was relatively equally distributed between plasma and blood cells (Study AG13736-PDM-017). The blood-to-plasma ratios of axitinib *in vitro* in humans were 0.81 and 0.79 at concentrations of 0.39 µg/mL and 3.9 µg/mL, respectively.

In the human mass balance study A4061003, the mean whole blood to plasma $AUC_{0-\infty}$ ratio

(AUC_R) was 0.488, indicating that the radioactivity was preferentially retained in the plasma component of blood.

Tissue Distribution

Following a 1 mg axitinib intravenous dose, the geometric mean (CV%) volume of distribution is 68 L (23%) (Study A4061007), which suggests that axitinib is extensively distributed to peripheral tissues. Also see section 2.2.13.

Transporter Proteins

Axitinib is a substrate for P-glycoprotein, UGT1A1, BCRP, OAT1B1 and OAT1B3 *in vitro*. Axitinib inhibits P-gp, with an IC_{50} of 4.5 µM *in vitro*. No studies have been conducted with other transporter proteins. See sections 2.4.5 and 2.4.6.

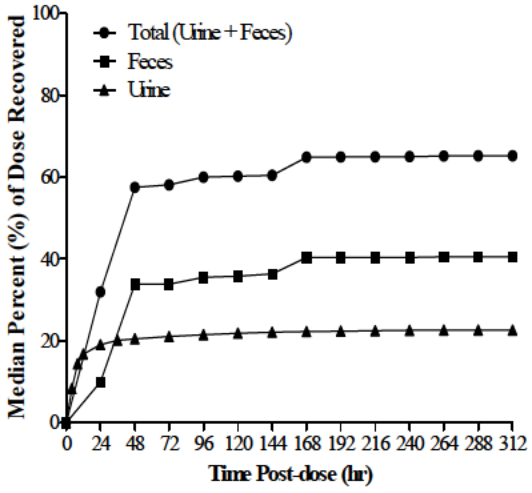
2.2.11 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The phase 1, open-label, single dose, mass balance study of [^{14}C]-labeled axitinib in healthy male subjects suggests that hepatic is a major route of elimination (Study A4061033, PDM-043).

Eight healthy male volunteers received a single dose of 5 mg (containing 100 µCi) of [^{14}C]-labeled axitinib (Figure 6) after an overnight fast. While urinary recovery was generally consistent across the 8 subjects in the study, the fecal recovery in 2 of 8 subjects was low (2.5% and 12.7%), possibly due to low fecal output. Therefore, those two individual data were excluded from the results reported below.

- The median total recovery of radioactivity in urine and feces combined was approximately 65.2% with approximately 22.7% (range 17.7 – 28.2%) recovered in urine and 40.6% (range 29.8 – 60.2%) recovered in feces.
- Axitinib was not detected in the urine; the carboxylic acid M5 represented the predominant metabolite (approximately 6% of the dose), followed by M12 (approximately 4% of the dose), M7 (approximately 3% of the dose), M9 (approximately 2% of the dose), and M8a (approximately 1% of the dose).
- The major component in feces was axitinib, with a mean recovery of 12% of the dose. All fecal metabolites together accounted, on average, for a mean recovery of 16% of the dose.

Figure 6. Median Cumulative Percent of Radioactive Dose Recovered in Urine and Feces at Specified Intervals after a Single 5 mg (100 µCi) Oral Dose of [^{14}C]-axitinib to Healthy Male Subjects in Study A4061003 (N=6).



2.2.12 What are the characteristics of drug metabolism?

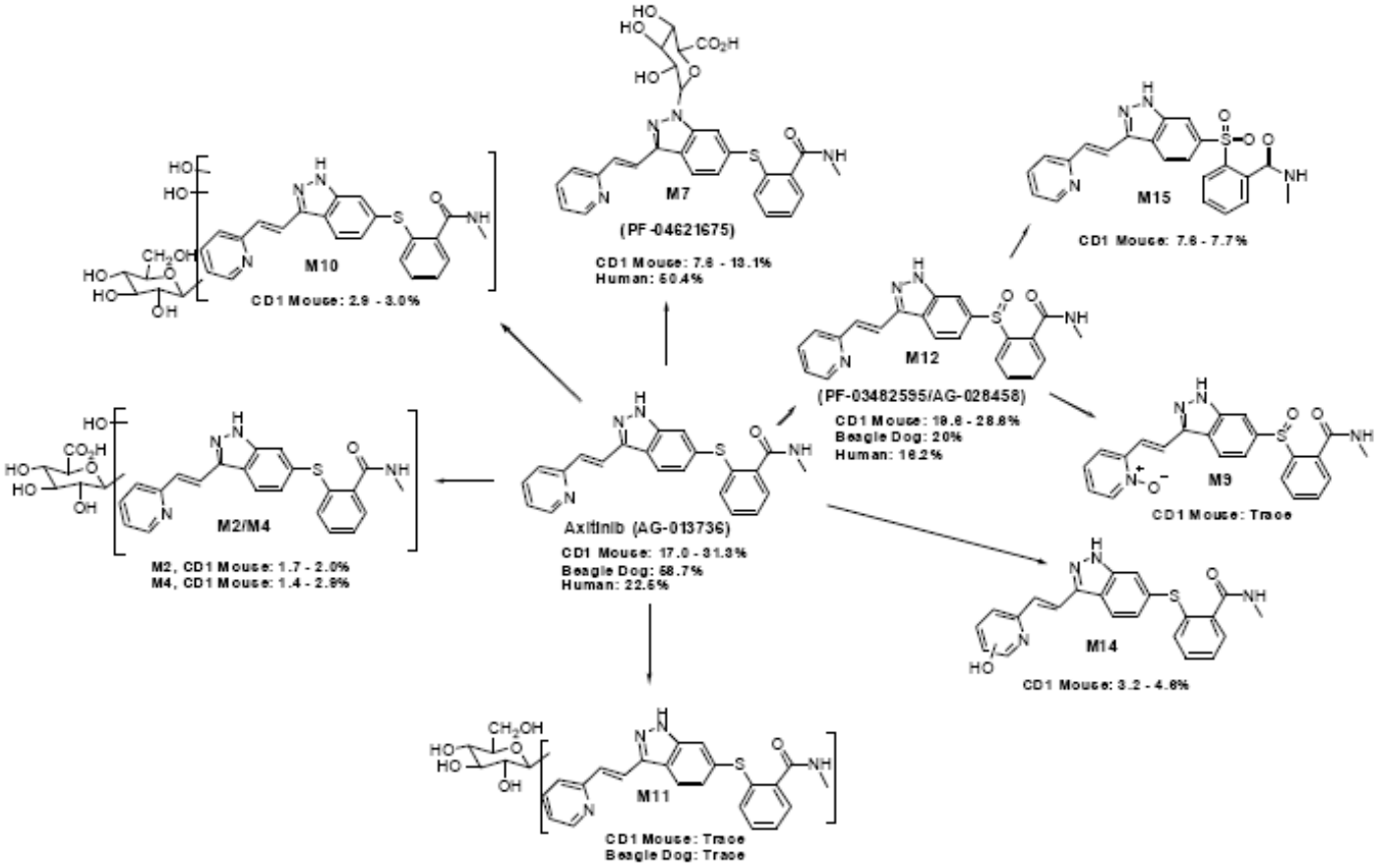
Axitinib undergoes extensive metabolism to a variety of primary and secondary metabolites, which are mediated by cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGT). Metabolic pathways included depyridinylation followed by formation of a carboxylic acid (M5), glucuronidation (M7), methyl hydroxylation followed by glucuronidation (M8a), mixed sulfoxidation/N-oxidation (M9), sulfoxidation (M12), mono-oxygenation on the pyridine ring (M12a and M14), and sulfonation (M15).

The main circulating metabolites in human plasma are the glucuronide M7 and the sulfoxide M12, accounting for about 50% and 16% of exposure, respectively (about 66% together). Unchanged parent axitinib accounts for about 22% of exposure. The M12 and M7 metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Based on in vitro studies, CYP3A4 is involved in the formation of the phase 1 metabolites. UGT1A1 is involved in the formation of M7.

The proposed metabolites of axitinib in plasma are presented in Figure 7.

Figure 7. Proposed *In Vivo* Axitinib Metabolic Schema.



2.2.13 What are the characteristics of drug excretion?

Elimination

In Study A4061003**,** the median (range) total recovery of radioactivity in urine and feces combined was approximately 65.2% (51.3% - 77.9%). The median (range) of dose recovered in feces was 40.6% (29.8% - 60.2%); and 22.7% (17.7% - 28.2%) was recovered in urine through the last collection interval.

Urine samples were collected at intervals of 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, and then at every 24 hour intervals through 168 hours (7 days) post-dose (discharge). Fecal samples were collected ad libitum at 24 hour intervals from pre-dose through 168 hours (7 days) post-dose (discharge). To be eligible for discharge on day 7 (168 hours post-dose), the radioactivity in subjects urine and fecal sample was to contain <1% of the administered radiolabeled dose.

Clearance

The geometric mean clearance (CV%) of axitinib was 21 L/h (44%) following a 1 mg intravenous dose in healthy volunteers (Study A4061007).

Volume of Distribution

The geometric mean volume of distribution (CV%) of axitinib was 68 L (23%) following a 1 mg intravenous dose in healthy volunteers (Study A4061007). Also see section 2.2.10.

Half-life

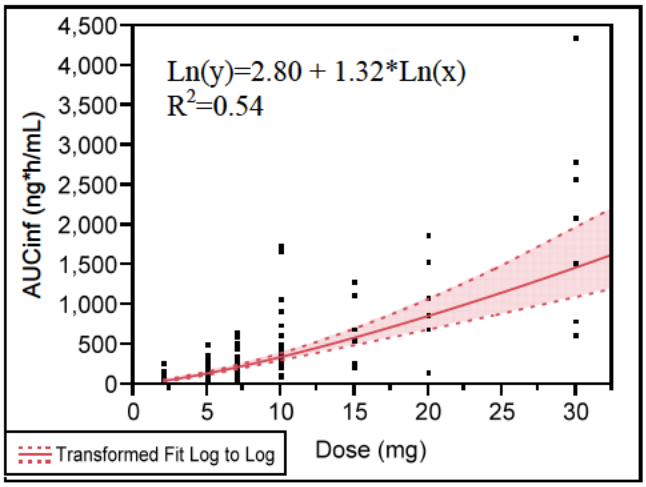
Axitinib's mean terminal elimination half-life ranges between 2.5 – 6.1 hours following single doses of 5 mg in healthy subjects and patients (Table 3). This is consistent with twice daily dosing proposed by the sponsor. Also see sections 2.2.8.1).

2.2.14 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

The doses of 1, 3, 5, 7, 10, 15, 20, and 30 mg were evaluated in the fed state across 4 studies (Studies A4060010, A4061019, A40601044, and A4061050). The PK of axitinib appears to increase with an increase in dose. Although the analysis of dose proportionality is confounded due to the presence of large inter-individual variability in exposure, there does not appear to be a major deviation from dose proportionality for doses between 1 - 20 mg at steady-state.

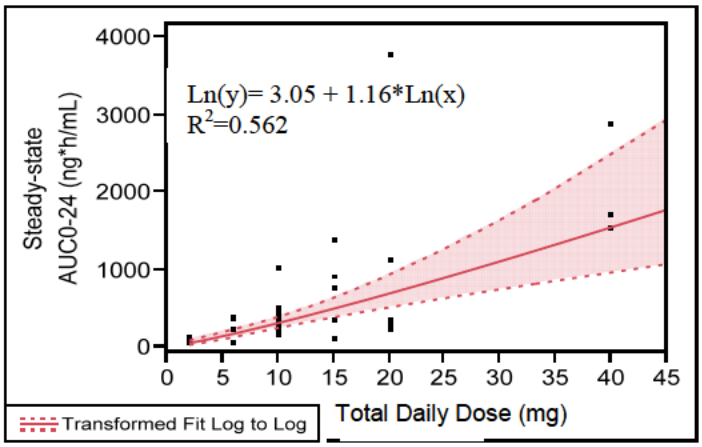
Single dosing: Using AUCinf data from single dosing (studies A4060010, A4061044, A4061050), a power model was applied to test dose proportionality (Figure 8). The slope for the power model on logarithmic scale is 1.32 for AUCinf with a 90% confidence interval of (1.05, 1.55).

Figure 8. Single dose Log AUCinf (ng*h/mL) vs. Log of Dose (mg) in the Dose Proportionality Studies (A4060010, A4061044, and A4061050) in the Dose Range of 2 to 30 mg.
The shaded area represents the 90% confidence interval of the slope.



Multiple dosing: Using AUC0-24 data from Cycle 1, Day 15 bid dosing (study A4060010 (N=34)) and following 3 days of bid dosing (study A4061019 (N=14), a power model was applied to test dose proportionality (Figure 9). The slope for the power model on logarithmic scale is 1.16 for AUC0-24 with a 90% confidence interval of (0.80, 1.52).

Figure 9. Steady-state Log AUC0-24 (ng*h/mL) vs. Log of the Total Daily Dose (mg) in the Dose Proportionality Studies (A4060010 and A4061019) in the Dose Range of 1 to 20 mg Twice Daily.
The shaded area represents the 90% confidence interval of the slope.



2.2.15 How do the PK parameters change with time following chronic dosing?

In patients with advanced solid tumors (Study A4061044), axitinib accumulation was ~1.4-fold following 5 mg twice daily at steady-state as compared to a single 5 mg dose (
Table 4). The inter-subject variability was approximately 80% for both Cmax and AUC after single and multiple dosing; see section 2.2.8.1.

2.2.16 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on the population PK modeling, between-subject variability for clearance and volume of distribution was 60% and 40%, respectively after adjusting for significant covariates. The significant covariates from the model failed to explain the variability noted in axitinib pharmacokinetic to any appreciable extent (<5%), see section 2.2.8.1.

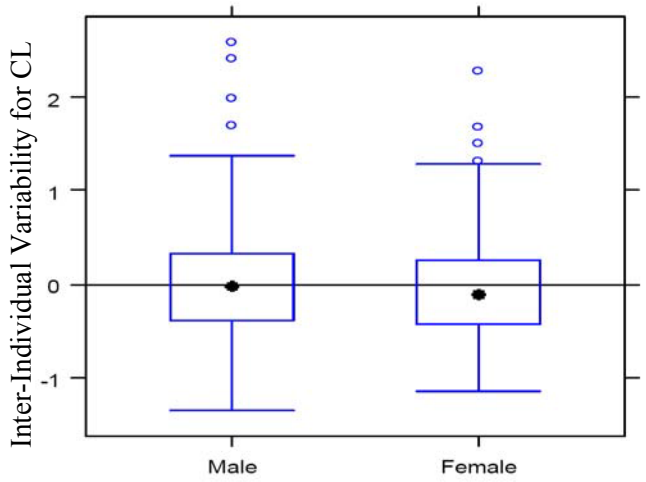
2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, gender, race, body weight, BSA, or renal function on the pharmacokinetics of axitinib. The applicant's population pharmacokinetic (popPK) model did not identify any clinically relevant impact of these covariates on clearance.

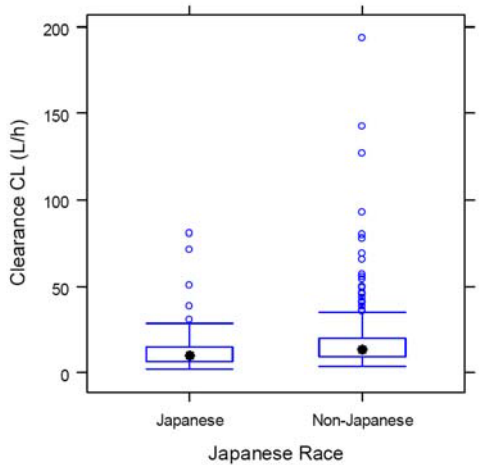
Relationship between Gender and Exposure
Based on the popPK analysis, there was no effect of gender on clearance of axitinib (Figure 10).

Figure 10. No effect of gender on the clearance of axitinib.
(Source: Sponsor's pmar-00079 study report, Page 157)



Relationship between Race and Exposure
Based on the population pharmacokinetic analysis, it was observed that Japanese patients had 25% lower clearance than the non-Japanese patients (Figure 11). However, based on a dedicated study (A4061026), in which PK of 20 Caucasians and 20 Japanese patients was compared using intensive PK sampling, there was no difference observed in the Cmax and AUC.

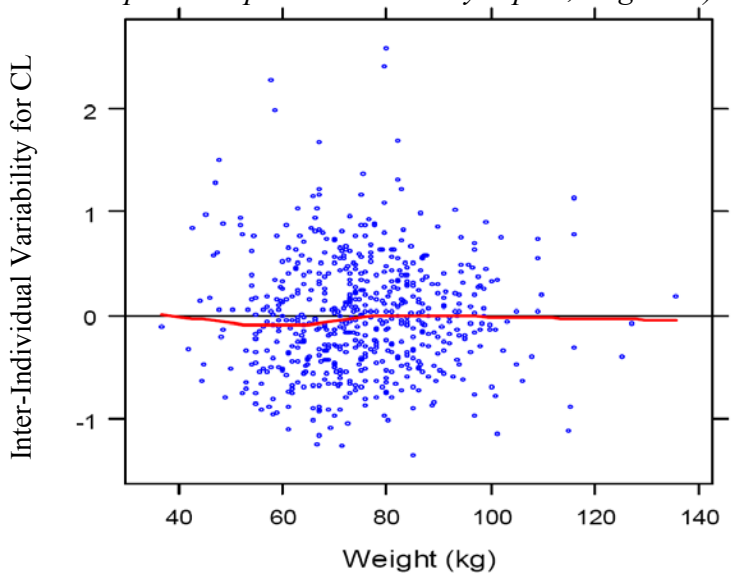
Figure 11. Axitinib clearance in Japanese vs. non-Japanese patients from the popPK model.
(Source: Sponsor's pmar-00079 study report, Page 156)



Relationship between Weight and Exposure

Based on the population pharmacokinetic analysis, there was no effect of body weight on clearance of axitinib (Figure 12). Weight was significant covariate on volume of distribution. However, inclusion of weight reduced the inter-individual variability for volume of distribution by only 4% (44 to 40%).

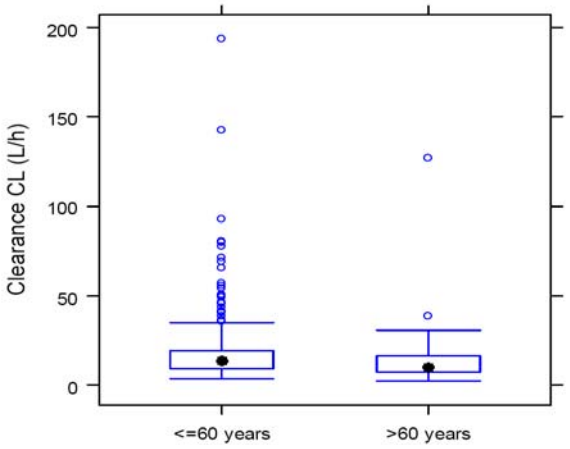
Figure 12. No effect of weight on the clearance of axitinib.
(Source: Sponsor's pmar-00079 study report, Page 162)



Relationship between Age and Exposure

Age was tested both as a continuous and binary (age <60 and age >60 years) covariate. When used as a binary covariate, age was found to affect axitinib exposures, such that subjects >60 years had a 21% decrease in clearance (Figure 13). This decrease in clearance is not considered to be clinically relevant.

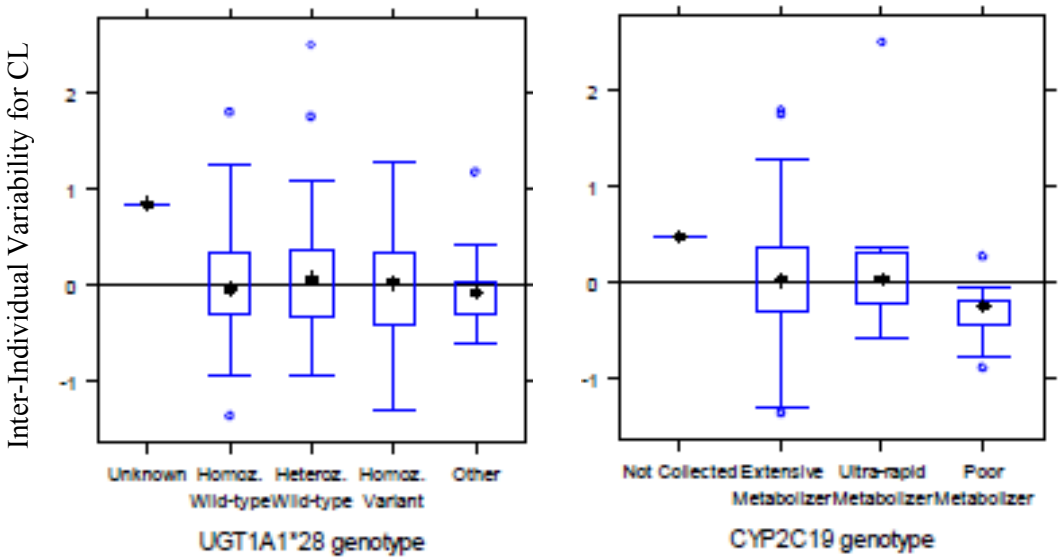
Figure 13. Axitinib clearance in <60 and >60 year subjects.
(Source: Sponsor's pmar-00079 study report, Page 165)



Relationship between Genotype and Exposure

The potential effect of selected polymorphisms in UGT1A1 and CYP2C19 on axitinib pharmacokinetic variability was evaluated using population pharmacokinetic analysis of pooled data from 10 healthy volunteer phase 1 studies (n=337). For UGT1A1*28, the popPK dataset included 35 subjects who were homozygous for the UGT1A1*28 allele. For CYP2C19, the popPK dataset included 8 subjects categorized as ultra-rapid metabolizers, and 15 subjects categorized as poor metabolizers. There was no apparent effect of these gene polymorphisms on axitinib clearance (Figure 14). This is consistent with the *in vitro* observation that axitinib is metabolized primarily by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19 and UGT1A1.

Figure 14. No effect of UGT1A1*28 (left) and CYP2C19 (right) genotype on axitinib clearance.
(Source: Sponsor's pmar-00075 study report, Page 136, 138)



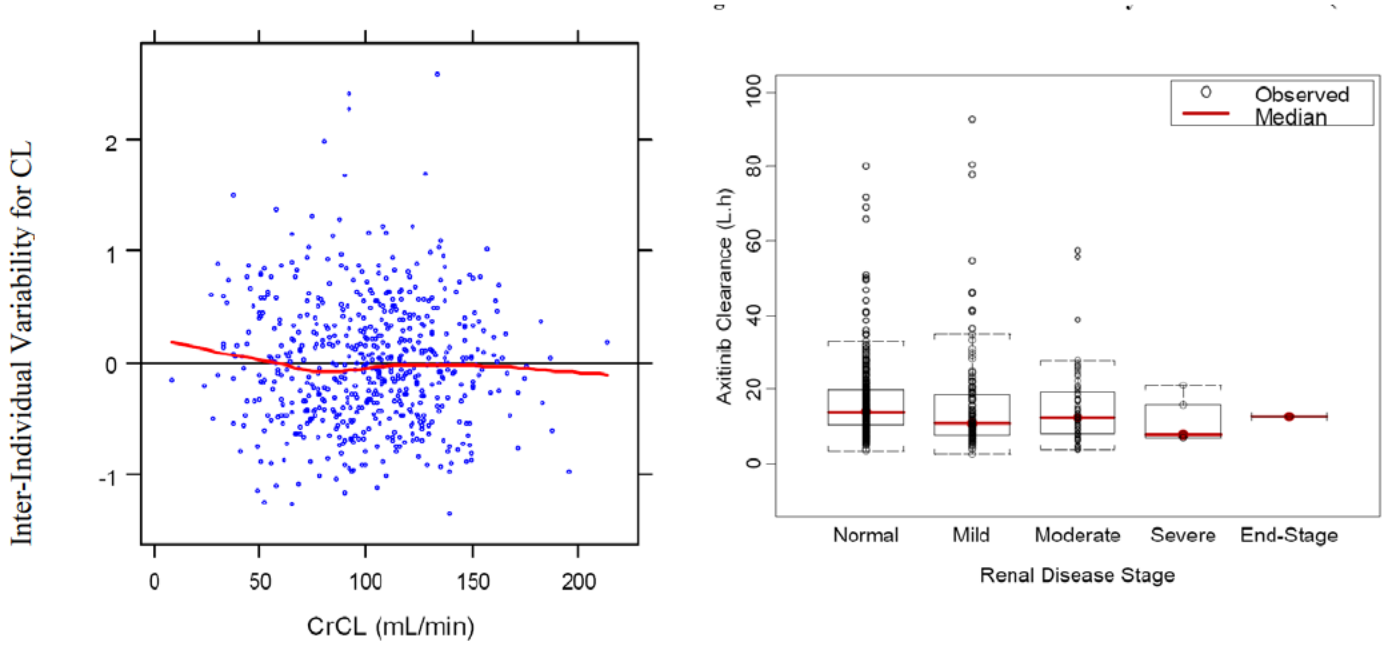
Selected polymorphisms in UGT1A1 and CYP2C19 and in genes for other drug metabolizing enzymes and transporters associated with axitinib disposition were also assessed using a meta-analysis of pooled data from 11 healthy volunteer phase 1 studies. According to this analysis, there did not seem to be a clinically meaningful correlation between the examined polymorphisms and axitinib plasma exposure ($AUC_{0\text{-}inf}$). However, conclusive results could not be drawn for some of the gene variants for which only a limited number of subjects were assayed. For details, refer to Pharmacometrics Review and Genomics Group Review in Appendix 4.1 and 4.2, respectively.

Relationship between Renal Impairment and Exposure

The applicant did not conduct a dedicated organ impairment trial to assess the effect of renal impairment on axitinib exposure. Based on the population PK analysis, baseline renal function (creatinine clearance estimated using Cockroft-Gault equation) did not have a significant effect on the clearance of axitinib (Figure 15). The baseline renal function data included in the analysis comprised of 381 subjects with normal renal function (CrCL > 90 mL/min), and 139, 64, 5, and 1 subjects with mild (CrCL 60 - 89 mL/min), moderate (CrCL 30 – 59 mL/min), severe (CrCL 15 – 29 mL/min), and end-stage (CrCL < 15 mL/min) pre-existing renal impairment, respectively. As only one subject was enrolled that had end-stage renal impairment, a definitive conclusion regarding the effect of end-stage renal impairment on axitinib exposure cannot be made.

Figure 15. No effect of CrCL in axitinib clearance (left) and individual observed and median with 25th - 75th percentile range Axitinib Clearance (L/h) after Administration of 5 mg in Healthy Volunteers and/or Patients with Normal (N=381), Mild (N=139), Moderate (N=64), Severe (N=5), or End-stage (N=1) Renal Impairment (right).

(Source: (left) Sponsor's pmar-00079 study report, Page 166: Right: Sponsor's pmar-00079 study report, Page 67)



Relationship between Hepatic Impairment and Exposure

In a dedicated hepatic impairment trial (A4061036), systemic exposure (total and unbound Cmax and AUC) of axitinib for the mild hepatic impairment cohort (Child-Pugh Classification A) was comparable to that in the normal hepatic function cohort. The geometric mean Cmax and AUC for the mild group were approximately 11% and 22% lower, respectively, than that in the normal hepatic function cohort (Table 5, Figure 16). However, based on geometric mean estimates, the axitinib (total and unbound) Cmax and AUC were approximately 1.3-fold and 2-fold greater, respectively, in the moderate hepatic impairment group (Child-Pugh Classification B) compared to the normal hepatic function group (Table 5, Figure 16). The mean elimination $T_{1/2}$ was approximately 2.4 hours longer for the moderate hepatic impairment cohort compared to the normal hepatic function cohort (Table 6). Inter-subject variability (CV%) in Cmax and AUC in the normal and moderate impairment cohorts was between 44 – 69%, while it was between 127 – 180% in the mild hepatic impairment cohort. The increase in inter-individual variability in subjects with mild hepatic impairment was attributed to 2 subjects who had very low observed plasma concentrations (the reason for the low concentrations is unknown). Regarding safety, there were no Grade 3/4 toxicities reported.

Table 5. Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Axitinib (total and unbound) Comparing Healthy Volunteers with Mild or Moderate Hepatic Impairment to Volunteers without Hepatic Impairment in Study A4061036.

Parameter	Comparisons	Geometric Mean		T/R (%)	90% CI
		Test	Ref		
Cmax (ng/mL)	Mild vs. Normal	27.0	30.4	88.6	49.2, 159.6
	Moderate vs. Normal	38.9	30.4	127.7	70.9, 229.9
AUC_{inf} (ng*h/mL)	Mild vs. Normal	122	156	78.3	39.9, 153.8
	Moderate vs. Normal	304	156	168.3	99.5, 383.2
AUC_{last} (ng*h/mL)	Mild vs. Normal	116	148	78.1	38.7, 157.8
	Moderate vs. Normal	295	148	198.9	98.5, 401.7

Plasma samples were collected up to 144 hours post-dose.
Normal hepatic function was the Reference (Ref). Mild and moderate hepatic impairment were the Test treatments.

Figure 16. Individual and Geometric mean with 95% CI Axitinib (total and unbound) AUC_{last} (ng*h/ml) after Administration of 5 mg in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study A4061036.

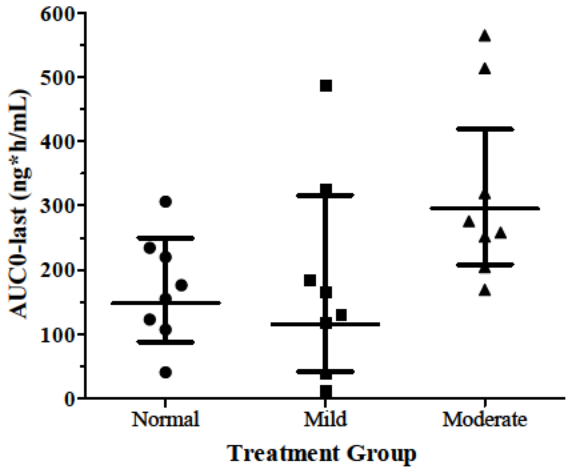


Table 6. Geometric mean (CV%) Pharmacokinetic Parameters for Axitinib (total and unbound) after Administration of 5 mg in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study A4061036.

Parameters	Normal (N=8)	Mild (N=8)	Moderate (N=8)
Cmax (ng/mL)	30.4 (50)	27.0 (127)	38.8 (50)
Tmax[a] (h)	3.5 (2.0 – 4.0)	2.75 (1.0 – 4.0)	4.0 (1.5 – 4.0)
AUC_{inf} (ng*h/mL)	156 (63)	122 (167)	304 (44)
$AUC_{0\text{-last}}$ (ng*h/mL)	148 (69)	116 (180)	295 (44)
$T_{1/2}$ (h)	4.7 (80)	3.6 (84)	7.1 (91)
CL/F (L/h)	32.1 (63)	41.0 (167)	16.4 (44)
Vd/F (L)	166 (52)	163 (87)	128 (67)
Tmax is reported as median (range); t½ is reported as mean (CV%). Plasma samples were collected up to 144 hours post-dose.			

Mild and moderate hepatic impairment did not appear to alter the plasma protein binding for axitinib, where the axitinib unbound fraction in plasma (fu) was 0.3% to 0.4% (Table 7). Axitinib unbound PK parameters followed a similar trend as total PK parameters. Mild hepatic impairment did not alter unbound axitinib plasma exposure (Cmax and AUC) compared to normal hepatic function. However, there was a 1.3-fold and 2-fold increase in axitinib unbound Cmax and AUC in subjects with moderate hepatic impairment compared to subjects with normal hepatic function (Table 8).

Table 7. Geometric mean (CV%) Pharmacokinetic Parameters for Axitinib (unbound) after Administration of 5 mg in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study A4061036.

Parameters	Normal (N=8)	Mild (N=5*)	Moderate (N=8)
$Cmax_{unbound}$ (ng/mL)	0.123 (46)	0.132 (47)	0.159 (97)
$AUC_{last\ unbound}$ (ng*h/mL)	0.601 (61)	0.671 (81)	121 9106)
$CL/F_{unbound}$ (L/h)	132000 (56)	121000 (82)	67100 (109)
$Vd/F_{unbound}$ (L)	41100 (57)	42400 (40)	31300 (121)
fu	0.0041 (25)	0.003 (50)	0.0041 (134)
*N=5 because 3 subjects were excluded due to limited plasma volume when performing the protein binding assay.			

Table 8. Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Axitinib (unbound) Comparing Healthy Volunteers with Mild or Moderate Hepatic Impairment to Volunteers without Hepatic Impairment in Study A4061036.

Parameter	Comparisons	Geometric Mean		T/R (%)	90% CI
		Test	Ref		
$Cmax_{unbound}$ (ng/mL)	Mild vs. Normal	0.13	0.12	106.8	58.2, 196.0
	Moderate vs. Normal	0.16	0.12	128.8	(75.6, 219.3)
$AUC_{last\ unbound}$ (ng*h/mL)	Mild vs. Normal	0.67	0.60	111.7	54.4, 229.4
	Moderate vs. Normal	1.21	0.60	200.6	106.7, 377.2
fu	Mild vs. Normal	0.003	0.004	73.8	37.4, 145.6
	Moderate vs. Normal	0.0041	0.0040	100.9	55.6, 183.0
Normal hepatic function was the Reference (Ref). Mild and moderate hepatic impairment were the Test treatments.					

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

- Renal: No dose adjustment is necessary for patients with mild, moderate, or severe renal impairment. No dose adjustments can be recommended for patients with end-stage renal impairment due to insufficient data. See section 2.3.1
- Hepatic: No dose adjustment is necessary for patients with mild hepatic impairment. A 50% reduction in dose is needed for patients with moderate hepatic impairment. Axitinib has not been studied in patients with severe hepatic impairment and no dose adjustments can be recommended. See section 2.3.1.
- Pediatric patients: The safety and effectiveness have not been established in pediatric patients.

2.3.3 What pregnancy and lactation use information is there in the application?

The safety and effectiveness of axitinib have not been established in pregnancy and in lactating women.

2.4 EXTRINSIC FACTORS

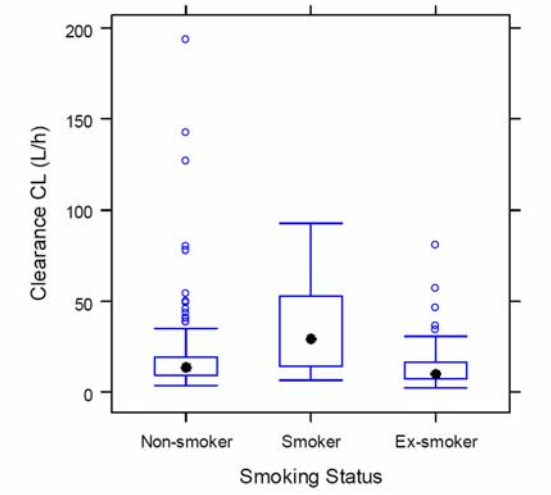
2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, and alcohol use on the dose-exposure and/or dose-response for axitinib have not been assessed in formal clinical studies.

Smoking

The effect of smoking status was evaluated using population PK analysis. The dataset included 434 non smokers, 19 active smokers and 137 ex-smokers. The analysis indicated that the clearance in active smokers was higher (102%) however the smoking effect was not well defined with a standard error of 40% (Figure 17). The number of current smokers in this dataset is only 19 (3%) and thus the results should be interpreted with caution. The sponsor mentions that the effect of smoking will be adequately characterized in future studies, like NSCLC trials, where higher proportion of current smokers is expected. Given that the axitinib dose is titrated up based on tolerability, it is considered acceptable that the sponsor will adequately characterize the effect of smoking status on axitinib PK in future studies.

Figure 17. Axitinib clearance in non-smokers, active-smokers and ex-smokers.
(Source: Sponsor's pmar-00079 study report, Page 158)



Drug-drug interactions

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes. *In vitro* bases exist for potential *in vivo* drug-drug interactions between axitinib with CYP3A4 inhibitors and inducers, CYP1A2 or CYP2C8 substrates, P-gp substrates and inhibitors, UGT1A1 inhibitors and inducers, and gastric pH elevating agents.

CYP3A4 was identified as the major CYP isozyme responsible for axitinib metabolism (section 2.4.3). Inhibitors and inducers of CYP3A4 are expected to affect the pharmacokinetics of axitinib (section 2.4.4), which was confirmed by *in vivo* studies with ketoconazole and rifampin (section 2.4.8).

Axitinib was identified as an inhibitor of CYP1A2 (Ki = 0.7 μM for phenactin) and CYP2C8 (Ki = 0.5 μM for paclitaxel) *in vitro* (section 2.4.4).

Axitinib was identified as a substrate and inhibitor of P-gp *in vitro*. Axitinib has the potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp (section 2.4.5).

The aqueous solubility of axitinib is pH dependent, with higher pH resulting in lower solubility (section 2.5.1), which raises the question about the potential for gastric pH elevating agents (such as proton pump inhibitors (PPI), H2 blockers, or antacids) to alter the solubility of axitinib. An *in vivo* study was conducted with the PPI, rabemeprazole, where a 15% decrease in exposure was observed, which is not considered clinically significant (sections 2.2.9 and 2.4.8).

2.4.3 Is the drug a substrate of CYP enzymes?

The *in vitro* screen (study PDM-019) suggests that that axitinib is primarily metabolized by CYP3A4, while CYPlA2, CYP2C19 and CYP3A5 contribute to a lesser extent. These four P450 isoforms (CYP3A4, CYP3A5, CYP1A2, and CYP2C19) generated all the oxidative metabolites, with M12 being the major oxidative metabolite. Similarly, the human mass balance study (study A4061003, PDM-043) showed that the M12 metabolite was found in plasma and urine.

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

***In vitro* inhibition**

Axitinib demonstrated inhibitory effect on CYP1A2 and CYP2C8.

The PK drug-drug interaction potential of axitinib was evaluated using human liver microsomes (study PDM-020). All CYP substrates used were FDA preferred and acceptable chemical substrates for *in vitro* experiments. The inhibition of CYP2B6 was not evaluated. The [I]/Ki ratios for only CYP1A2 and CYP2C8 are estimated as >0.1, given the observed mean Cmax at steady state of ~30 ng/mL (0.078 µM) on Day 15 of Cycle 1 following 5 mg bid (Table 4).

Table 9. Ki values (µM) for axitinib inhibition of CYP activities in human liver microsomes (study PDM-020).

P450 Isozyme	Substrate	Ki (µM)	[I]/Ki calculated from Cmax 30 ng/mL (0.077 µM)
CYP1A2	phenacetin	0.7	**0.11**
CYP2A6	coumarin	ND	<0.001
CYP2B6	n/a	n/a	n/a
CYP2C8	paclitaxel	0.5	**0.15**
CYP2C9	tolbutamide	52.2*	<0.001
CYP2C19	S-mephenytoin	ND	<0.001
CYP2D6	dextromethorphan	ND	<0.001
CYP2E1	chlorzoxazone	ND	<0.001
CYP3A4	testosterone	8.3	0.009
*Due to limited solubility, axitinib concentrations >50 µM could not be achieved in HLM. Maximum inhibition of CYP2C9 at 50 µM of axitinib was only 51%. Therefore, the Ki value reported for this isoform may not be accurate.			

***In-vitro* time-dependent inhibition (TDI)**

The effect of axitinib on CYP1A2-dependent phenacetin O-deethylation activity in human liver microsomes was evaluated (study PDM-039). Axitinib 2.5 µM inhibited ~90% of CYP1A2-dependent activity (IC50 values ranged from 0.2-0.3 µM) and did not show TDI toward CYP1A2. The concentrations of axitinib used in this study were above clinically relevant maximum plasma concentrations.

***In vivo* inhibition**

An *in vivo* study with paclitaxel (CYP2C8 substrate) in patients with advanced cancer was conducted to assess the potential inhibition of CYP2C8 by axitinib. The study demonstrated that coadministration did not increase paclitaxel plasma concentrations, indicating a lack of CYP2C8 inhibition (section 2.4.8). Of note, the sponsor used a SymCYP modeling and simulation approach to assess the potential inhibition of CYP1A2 by axitinib (data not presented in this review).

***In vitro* induction**

An *in vitro* study (study 764-05388) investigated the potential of axitinib to induce CYP1A1/2 (probe resorufin) and CYP3A4 (probe testosterone) in two and three lots, respectively, of fresh human hepatocytes. Axitinib (up to 1.29 µM) caused no significant induction in 7-

ethoxyresorufin O-dealkylation (0.5 – 2.7-fold increase) or in testosterone 6β-hydroxylase activity (0 – 1.1-fold increase), suggesting that axitinib is not associated with induction of CYP1A1/2 or CYP3A4 activity, respectively. The positive controls showed positive induction signals in the same system. Based on the FDA drug-drug interaction guidance if axitinib is not an inducer of CYP3A4 then it can be concluded that it is not an inducer of 2C8, 2C9, or 2C19.

2.4.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?

P-gp Substrate

Yes, *in vitro* study suggested that axitinib is a substrate for P-gp. In *in vitro* studies, the bi-directional transport of axitinib was measured in Caco-2 cells (study PDM-021) and MDCK-MDR1 cells (study 10Dec0811/1529) in the apical (A) to basolateral (B) and B to A directions. Axitinib had a high permeability in both A to B and B to A directions in Caco-2 cells, with an efflux ratio of 6.2. In MDCK-MDR1 cells, the axitinib 1 μM efflux ratio was 2.7 (Table 10). In the presence of the Pgp inhibitor, cyclosporine A, the transport of axitinib was significantly reduced in both directions, resulting in a reduced efflux ratio of <0.5 (Table 10). Since the inhibitor decreased the flux ratio by more than 50% the results indicate that axitinib is a Pgp substrate.

Table 10. Effect of increasing Axitinib (AG-013736) concentration on MDR1-MDCK permeability, efflux and inhibition.

AG-013736 Concentration (μM)	MDR1-MDCK Papp ($x10^{-6}$ cm/sec)			MDR1-MDCK + CsA Papp ($x10^{-6}$ cm/sec)		
	AB	BA	BA/AB Ratio	AB	BA	BA/AB Ratio
0.5	56	80	1.4	32	15	0.46
1.0	20	55	2.7	29	11	0.39
2.0	27	46	1.7	32	13	0.41
3.0	23	24	1.0	30	12	0.40
5.0	19	30	1.6	36	14	0.37
10.0	26	28	1.1	30	13	0.43

P-gp Inhibition

Yes, axitinib is an inhibitor of P-gp mediated transport *in vitro*, with an estimated IC_{50} of 4.5 μM on digoxin efflux. An *in vitro* study (study 21Jan09/055543) was performed to assess the Pgp inhibitory effect of axitinib. This was done by measuring [^{3}H]-digoxin (5 μM) as a probe substrate in Caco-2 cells. Eleven concentrations of axitinib (between 0.1 to 75 μM) were used for the study. The data showed that axitinib is a concentration-dependent inhibitor of digoxin efflux (Table 11). However, the experiment was limited by solubility and the sponsor excluded data from 20 μM and above from all calculations.

Table 11. Digoxin Papp and net secretory flux values across Caco-2 cell monolayers in the presence of increasing concentrations of axitinib.

Concentration of AG-013736 (μM)	Mean A-B Papp ($x10^{-6}$cm/s, ±SD) (n=3)	Mean B-A Papp ($x10^{-6}$cm/s, ±SD) (n=3)	Net Secretory Flux (nmol/cm^2/h)	Degree of digoxin flux (%)
0	1.95 ± 0.15	14.98 ± 1.23	0.23	
0.1	2.36 ± 0.32	13.57* ± 0.73	0.20	85.99
1	3.81 ± 0.37	12.98 ± 0.15	0.17	70.38
3	3.89* ± 0.22	10.80 ± 0.23	0.12	53.01
5	3.95 ± 0.10	9.76 ± 0.30	0.10	44.58
7	2.54 ± 0.07	6.89 ± 0.06	0.08	33.32
10	3.65 ± 0.13	9.46 ± 0.28	0.10	44.28
20	3.48 ± 0.15	9.86 ± 0.11	0.11	48.97
30	3.19 ± 0.11	11.20 ± 0.06	0.14	61.49
40	3.15* ± 0.12	11.08 ± 0.45	0.14	60.85
50	3.07 ± 0.09	10.52 ± 0.09	0.13	57.15
75	3.20 ± 0.09	10.37 ± 1.16	0.13	55.21

*mean of *n* = 2 ± range

2.4.6 Are other metabolic/transporter pathways important?

Uridinediphosphate glucuronosyl transferase (UGT)

In humans, M7 represented the predominant circulating metabolite accounting for ~50% of the circulating radioactivity. M7 was also present in low levels in human urine but not in feces (studies A4061003, PDM-043). An *in vitro* study (study PDM-048) was conducted with a panel of uridinediphosphate glucuronosyl transferase (UGT) isoforms (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17) to identify the isoform(s) responsible for the *in vivo* glucuronidation of axitinib in humans. Results indicated that the major human circulating metabolite, M7 (an N-glucuronide of axitinib), was mediated by UGT1A1.

In vitro study (study 301040127), determined whether axitinib inhibited human UGT1A1 catalytic activity, measured using 17β-estradiol as a model substrate and cDNA-expressed UGT1A1 as the enzyme source. The bilirubin positive control inhibited the UGT1A1 catalytic activity with an IC_{50} value of 12.3 μM, demonstrating that the test system was performing properly. The results show that axitinib did not inhibit the UGT1A1 catalyzed 17β-estradiol glucuronidation activity by 50% at the highest tested concentration of 30 μM; therefore an IC_{50} value could not be calculated.

Others (e.g., BCRP, OAT, OCT)

In vitro study suggested that axitinib is a BCRP substrate. In an *in vitro* study (study 10Dec0811/1529), the bi-directional transport of axitinib was measured in Madin-Darby canine kidney (MDCK)-BCRP cells in the apical (A) to basolateral (B) and B to A directions. Axitinib had a high permeability in both A to B and B to A directions in MDCK-BCRP cells, with an efflux ratio of 3.4 at the axitinib 1.0 μM concentration (Table 12). In the presence of the BCRP inhibitor, cyclosporine A, the transport of axitinib was significantly reduced in both directions, resulting in a reduced efflux ratio of <0.5 (Table 12).

Table 12. Effect of increasing axitinib concentration on BCRP-MDCK permeability, efflux and inhibition.

AG-013736 Concentration (μM)	BCRP-MDCK Papp ($x10^{-6}$ cm/sec)			BCRP-MDCK + CsA Papp ($x10^{-6}$ cm/sec)		
	AB	BA	BA/AB Ratio	AB	BA	BA/AB Ratio
0.5	42	92	2.2	33	16	0.49
1.0	18	60	3.4	31	15	0.48
2.0	27	39	1.5	37	14	0.37
3.0	18	29	1.6	32	14	0.43
5.0	18	39	2.1	37	17	0.45
10.0	24	25	1.0	34	13	0.39

Axitinib-mediated inhibition of BCRP was not evaluated.

In vitro experiments (study 10Dec08/111529) showed that axitinib is a substrate for OATP1B1 and OATP1B3 (Table 13).

Table 13. Effect of increasing axitinib concentration on OATP efflux.

Target AG-013736 Conc. (μM)	OATP Uptake Rate (pmoles/min)		
	OATP-2B1	OATP-1B1	OATP-1B3
0.5	NA	0.06 ± 0.11	0.11 ± 0.01
1	NA	-0.03 ± 0.02	0.09 ± 0.08
2	NA	0.59 ± 0.19	1.01 ± 0.07
3	NA	0.84 ± 0.01	1.49 ± 0.01
4	NA	0.66 ± 0.21	1.35 ± 0.36
5	NA	0.58 ± 0.05	0.81 ± 0.06
7.5	NA	0.79 ± 0.90	1.25 ± 0.99
10	NA	1.59 ± 1.09	0.95 ± 1.80

Note: 'NA' indication for OATP-2B1 is due to lack of uptake for this transporter in the study.

Axitinib-mediated inhibition of OATP transporters was not evaluated.

Axitinib has not been evaluated as a substrate for renal secretory transporters (organic cation transporter [OCT2], and organic anion transporters [OAT] 1 and 2).

2.4.7 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, c-administration of other drugs is not specified in the label. Axitinib 5 mg twice daily is to be used as monotherapy for the treatment of advanced RCC.

2.4.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. Drug-drug interaction studies with ketoconazole and rifampin demonstrated that concomitant use of strong inhibitors or inducers of CYP3A4/5 should be avoided. However, if a strong CYP3A4/5 inhibitor must be co-administered, the axitinib dose should be reduced by half.

A drug-drug interaction study with paclicaxel (a CYP2C8 substrate) demonstrated that coadministration of axitinib did not increase paclitaxel plasma concentrations, indicating a lack

of CYP2C8 inhibition.

A pharmacokinetic sub-study within study A40610010 evaluated the potential for a drug-drug interaction with rabeprazole. In the presence of rabeprazole, there was only a 15% decrease in axitinib AUC, which is not considered clinical significant. Therefore, no axitinib dose adjustment is recommended.

Drug Interaction with Strong CYP3A4 Inhibitor

Trial A4061004 was a randomized, open-label, 2-period, 2-treatment, 2-sequence, crossover, single-dose study of axitinib alone or with ketoconazole in the fasted state to healthy adult volunteers. Before the start of the first treatment period, there were lead-in baseline and placebo days. Each subject received Treatment A (5 mg axitinib on Day 1) and Treatment B (400 mg ketoconazole daily on Days 1 – 7; and 5 mg axitinib on Day 4). There was a 14 day washout between treatment periods.

The pharmacokinetic parameters of axitinib are summarized in

Table 14. Results suggested that compared to axitinib administration alone, the coadministration of ketoconazole increases the AUC_{inf} and C_{max} of axitinib by a mean of 106% and 50%, respectively (Table 15, Figure 18).

Table 14. Geometric mean (95% CI) pharmacokinetic parameters of axitinib with and without multiple doses of ketoconazole.

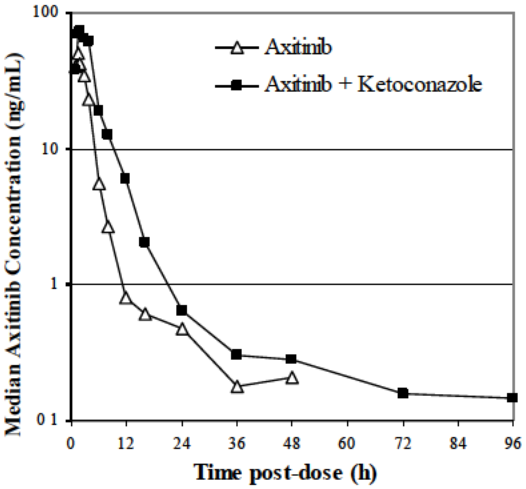
PK Parameter (units)	Axitinib 5 mg (N=32)	Axitinib 5 mg + Ketoconazole 400 mg qd (N=28)
AUC_{inf} (ng*h/mL)	200 (164, 244)*	409 (335, 500)
AUC_{last} (ng*h/mL)	193 (159, 235)	406 (331, 497)
Cmax (ng/mL)	51 (44, 59)	77 (66, 91)
Tmax (h)	1.5 (1, 3)	2.0 (1.0, 4.1)
t½ (h)	6.5 (4.2, 9.1)	10.8 (8.5, 13.8)
Vz/F (L)	235 (180, 308)	191 (145, 250)
CL/F (L/h)	24.9 (20.5, 30.4)	12.2 (10.0, 14.9)
*N=31; Tmax: median (range).		

Table 15. Effect of multiple doses of ketoconazole on the pharmacokinetics of single dose of axitinib in Study A40601004. Test = AG-013736 (axitinib) 5 mg + ketoconazole 400 mg qd (N=28); Reference = axitinib 5 mg (AUC, N=31; Cmax: N=32).

	Geometric LS Mean (95% CI)		Statistical Comparison ([AG-013736 + ketoconazole]/ [AG-013736])	
PK Parameter (unit)	AG-013736 (n=31)	AG-013736 + Ketoconazole (n=28)	Geometric LS Mean Ratio	90% CI
$AUC_{0-\infty}$ (ng*hr/mL)	196.7 (162.0, 238.8)	404.8 (332.2, 493.2)	2.06	1.84, 2.30
AUC_{last} (ng*hr/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

LS = least squares, CI = confidence interval

Figure 18. The median time-concentration profiles of axitinib in healthy subjects on a semi-log scale, following a single 5 mg oral axitinib dose alone (N=31) or coadministered with 400 mg ketoconazole once daily (N=28) in a 2-treatment, 2-period, 2-sequence crossover design.



Based on the above results, co-administration of axitinib with strong CYP3A4/5 inhibitors should be avoided. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be coadministered, a dose decrease of axitinib to approximately half the dose should be considered for axitinib. If co-administration of the strong inhibitor is discontinued, the axitinib dose should be returned (after 3-5 half-lives of the inhibitor) to the dose used prior to initiation of the strong CYP3A4/5 inhibitor.

Drug interaction with strong CYP3A4 inducer

Study A4061026 was a randomized, open-label, 2-period, 2-treatment, 2-sequence, crossover single-dose study of axitinib alone or with the strong CYP3A inducer, rifampin, in the fasted state to healthy adult volunteers. All subjects (N=40) received Treatment A (axitinib 5 mg x 1 on day 1) and 39 subjects received Treatment B (axitinib 5 mg po x 1 on day 8 + rifampin 600 mg po days 1-9). There was at least a 7-day washout between Day 1 of Treatment A and Day 1 of Treatment B for sequence 1 (AB), and at least a 21-day washout between Day 9 of Treatment B and Day 1 of Treatment A for sequence 2 (BA).

The pharmacokinetic parameters of axitinib are summarized in Table 16. Compared to axitinib alone, the co-administration of rifampin decreases the AUC_{inf} and C_{max} of axitinib by ~80% and ~70%, respectively (Table 17,

Figure 19). However, given that axitinib is a substrate for both CYP3A4 and OATP (1B1 and 1B3), the simultaneous administration of axitinib with rifampin (a CYP3A substrate and OATP inhibitor) may have underestimated the CYP3A enzyme induction.

Table 16. Geometric mean (CV%) pharmacokinetic parameters of axitinib with and without multiple doses of rifampin.

PK Parameter	Axitinib 5 mg	Axitinib 5 mg + Rifampin

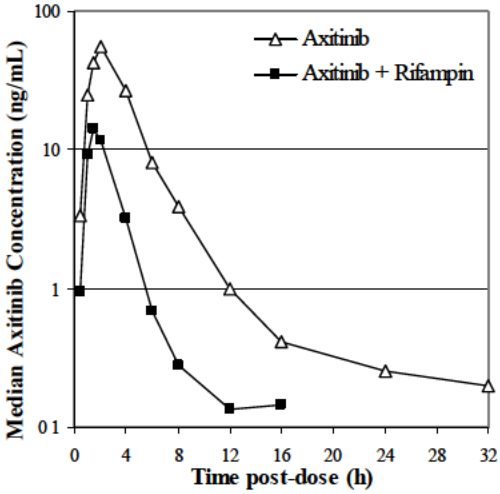
(units)	(N=40)	600 mg qd (N=39)
AUC_{inf} (ng*h/mL)	190 (61)	40 (80)*
AUC_{last} (ng*h/mL)	187 (61)	37 (83)
Cmax (ng/mL)	50 (62)	14 (79)
Tmax (h)	1.5 (0.5, 4.0)	1.5 (1.0, 4.0)
t½ (h)	7.7 (145)	2.5 (188)*
Vz/F (L)	199 (199)	296 (209)*
CL/F (L/h)	26.3 (91)	123.5 (84)*
*N=38; Tmax: median (range); t½ arithmetic mean (CV%).		

Table 17. Effect of multiple doses of rifampin (600 mg once daily) on the single-dose pharmacokinetic parameters of axitinib. Test = axitinib 5 mg + Rifampin 600 mg QD; Reference = axitinib 5 mg.

Parameter (units)	Adjusted Geometric Mean		Ratio of Adjusted Means (%)	90% CI for Ratio (%)
	AG-013736 5 mg with Rifampin N=39	AG-013736 5 mg Alone N=40		
AUC_{inf} (ng.h/mL)	39.39	190.25	20.70	(18.04, 23.75)
$AUCl_{ast}$ (ng.h/mL)	37.52	187.26	20.04	(17.41, 23.06)
C_{max} (ng/mL)	14.53	50.13	28.98	(24.07, 34.90)

CI=confidence interval

Figure 19. The median time-concentration profiles of axitinib in healthy subjects on a semi-log scale, following a single 5 mg oral axitinib dose alone (N=40) or coadministered with 600 mg rifampin once daily (N=39) in a 2-treatment, 2-period, 2-sequence crossover design.



Based on the above results, coadministration of axitinib with strong CYP3A4/5 inducers should be avoided. Additionally, moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

Drug interaction with sensitive CYP2C8 substrate

Study A4061019 was conducted to assess the potential for drug-drug interaction with paclicaxel, a CYP2C8 substrate, in patients with advanced solid tumors. In this trial, Cohorts 1-3 evaluated axitinib 5 mg bid in combination with paclitaxel 200 mg/m^2 over 3 h + carboplatin AUC 6 mg.min/mL every 3 weeks (1 Cycle=21d). Cohort 4 evaluated axitinib 5 mg bid in combination with paclitaxel 90 mg/m^2 weekly over 1 hr (Days 1, 8, and 15 of 28 day cycles). Patients took axitinib in the fed state orally every 12 hours.

For Cohorts 1-3 (paclitaxel/carboplatin), the pharmacokinetic profile of axitinib was characterized without (Day -1) and with (Day 1) chemotherapy. In Cycle 2, axitinib dosing was interrupted one day prior to chemotherapy so that the pharmacokinetic profile of chemotherapy without axitinib could be characterized; axitinib dosing was resumed on day 3. Pharmacokinetic parameters of paclitaxel (in combination with carboplatin) in Cohorts 1-3 were similar in the presence and absence of axitinib (

Table 18).

Table 18. Mean (CV%) every 3 week paclitaxel plasma pharmacokinetic parameters for Cohorts 1-3. Data from 2 subjects were excluded due to PK samples not being collected on Cycle 1 Day 1.

Treatment	C_{max}[a] (ng/mL)	AUC_{inf}[a] (ng.h/mL)	CL (L/h)	Vz (L)	$t_{1/2}$ (h)
Paclitaxel (in combination with carboplatin) alone (n = 12)	6182 (34)	20266 (28)	21.6 (43)	285 (82)	8.36 (26)
Paclitaxel (in combination with carboplatin) + AG-013736 (n = 12)	7182 (24)	23320 (34)	18.2 (24)	229 (31)	8.64 (12)

[a] Dose normalized to Cycle 1 Day 1 dose.

For Cohort 4, the pharmacokinetic profile of axitinib in combination with paclitaxel was evaluated on Day 8 with the second dose of paclitaxel. The pharmacokinetic profile of axitinib alone was evaluated on Day 22. In Cycle 2, axitinib dosing was interrupted three days prior to paclitaxel dosing so that the pharmacokinetic profile of paclitaxel without axitinib could be characterized; axitinib dosing was resumed on day 3. Pharmacokinetic parameters of weekly paclitaxel were similar in the presence and absence of axitinib (Table 19).

Table 19. Mean (CV%) weekly paclitaxel plasma pharmacokinetic parameters for Cohort 4. Data from 1 subject excluded due to PK samples not being collected on Cycle 2 Day 1.

Treatment	C_{max}[a] (ng/mL)	AUC_{inf}[a] (ng.h/mL)	CL (L/h)	Vz (L)	$t_{1/2}$ (h)
Paclitaxel alone (n = 6)	3821 (27)	5942 (24)	30.5 (20)	555 (26)	12.5 (8)
Paclitaxel + AG-013736 (n = 6)	4053 (27)	6157 (29)	28.8 (26)	521 (41)	12.4 (26)

[a] Dose normalized to Cycle 1 Day 8 dose.

Axitinib does not appear to alter paclitaxel pharmacokinetics.

Drug interaction with proton pump inhibitor

A pharmacokinetic sub-study within Study A40610010 evaluated the potential for drug-drug interactions with rabeprazole. Study A40610010 was a Phase 1, open-label, dose-escalation

study designed to evaluate the safety, tolerability, and pharmacokinetics of axitinib and to determine the maximum tolerated dose when given twice daily to subjects with advanced solid tumors. In the sub-study, six subjects received their morning axitinib 5 mg dose on Day 29 (Cycle 2, Day 1) followed by the collection of pharmacokinetic samples for 12 hours. For the next 5 days (ie, on Day 30 [Cycle 2, Day 2] through Day 34 [Cycle 2, Day 6]), subjects received rabeprazole, 20 mg once a day, approximately 3 hours before the axitinib 5 mg morning dose. On Day 34 (Cycle 2, Day 6), pharmacokinetic samples were collected for 12 hours after the axitinib 5 mg morning dose. Patients in the sub-study took axitinib in the fasted state (no food or beverages 2 hours before through 2 hours after dosing); rabeprazole doses could be taken with or without food. In the presence of rabeprazole, a 42% decrease in axitinib Cmax was observed. However, there were only a 15% decrease in AUC_{0-24} was observed (Table 20). The axitinib median Tmax was 2.0 hours with and without rabeprazole. The mean half-life was also similar with (3.7 hours) and without (3.3 hours) rabeprazole.

Table 20. Comparison of Plasma Pharmacokinetics of axitinib in the presence and absence of rabeprazole.

	C_{max} (ng/mL)		AUC_{0-24} (ng.hr/mL)	
	Axitinib with rabeprazole	**Axitinib alone**	**Axitinib with rabeprazole**	**Axitinib alone**
Geometric Mean	30.5	52.9	345	404
Geometric LS Mean Ratio (90% CI)[a]	0.58 (0.26, 1.30)		0.85 (0.59, 1.23)	

C_{max} = maximal plasma concentration; AUC_{0-24} = area under the plasma concentration-time profile from 0 to 24 hours after dosing (estimated as twice the AUC_{0-12} for BID dosing)

[a] Geometric LS Mean ratio. Ratio was defined as the ratio of with rabeprazole group to without rabeprazole group.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Based on the data submitted, axitinib appears to be a Biopharmaceutics Classification System Class (b) (4) drug (b) (4) The sponsor may file a Biopharmaceutics Classification System application with the FDA for an official determination to be made for axitinib.

Solubility

Axitinib had low soluble in aqueous media over a wide range of pH value and lower pH values resulted in higher solubility. Table 21 summarizes the solubility results in aqueous media as a function of pH after equilibration for at least 24 hours at 20°C.

Table 21. Solubility of Axitinib in Aqueous Media as a Function of pH at 20°C for at least 24 Hours.

Aqueous Solution	Solubility (microgram/mL)
Water pH 7.5	0.2
0.1N HCl, pH 1.1	1841
0.06N HCl pH 1.7	320
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 2.2	75
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 2.9	12
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 3.7	2.3
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 4.0	1.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 4.4	0.5
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 5.2	0.3
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 6.0	0.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 7.0	0.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 7.8	0.2

Axitinib solubility was also low in organic solvents. Table 22 summarizes the solubility results in various organic solvents after equilibration for at least 24 hours at 20°C.

Table 22. Solubility of Axitinib in Organic Solvents after Equilibration for at least 24 hours at 20°C.

Solvent	Solubility (mg/mL)
Acetonitrile	0.2
Dimethylsulfoxide (DMSO)	>13.5
Ethanol	1.4
Isopropyl alcohol	0.7
Methanol	0.9
Acetone	0.5
Ethyl Acetate	0.2
Tetrahydrofuran	1.4
N,N-Dimethylacetamide (DMA)	137

Permeability

In humans, the absolute bioavailability of oral axitinib was determined to be 58% (see section 2.2.9).

Study AG013736-PDM-021 performed using Caco-2 cell monolayers indicated that axitinib has a moderate to high apparent permeability. Permeability to axitinib was higher in the basolateral-to-apical direction (86.2 x 10^{-6} cm/s), compared to apical-to-basolateral direction (13.8 x 10^{-6} cm/s).

In rat *in situ* Single Pass Intestinal Perfusion (SPIP) studies, internal permeability standards metoprolol tartrate and ranitidine HCl were used. The permeability of axitinib was evaluated at concentrations of 20.0, 2.0, and 0.2 µg/mL, which correspond to 1x, 0.1x, and 0.01x 5mg dose in 250 mL, respectively. The test (axitinib) to reference (metoprolol) ratios (T/R) observed were 1.280, 1.120, and 7.064 at the high, mid, and low concentrations respectively.

2.5.2 What is the composition of the to-be-marketed formulation?

The commercial formulation is a film-coated immediate release formulated tablet (b) (4) for oral administration at two axitinib dosage strengths of 1 mg and 5 mg. During the clinical development program, (b) (4) axitinib formulations ((b) (4) oral and 1 intravenous) were use (b) (4)

The composition of the to-be-marketed formulations (Formulated Tablet (b) (4) FCIR 1 mg and 5 mg), is listed in Table 23. The to-be-marketed formulations are the same formulations used in the phase 3 RCC trial A4061032.

Table 23. Composition of Axitinib Film-Coated Immediate Release 1 mg and 5 mg Tablets.

Component	Function	Reference to Standard	Theoretical Unit and/or Formula (mg)	
			1 mg	5 mg
Axitinib	Active	Pfizer	1.000[1]	5.000[1]
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph.Eur., JP		(b) (4)
Lactose Monohydrate		NF, Ph.Eur., JP		
Croscarmellose Sodium		NF, Ph.Eur., JP		
Magnesium Stearate		NF, Ph.Eur., JP		
(b) (4)				
Film Coat				
Opadryl® II Red 32K151441		Pfizer[3]		
(b) (4)		USP, Ph. Eur., JP		
Total Finished Product				
NF, National Formulary; USP, United States Pharmacopeia; Ph.Eur., the European Pharmacopeia; JP, Japanese Pharmacopeia				

(b) (4)

2.5.3 What moieties should be assessed in bioequivalence studies?

Axitinib, the active ingredient of drug product, should be assessed in bioequivalence studies. Also see section 2.2.3.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study A4061053 was a phase 1, single dose, open-label, three-period, crossover study to determine the effect of food on the pharmacokinetics of axitinib (Form XLI (b) (4)) in healthy subjects. The three periods tested the effect of fasting (overnight fast and no food for 4 hours post dose), a moderate fat meal (500 - 700 total calories of calories with 30% from fat, 55% from carbohydrate, and 15% from protein) or a high fat meal (total calories of ~1000 with 60% from fat, 25% from carbohydrate, and 15% from protein) on the PK of axitinib. PK samples were collected up to 24 hours post dose and a 7 day wash-out was used between

treatments. At 5 mg, while the fed vs fasted states did not meet the 0.8 – 1.25 bioequivalence range, the differences between fed and fasted were not clinically significant. The median axitinib Tmax and mean $T_{1/2}$ were not affected by administration of food (Table 24). Compared with the fasted state, the geometric mean for axitinib Cmax and AUC_{∞} decreased by approximately 16% and 10%, respectively, when administered with a moderate-fat meal and increased by approximately 11% and 19%, respectively, when administered with a high-fat meal (Table 25).

Table 24. Descriptive Summary of Pharmacokinetic Parameters of Axitinib 5 mg Administration under Fasting Conditions, after administration with a Standardized Moderate-fat Meal, or a High-fat Meal in Study A4061053.

	Parameter Summary Statistics[a] by Treatment		
Parameter (units)	AG-013736 Form XLI Overnight Fasted	AG-013736 Form XLI Fed (high-fat[b])	AG-013736 Form XLI Fed (moderate-fat[c])
N, n	30, 25	30, 29	30, 27
AUC_{inf} (ng·h/mL)	145 (55)	162 (50)	125 (60)
AUC_{last} (ng·h/mL)	119 (70)	152 (55)	111 (67)
C_{max} (ng/mL)	25.9 (93)	28.8 (51)	21.8 (61)
T_{max} (h)	2.00 (1.0-6.0)	3.00 (2.0-6.0)	2.75 (1.0-6.0)
$t_{1/2}$ (h)	3.00 (41)	2.97 (41)	3.28 (43)
CL/F (L/h)	34.4 (55)	30.9 (50)	39.9 (60)
V_z/F (L)	137 (55)	123 (49)	173 (52)

N = number of subjects; n = number of subjects for $t_{1/2}$, AUC_{inf}, CL/F, and V_z/F; other parameters are defined in
[a] Geometric mean (geometric CV%) for all except: median (range) for T_{max}; arithmetic mean (CV%) for $t_{½}$.
[b] 15% protein, 25% carbohydrate, and 60% fat (approximately 1000 calories)
[c] 15% protein, 55% carbohydrate, and 30% fat (500-700 calories)

Table 25. Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Axitinib Comparing Administration of 5 mg under Fasting Conditions Versus Administration with Standardized Moderate-fat or High-fat Meals in Study A4061053.

	Adjusted Geometric Mean		Adjusted Geometric Mean Ratio	
Parameter (units)	Test	Reference	(Test/Reference)[a]	90% CI for Ratio
AG-013736 Form XLI Fed (High-Fat[b]) vs Overnight Fasted				
AUC_{inf} (ng·h/mL)	162.35	136.03	119.35	106.17, 134.17
AUC_{last} (ng·h/mL)	152.48	119.25	127.86	113.93, 143.50
C_{max} (ng/mL)	28.79	25.89	111.19	95.10, 129.99
AG-013736 Form XLI Fed (Moderate-Fat[c]) vs Overnight Fasted				
AUC_{inf} (ng·h/mL)	121.77	136.03	89.52	79.63, 100.64
AUC_{last} (ng·h/mL)	110.69	119.25	92.82	82.71, 104.17
C_{max} (ng/mL)	21.83	25.89	84.32	72.13, 98.59

[a] The ratios (and 90% CIs) are expressed as percentages. Overnight fasting is the reference treatment. High-fat, high-calorie meal and moderate-fat, standard-calorie meal are the test treatments.
[b] 15% protein, 25% carbohydrate, and 60% fat (approximately 1000 calories)
[c] 15% protein, 55% carbohydrate, and 30% fat (500-700 calories)

During clinical development, axitinib was dosed in both the fasted and fed states within the single and multiple dose studies. In the pivotal phase 3 clinical trial in patients with advanced RCC (A4061032), axitinib was administered with food. Axitinib dosing without regards to food is proposed by the applicant.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

Yes. Please refer to biopharmaceutical review for more information.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes. All the submitted clinical pharmacology related studies analyzed samples for axitinib. The main circulating metabolites, the glucuronide M7 and the sulfoxide M12 are considered inactive and were not measured in clinical trials; see sections 2.2.3 and 2.2.12.

2.6.2 Which metabolites have been selected for analysis and why?

All the submitted clinical pharmacology related studies analyzed samples for axitinib. The main circulating metabolites, the glucuronide M7 and the sulfoxide M12 are considered inactive and were not measured in clinical trials.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Axitinib is highly bound to human plasma proteins (>99%) (section 2.2.10). The total concentration of axitinib in plasma was measured in the clinical trials. In Study A4061036, the geometric mean (CV%) for the unbound fraction (fu) of axitinib in plasma from subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment were 0.0041 (25), 0.0030 (50), and 0.0041 (134%), respectively (Table 7). Therefore, the measurement of total concentrations in clinical trials is acceptable.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)

The bioanalytical methods used to measure axitinib concentrations in human plasma and urine pharmacokinetic samples were developed and validated at (b) (4) Axitinib concentrations were determined using high performance liquid chromatography (HPLC) coupled with tandem mass spectrometric (MS/MS) detection. Methods used for each study are summarized in

Clinical Study Number	Analytical Method Used	Axitinib Assay Range
A4060010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT01 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT01) 1 – 500 ng/mL (AGOT02)
A4061003	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT02)
A4061004	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061006	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061007	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL (AGOT00, AGOT07)
A4061011	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061012	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL mL (AGOT00, AGOT07)
A4061013	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061014	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061015	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061016	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061018	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL

. Details of each method are described in the respective validation reports.

Initially, 2 plasma assays were validated (AGOT00, AGOT01) to cover the expected broad range of concentrations in the first-in-human Phase 1 dose escalation study (A4060010) with ranges of:

- 0.1 – 25 ng/mL (Method AGOT00; Validation Report RSAX-CVC; and Method AGOT07; Revalidation Report RSAX-CVD)
    - Method AGOT07, a modified version of AGOT00, was used in addition to AGOT00 for Studies A4061010 and A4061012. The name of Method AGOT00 was simply changed to Method AGOT07 following Method AGOT00 Revision 3.
- 1.0 – 500 ng/mL (Method AGOT01; Validation Report RSAX-CVA).

The higher sensitivity assay (AGOT00) was then used for several subsequent studies

Clinical Study Number	Analytical Method Used	Axitinib Assay Range
A4060010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT01 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT01) 1 – 500 ng/mL (AGOT02)
A4061003	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT02)
A4061004	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061006	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061007	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL (AGOT00, AGOT07)
A4061011	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061012	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL mL (AGOT00, AGOT07)
A4061013	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061014	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061015	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061016	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061018	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL

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For the bioequivalence study A4061021, an assay (Method AGOT04; Validation Report RSA00037LX) with comparable sensitivity to AGOT00 with a range of 0.1 – 100 ng/mL was used.

- The observed intra-patient pharmacokinetic variability was higher in study A4061021 than in previous studies. Even though the new assay could not be linked directly to the higher pharmacokinetic variability, the different sample extraction techniques used in AGOT00 and AGOT04 may have been a factor.

- Therefore, another plasma assay (Method AGOT09; Validation Report RSA00053LX) using the same sample extraction technique used in AGOT00 with a range of 0.5 – 100 ng/mL was developed.
    - AGOT09 was used in the Phase 3 RCC Study (A4061032).

A urine assay was validated with a range of 1.0 – 500 ng/mL (Method AGOT02; Validation Report RSAX-CVB).

Table 26. Summary of Bioanalytical Methods Used in Clinical Studies for Pharmacokinetic Measurements of Axitinib.

Clinical Study Number	Analytical Method Used	Axitinib Assay Range
A4060010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT01 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT01) 1 – 500 ng/mL (AGOT02)
A4061003	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT02)
A4061004	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061006	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061007	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL (AGOT00, AGOT07)
A4061011	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061012	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL mL (AGOT00, AGOT07)
A4061013	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061014	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061015	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061016	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061018	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL

Clinical Study Number	Analytical Method Used	Axitinib Assay Range
A4061019	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061021	Laboratory Method for the Analysis of AG-013736 in K_3EDTA Human Plasma by LC/MS/MS LM Number: AGOT04	0.1 – 100 ng/mL
A4061022	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061023	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061026	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061028	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061032	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061033	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061035	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061036	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061037	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061044	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061046	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061047	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061050	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061052	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061053	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL
A4061063	Laboratory Method for the High Range Assay Analysis of AG-013736 in Na, K_2, or K_3 EDTA Human Plasma by LC/MS/MS LM Number: AGOT09	0.5 – 100 ng/mL

In the mass balance study (A4061003), axitinib was analyzed in human plasma and urine samples by validated LC-MS/MS methods. Profiling and identification of metabolites were also performed in plasma, urine, and fecal samples (study PDM-043). Total radioactivity in plasma, urine, and fecal samples was determined by liquid scintillation counting (LSC). Metabolite profiling and structure elucidation were performed using HPLC coupled in-line with radiochemical detection (ARC/(β-RAM) and MS detection with electrospray (ESI) source in positive mode. Details of the method are described in the validation report.

Validated bioanalytical method for paclitaxel used in Study A4061019: Concentrations of paclitaxel (CYP2C8 probe) for CYP450-dependent metabolism was measured in human plasma samples from study A4061019 at (b) (4) by HPLC-MS/MS using an assay validated at (b) (4) (Validation report 2100-404).

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The validated LC-MS/MS methods for plasma and urine axitinib pharmacokinetics analyses were used in the Clinical Pharmacology studies submitted in this NDA.

Of note, subsequent to method validation and sample analysis for the studies listed in

Clinical Study Number	Analytical Method Used	Axitinib Assay Range
A4060010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT01 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT01) 1 – 500 ng/mL (AGOT02)
A4061003	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT02)
A4061004	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061006	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061007	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL (AGOT00, AGOT07)
A4061011	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061012	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL mL (AGOT00, AGOT07)
A4061013	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061014	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061015	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061016	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061018	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL

, the sponsor discovered that the matrix calibration standards and/or QC sample pools used to make calibration standards and QCs for individual sample analysis runs were prepared with a 1% bias from the expected nominal concentrations. For methods AGOT00, AGOT04, and AGOT07, matrix calibration standards and QCs were both 1% lower than nominal concentrations. For method AGOT09, only the matrix calibration standards were 1% lower than nominal concentration; the matrix QCs was prepared correctly. For methods, AGOT01 and AGOT02, the matrix calibration standards and QCs were prepared in accordance with expected nominal concentrations. Since the 1% bias was within acceptable bioanalytical variability and was also within observed pharmacokinetic parameter variability for the studies listed in

Clinical Study Number	Analytical Method Used	Axitinib Assay Range
A4060010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT01 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT01) 1 – 500 ng/mL (AGOT02)
A4061003	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00 Laboratory Method for Analysis of AG-013736 in Human urine LM Number: AGOT02	0.1 – 25 ng/mL (AGOT00) 1 – 500 ng/mL (AGOT02)
A4061004	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061006	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061007	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061010	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL (AGOT00, AGOT07)
A4061011	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061012	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00, AGOT07	0.1 – 25 ng/mL mL (AGOT00, AGOT07)
A4061013	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061014	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061015	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061016	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL
A4061018	Laboratory Method for the Analysis of AG-013736 in K_3 or Na EDTA Human Plasma by LC/MS/MS LM Number: AGOT00	0.1 – 25 ng/mL

, the bias was not considered to have an effect on any pharmacokinetic results and conclusions.

Unless specified, for each axitinib plasma and urine method below, results for axitinib were calculated using peak area ratios of analyte to internal standard and calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression. For the inter- and intra-assay evaluations, a mean %bias of ≤ ±15% from theoretical was considered acceptable for each calibration standard, except at the lowest calibration standard, where a mean %bias of ≤.±20% from the theoretical was considered acceptable. The methods were appropriate for analyses of axitinib plasma concentrations in all the trials.

Methods AGOT00 / Validation RSAX-CVC: This method was developed to support axitinib in EDTA human plasma sample analyses. The assay was validated over the concentration range of 0.100 to 25 ng axitinib/mL of human plasma using a 200-µL sample.

- Method AGOT00 / Partial ReValidation RSAX-CVD: This method was developed to support axitinib in Na EDTA or K3 EDTA human plasma sample analyses. The assay was validated over the concentration range of 0.100 to 25 ng axitinib/mL of human plasma using a 200-µL sample. For the inter- and intra-assay evaluations, a mean %bias of ≤ 15% from theoretical was considered acceptable for all levels with the exceptions of the lowest calibration standard and QC LLOQ, where a mean %bias of ≤ 20% from the theoretical was considered acceptable. The methods were appropriate for analyses of axitinib plasma concentrations in all the trials.
    - Method AG0T07: This method is a modified version of Method AG0T00 described above. The name of Method AGOT00 was simply changed to AGOT07 following AGOT00 Revision 3.

Method AGOT01 / Validation RSAX-CVA: This method was developed to support axitinib in EDTA human plasma sample analyses. The assay was validated over the concentration range of 1.00 to 500 ng axitinib/mL of human plasma using a 100-µL sample.
Method AGOT04 / Validation RSA00037LX: This method was developed to support axitinib in K3 EDTA human plasma sample analyses. The assay was validated over the concentration range of 0.100 to 100 ng axitinib/mL of human plasma using a 200-µL sample.
Method AGOT09 / Validation RSA00053LX: This method was developed to support axitinib in K3 EDTA human plasma sample analyses. The assay was validated over the concentration range of 0.500 to 100 ng axitinib/mL of human plasma using a 200-µL sample.
Method AGOT02 / Validation RSAX-CVB: This method was developed to support axitinib in human urine sample analyses. The assay was validated over the concentration range of 1.00 to 500 ng axitinib/mL of human urine using a 100-µL sample.
Validated bioanalytical method for paclitaxel used in Study A4061019: This HPLC with MS/MS detection method was developed to support paclitaxel in Na Heparin human plasma sample analyses. The assay was validated over the concentration range of 10 to 2000 ng paclitaxel/mL of human plasma using a 250-µL sample. Calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression. The concentration range in the calibration curve using diluted samples was in the appropriate range for analysis of paclitaxel concentrations.

2.6.6 What is the QC sample plan?

Unless specified, for the inter- and intra-assay evaluations, a mean %bias of ≤ ±15% from theoretical was considered acceptable for each QC sample, except at the LLOQ-QC, where a mean %bias of ≤ ±20% from the theoretical was considered acceptable.

Method AGOT00 / Validation RSAX-CVC: Six replicates of QC standards at 4 concentrations (0.100, 0.300, 2.00, and 20.0 ng/mL) were included in each analytical run.

- Method AGOT00 / Partial ReValidation RSAX-CVD: Six replicates of QC standards at 4 concentrations (0.100, 0.300, 2.00, and 20.0 ng/mL) were included in each analytical run. For the inter- and intra-assay evaluations, a mean %bias of ≤15% from theoretical was considered acceptable for all levels with the exceptions of the lowest calibration standard and QC LLOQ, where a mean %bias of ≤20% from the theoretical was considered acceptable.

- Method AG0T07: This method is a modified version of Method AG0T00 described above. The name of Method AGOT00 was simply changed to AGOT07 following AGOT00 Revision 3.

Method AGOT01 / Validation RSAX-CVA: Six replicates of QC standards at 4 concentrations (1.00, 3.00, 40.0, and 400 ng/mL) were included in each analytical run.
Method AGOT04 / Validation RSA00037LX: Six replicates of QC standards at 5 concentrations (0.100, 0.300, 3.00, 40.0, and 80.0 ng/mL) were included in each analytical run.
Method AGOT09 / Validation RSA00053LX: Six replicates of QC standards at 5 concentrations (0.500, 1.50, 7.00, 40.0, and 80.0 ng/mL) were included in each analytical run.
Method AGOT02 / Validation RSAX-CVB: Six replicates of QC standards at 4 concentrations (1.00, 3.00, 40.0, and 400 ng/mL) were included in each analytical run.
Validated bioanalytical method for paclitaxel used Study A4061019: Duplicates of QC standards at 3 concentrations (30.0, 600, and 1500 ng/mL) and triplicates at 5000 ng/ml were included in each analytical run. Regarding the assay performance, the precision (%CV) was 6.4% and accuracy (%RE) was 100.2% to 103.2%.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The red text is the proposed changes added by the clinical pharmacology reviewer and the sponsors proposed language that has not been accepted is crossed out.

(b) (4)

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

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

Application Number	202324
Submission Date	April 14, 2011
Compound (Dosing Regimen)	Axitinib
Clinical Division	DDOP
Primary PM Reviewer	Nitin Mehrotra, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.

Table of Contents

1 Summary of Findings
1.1 Key Review Questions
1.2 Recommendations
1.3 Label Statements
2 Pertinent Regulatory Background
3 Results of Sponsor's Analysis
3.1 Population PK analysis
3.2 Exposure-Response Analysis for Safety
4 Reviewer's Analysis
4.1 Exposure-Response Analysis for Safety

1 Summary of Findings

1.1 Key Review Questions

The following key questions were addressed in this pharmacometric review.

1.1.1 Is there evidence of exposure-response relationship for safety? Are the proposed dose reductions from 5 to 3 to 2 mg BID appropriate for the management of hypertension and proteinuria?

Yes, there is evidence of exposure-response relationship for hypertension, proteinuria, fatigue and diarrhea. Data from three phase 2 trials (A4061012 and A4061045 [N=116], A4061023 [N=62]) and the pivotal phase 3 trial (A4061032 [N=55]) were pooled to perform exposure-response analysis. Logistic regression analysis was conducted to determine whether the probability of hypertension, proteinuria, fatigue, and diarrhea increased with axitinib exposures (i.e., AUC before the adverse event). There was significant exposure-response observed for all of these adverse events (Figure 1 and Figure 2). The exposure-response relationship was significant

after adjusting for other confounding baseline factors such as age, baseline ECOG, patient type and baseline blood pressure.

Sponsor proposes a sequential dose reduction from 5 mg to 3 mg to 2 mg BID for the management of hypertension and proteinuria. We agree with the sponsor's proposal because these adverse events are exposure driven. For a typical patient, reduction of axitinib dose from 5 mg to 3 mg BID will reduce the risk of hypertension from 55 to 41%. Similar dose reduction for a patient experiencing proteinuria would reduce the risk of proteinuria from 16 to 12%. The actual reduction in these adverse events will vary depending on where the exposure of a patient lies on the exposure-response curve.

Figure 1. Exposure-dependent increase in hypertension (left) and proteinuria (right). Reduction of dose from 5 to 3 mg BID will reduce the risk of hypertension and proteinuria.

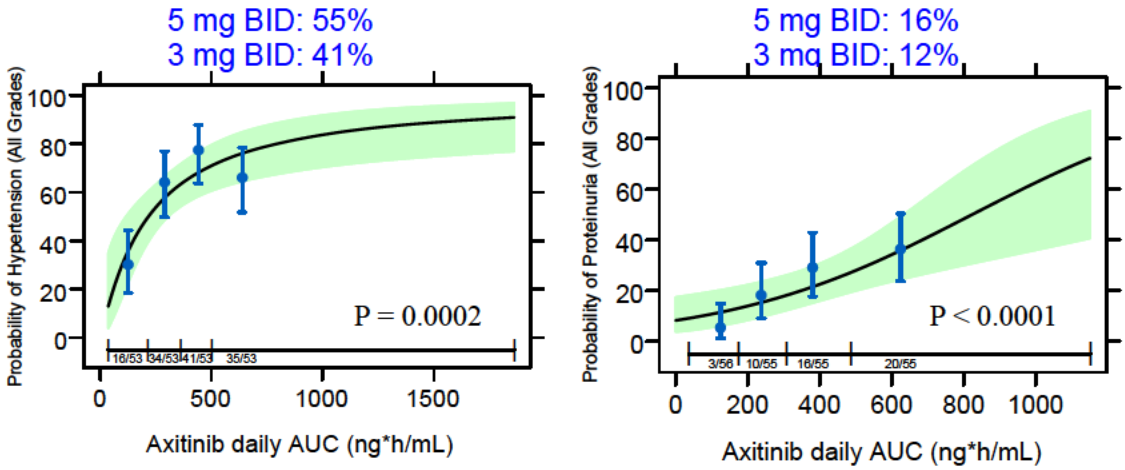
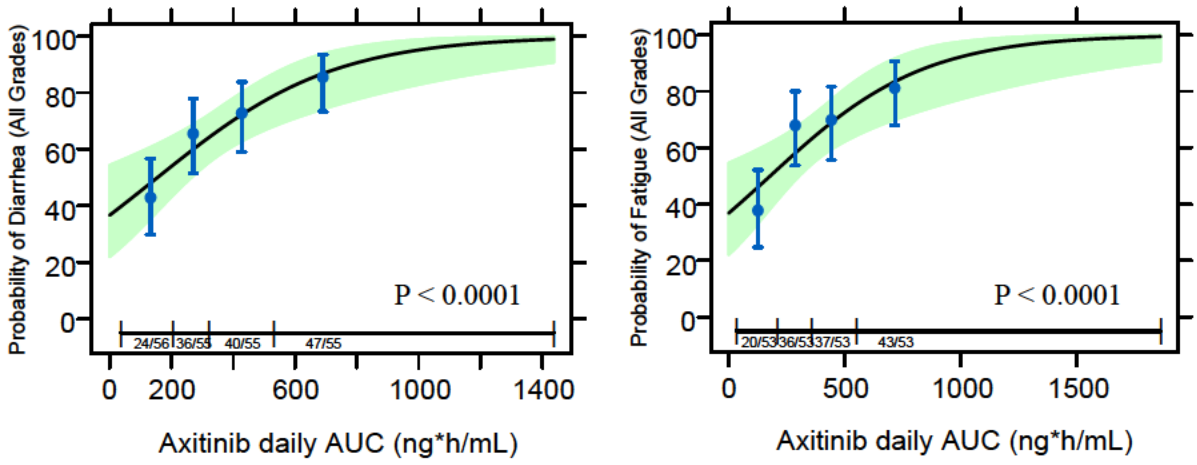


Figure 2. Occurrence of diarrhea and fatigue increases with axinitib exposures.



1.1.2 Is it appropriate to titrate the dose up to 10 mg BID based on tolerability?

Yes, the dose titration scheme proposed by the sponsor based on tolerability is reasonable and would reduce variability in axitinib exposures.

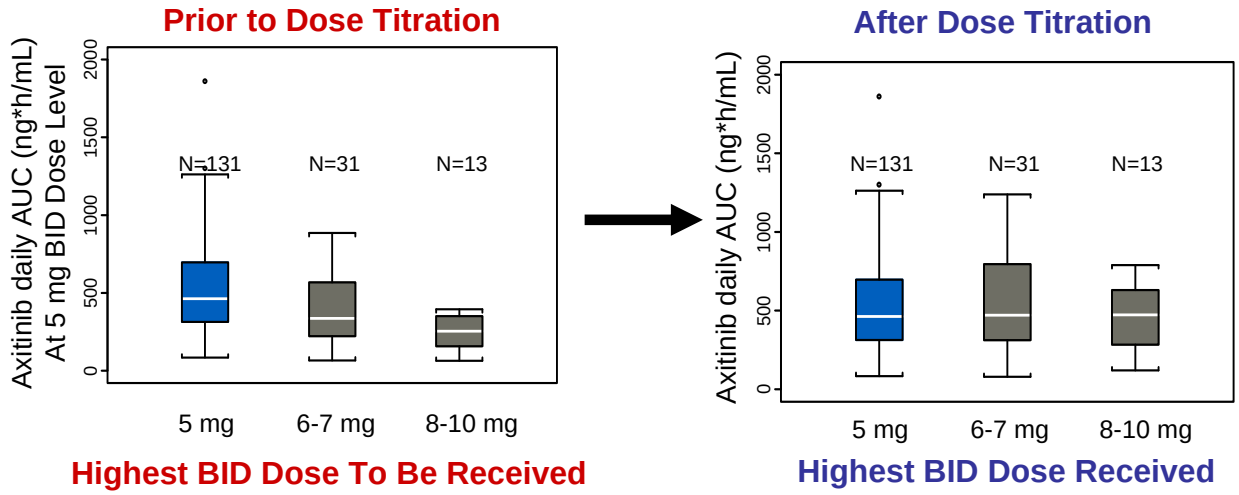
- There is considerable inter-individual variability (CV% =60%, after adjusting for covariates) in AUC following axitinib dose of 5 mg BID, which provides an opportunity to individualize the dose.
- It was observed that patients who were able to tolerate axitinib and required upward dose titration had lower initial exposures (higher clearance). This was consistent with our finding that adverse events were exposure driven and patients with lower exposures were likely to have lower adverse events.

The axitinib clinical starting dose is 5 mg BID. Patients who tolerate 5 mg BID may have the dose increased to 7 mg twice daily, and further to a maximum of 10 mg twice daily if they meet the following criteria:

- No Adverse drug reactions >Grade 2 for two consecutive weeks
- Normotensive
- Not receiving anti-hypertension medication

It is important to note that this dose titration scheme was implemented in the clinical development program of axitinib, both in the phase 2 trials and the pivotal trial. Sponsor conducted a retrospective analysis to evaluate the effect of dose titration on PK by pooling data from three phase 2 trials (A4061012, A4061023 and A4061035). Patients who were able to tolerate axitinib and received an increased dose appeared to have lower axitinib initial exposures at the initial 5 mg BID dose prior to the dose titration. Axitinib exposures in those subjects appeared to match those receiving a 5 mg BID dose following dose titrations to 6-7 mg (N=31) or 8-10 mg (N=13) twice daily (Figure 3).

Figure 3. Dose titration based on tolerability reduces variability in axitinib exposures.



Furthermore, the sponsor is evaluating the effect of dose titration on the PK, efficacy and safety of axitinib in a prospectively designed trial (A4061046).

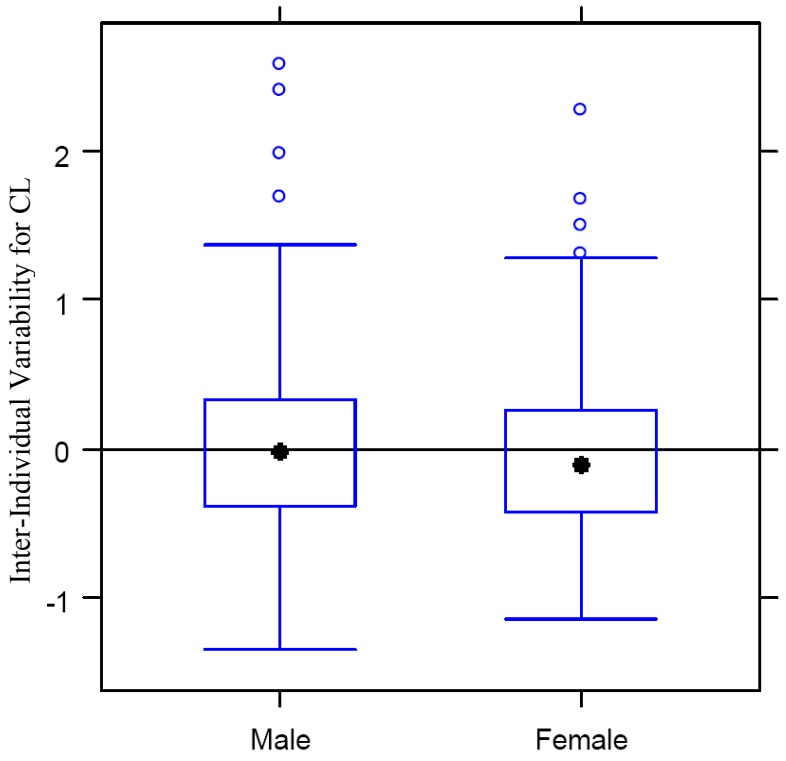
1.1.3 Is there an effect of gender, race, age, renal impairment or smoking status on pharmacokinetics of axitinib?

The effect of these covariates was examined using population PK analysis and the results are summarized below.

Gender

There was no effect of gender on clearance of axitinib (Figure 4).

Figure 4. No effect of gender on the clearance of axitinib



(Source: Sponsor's pmar-00079 study report, Page 157)

Race

Based on the population pharmacokinetic analysis, it was observed that Japanese patients had 25% lower clearance than the non-Japanese patients. This decrease in clearance is not considered to be clinically relevant given the high inter-individual variability observed in clearance of axitinib. Furthermore, based on a dedicated study (A4061026), in which PK data from 20 Caucasians and 20 Japanese patients were compared using intensive PK sampling, there was no difference observed in the C_{max} and AUC. Thus, we can conclude that race does not affect axitinib PK.

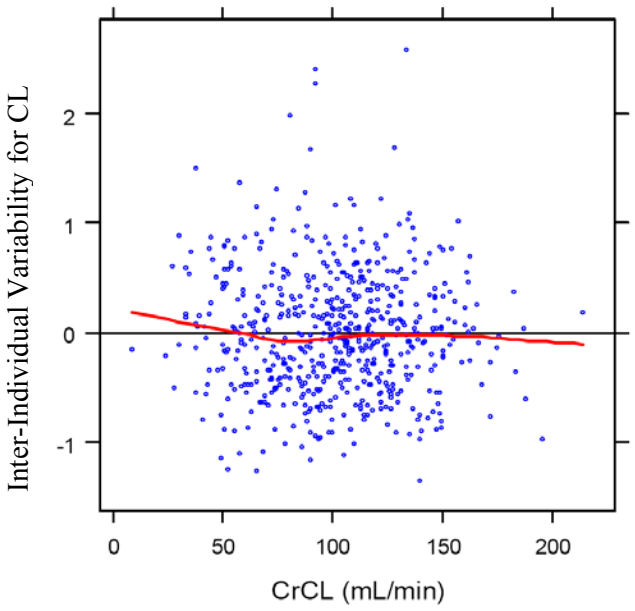
Age

Age was tested both as a continuous and binary (age <60 and age >60 years) covariate. When used as a binary covariate, age was found to affect axitinib exposures such that subjects >60 years had 21% decrease in clearance. A 21% decrease in clearance is not considered to be clinically relevant given the high inter-individual variability observed in clearance of axitinib.

Renal Impairment

The sponsor did not conduct a dedicated organ impairment trial to assess the effect of renal impairment on axitinib exposure. Based on the population PK analysis, mild, moderate or severe renal impairment did not have a significant effect on the clearance of axitinib (Figure 5). The baseline renal function data included in the analysis comprised of 381 subjects with normal renal function (CrCL > 90 mL/min), and 139, 64, 5, and 1 subjects with mild (CrCL 60 - 89 mL/min), moderate (CrCL 30 – 59 mL/min), severe (CrCL 15 – 29 mL/min), and end-stage (CrCL < 15 mL/min) pre-existing renal impairment, respectively. Because only one subject had end-stage renal impairment, a definitive conclusion cannot be made regarding the effect of end-stage renal impairment on axitinib PK.

Figure 5. No effect of CrCL in axitinib clearance.



(Source: Sponsor's pmar-00079 study report, Page 166)

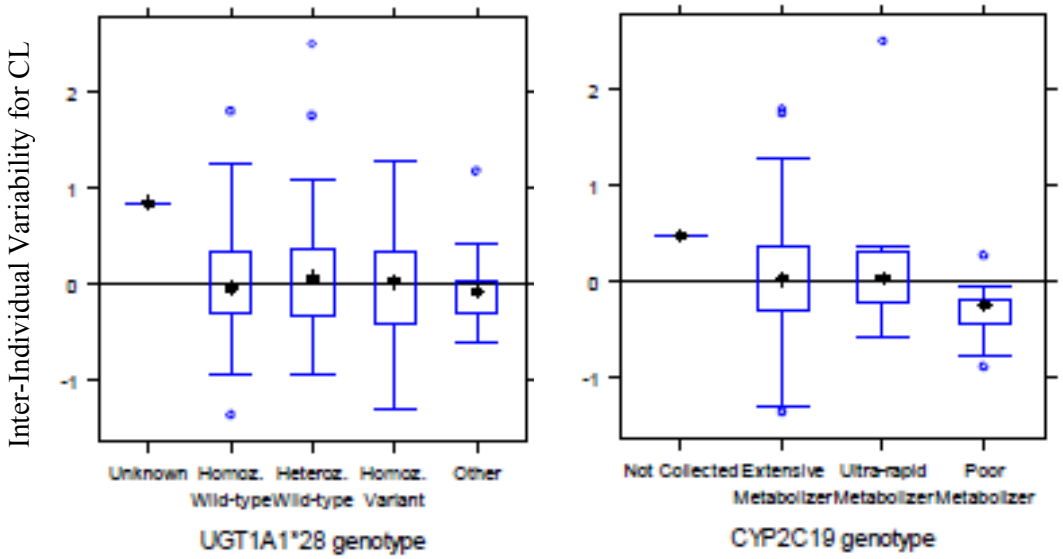
Smoking Status

The clearance in active smokers was higher (102%); however, the smoking effect was not well defined with a standard error of 40%. The dataset included 434 non smokers, 19 active smokers and 137 ex-smokers. The number of current smokers in this dataset was only 19 (3%) and thus the results should be interpreted with caution. Sponsor mentions that the effect of smoking will be adequately characterized in future NSCLC trials, where higher proportion of current smokers is expected.

1.1.4 Is there an effect of UGTA1A1 or CYP2C19 genotype on the pharmacokinetics of axitinib?

There was no effect of UGT1A1 and CYP2C19 gene polymorphisms on axitinib clearance (Figure 6). Effect of gene polymorphisms (UGT1A1 and CYP2C19) that are important for metabolism of axinitib PK was analyzed using population PK analysis in healthy volunteers. For UGT1A1*28, the population pharmacokinetic dataset included 35 subjects who were homozygous variant for the UGT1A1*28 genotype. For CYP2C19, the population pharmacokinetic dataset included 8 subjects categorized as ultra metabolizers and 15 subjects categorized as poor metabolizers. This finding is consistent with the observation that axitinib is metabolized primarily by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19 and UGT1A1.

Figure 6. No effect of UGT1A1*28 (left) and CYP2C19 (right) genotype on axitinib clearance



(Source: Sponsor's pmar-00075 study report, Page 136, 138)

1.1 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective.

1.2 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Section 8.7

(b) (4)

(b) (4)

No dedicated renal impairment trial for axitinib has been conducted. Based on the population pharmacokinetic analysis, no significant difference in axitinib clearance was observed in patients with pre-existing mild to severe renal impairment (15 mL/min ≤ creatinine clearance (CLcr) < 89 mL/min). [*see Clinical Pharmacology (12.3)*] No adjustment to the starting dose is needed for patients with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal diseases (CLcr < 15 mL/min).

Section 12.3
Pharmacokinetics in Specific Populations
(b) (4) **-Other Intrinsic Factors**

Population pharmacokinetic analyses (b) (4) indicate that there are no clinically relevant effects of age, gender, body weight, body surface area, race, renal function, UGT1A1 genotype, or CYP2C19 genotype on the clearance of axitinib.

Renal Impairment

(b) (4)

2 Pertinent Regulatory Background

Axitinib, a substituted indazole derivative, is an oral, potent, and selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3. Sponsor is seeking the indication for treatment of patients with advanced renal cell carcinoma (RCC). RCC is the third leading orologic cancer. There are six approved therapies for the treatment of RCC in US and other countries. Sunitinib, bevacizumab, temsirolimus, pazopanib, sorafenib and everolimus are approved for treatment of RCC with sorafenib and everolimus approved as second line therapies. Table 1 below summarizes the mechanism of action of the approved therapies, populations studied, along with the efficacy results.

Table 1: Treatment population and efficacy results of the approved therapies for RCC

	MoA	Study Population (Prior Treatment Received)	Primary Endpoint	Results PFS HR (95% CI) [Median (mo)]	Results OS HR (95% CI) [Median (mo)]	Results ORR (%)
Sorafenib[a] (vs. placebo)	VEGFR, PDGFR TKI	Systemic therapy (mainly IL-2/and/or interferon)	PFS/OS	0.44 (0.35, 0.55) [5.5]	0.88 (0.74, 1.04) [17.8]	10
Sunitinib[b] (vs. IFNα)	VEGFR, PDGFR, KIT, Flt-3, CSF-1R TKI	Treatment-naïve	PFS	0.42 (0.32, 0.54) [11.0]	0.82 (0.67,1.00) [26.4]	31
(single arm)		Cytokines	RR	[8.8 (95% CI: 7.8 – 13.5)]	[23.9]	33
Pazopanib[c] (vs. placebo)	VEGFR, PDGFR, Kit TKI	Treatment-naïve or cytokines	PFS	0.46 (0.34, 0.62) [9.2]	0.91 (0.71, 1.16) [22.9]	30
		Treatment-naïve		0.40 (0.27, 0.60) [11.1]	1.01 (0.72, 1.42) [22.9]	32
		Cytokines		0.54 (0.35, 0.84) [7.4]	NA	29
Bevacizumab + IFNα[d] (vs. IFNα)	Anti-VEGF antibody	Treatment-naïve	PFS	0.60 (0.49, 0.72) [10.2]	0.86 (0.72,1.04) [23]	30
Temsirolimus[e] (vs. IFNα)	mTOR inhibitor	Poor risk Treatment-naive	OS	0.66 (0.53,0.81) [5.5]	0.73 (0.58,0.92) [10.9]	8.6
Everolimus[f] (vs. placebo)	mTOR inhibitor	Sunitinib and/or sorafenib (others also allowed)	PFS	0.33 (0.25,0.43) [4.9]	0.87 (0.65, 1.15) [14.8]	2
		Sunitinib		0.34 (0.23, 0.51) [3.9]	NA	NA

CI=confidence interval; CSF-1R=colony stimulating factor receptor, FLT-3=Fms-like, HR: hazard ratio; IFN: interferon; IL: interleukin; KIT=stem cell growth factor receptor, TKI: tyrosine kinase inhibitor; LLN: lower limit of normal; mo : months; MoA: mechanism of action; mTOR: mammalian target of rapamycin; NA: not available; ORR: objective response rate; OS: overall survival; PDGFR: platelet-derived growth factor receptor; PFS: progression-free survival; PS: performance status; RR: response rate, ULN: upper limit of normal; VEGFR: vascular endothelial growth factor receptor;

[a] Sorafenib:all endpoints except OS reported in Escudier, 2007[16]; OS reported in Escudier, 2009.[17]

[b]Sunitinib: vs. IFNα, all endpoints except OS for comparison with IFNα reported in Motzer, 2007 (N Eng J Med)[18]; OS for comparison with IFNα reported in Motzer, 2009[19]; single arm endpoints reported in Motzer, 2007 (J Urol).[20]

[c]Pazopanib: All endpoints except OS in pazopanib FDA statistical review Table 2[21]; OS for overall treatment-naïve or cytokine reported in Sternberg, 2010[22]; OS in treatment-naïve, only, reported in NICE, 2010.[23]

[d]Bevacizumab: US Prescribing Information.[24]

[e]Temsirolimus: US Prescribing Information[25]; poor risk = ≥3 of the following factors: lactate dehydrogenase >1.5x ULN; hemoglobin <LLN; corrected serum calcium>10 mg/dl; <1 yr from original diagnosis; Karnofsky PS ≤70; ≥2 metastatic sites.

[f]Everolimus: PFS and ORR for prior sunitinib and/or sorafenib treatment in US Prescribing Information[26]; OS for prior sunitinib and/or sorafenib treatment and PFS for prior sunitinib in Motzer, 2010.[27]

(Source: Clinical overview, Table 2, Page 11)

A SPA agreement letter for the RCC phase 3 protocol A4061032 was issued on April 17, 2008. Sponsor conducted a single Phase 3, randomized, open-label, multi-center trial (A4061032) of axitinib compared with sorafenib in subjects with advanced RCC after failure of treatment with 1 prior therapy including sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s) (N=723). The primary endpoint was PFS as assessed by an IRC; secondary efficacy endpoints included OS, ORR, and duration of response (DR).

- PFS (IRC) results: Axitinib 6.7 mo; Sorafinib 4.7 mo
  - HR 0.67 [95% CI (0.54, 0.81); 1-sided p<0.0001]
- ORR (IRC) results: Axitinib 19.4%; Sorafinib 9.4%
  - HR 2.06 [95% CI (1.41, 3.00); 1-sided p<0.0001]

Sponsor also performed analysis of primary end point by dose level (daily dose of > 10 mg and ≤ 10 mg). In the axitinib arm, patients who received a total daily dose >10 mg or ≤ 10 mg had a median PFS (per IRC) of 6.6 months (95% CI: 4.7, 8.3) and 8.3 months (95% CI: 6.0, 10.2), respectively; in comparison, the sorafenib arm had a median PFS (per IRC) of 4.7 months (95% CI: 4.6, 5.6). This analysis may be interpreted with caution since the variability in axitinib PK is large and comparison of efficacy by doses may not be appropriate. Furthermore, time also may be a confounding factor since the patients were allowed to uptitrate to >10 mg daily total dose at anytime during the study. Also, based on the sponsor's safety analysis, the safety profile of axitinib in subjects who had at least one total daily dose > 10 mg was generally similar to that of subjects who did not have at least one daily dose above > 10 mg.

3 Results of Sponsor's Analysis

3.1 Population PK analysis

The sponsor conducted two types of population PK analyses:

- Population PK analysis in healthy volunteers (pmar-00075). The primary objective was to develop a model that describes axitinib PK in healthy volunteers with rich PK data and to evaluate the potential effect of UGT1A1*28 polymorphism and CYP2C19 metabolizing status on axitinib PK.
- Population pharmacokinetic analysis of axitinib in patients with metastatic renal cell carcinoma (including patients with solid tumors) and healthy volunteers (pmar-00079). The primary objective was to characterize axitinib PK in healthy volunteers and patients simultaneously and to identify potential covariates that may explain variability in axitinib PK.

3.1.1 Methods

The analysis was conducted based on the following strategy: base model development, random effect model development, inclusion of covariates, final model development, assessment of model adequacy (goodness of fit), and validation of the final model. NONMEM 7 Level 1.0 was used for all model estimation with FOCEI. Inter-subject variability was modeled using multiplicative exponential random effects of the form and residual variability was modeled using log-transformed error model. In the base model, the effects of drug formulation and food were initially tested on both bioavailability and absorption rate, to help characterize axitinib PK and to improve model stability prior to covariate selection.

For the population pharmacokinetic study pmar-00075, data from 337 subjects from 10 clinical studies was included. For the population pharmacokinetic study pmar-00079, data from 383 healthy volunteers and 207 patients were included.

3.1.2 Conclusions

The disposition of axitinib in healthy volunteers was described by a two compartmental model, with a lag time and first order absorption rate constant. For (b) (4) the rate of absorption and absolute bioavailability was increased by approximately 2- and 1.3 fold, respectively. There was no food effect observed for (b) (4) There was no effect of UGT1A1 and CYP2C19 genetic polymorphisms on axitinib PK.

Similar to results from population pharmacokinetic model in healthy volunteers, the disposition of axitinib was described by a two compartment model, which included a lag time and first absorption rate constant. The lag time from dose administration to the beginning of the first-order absorption was estimated to be 0.454 hours. Systemic clearance (CL) was estimated to be 14.6 L/hr and a central volume of distribution (Vc) for the central compartment was estimated to be 47.3 L. Inter-individual variability (IIV) was estimated to be 60% for CL and 40% for Vc.

When age was tested as a binary covariate (age < 60 and age > 60 years), it was observed that subjects with age > 60 years had a 21% decrease in clearance which is not considered to be clinically relevant. Japanese ethnicity was associated with 25% lower clearance based on the population PK analysis. However, a dedicated study comparing PK of axitinib in Japanese and Caucasians with intense PK sampling did not show any difference in axitinib PK. The population pharmacokinetic analysis dataset included 383 healthy volunteers, 26 patients with advanced

solid tumors, 122 patients with cytokine-refractory advanced RCC, and 59 patients with sorafenib-refractory advanced RCC .Results of this analysis indicate that there was no effect of tumor type on CL of axitinib and that axitinib exposure was similar between healthy volunteers and patients with advanced solid tumors including advanced RCC. Table 2 below shows the parameter estimates for the base, full and the final model. **Error! Reference source not found.** shows goodness of fit plots for the final population PK model.

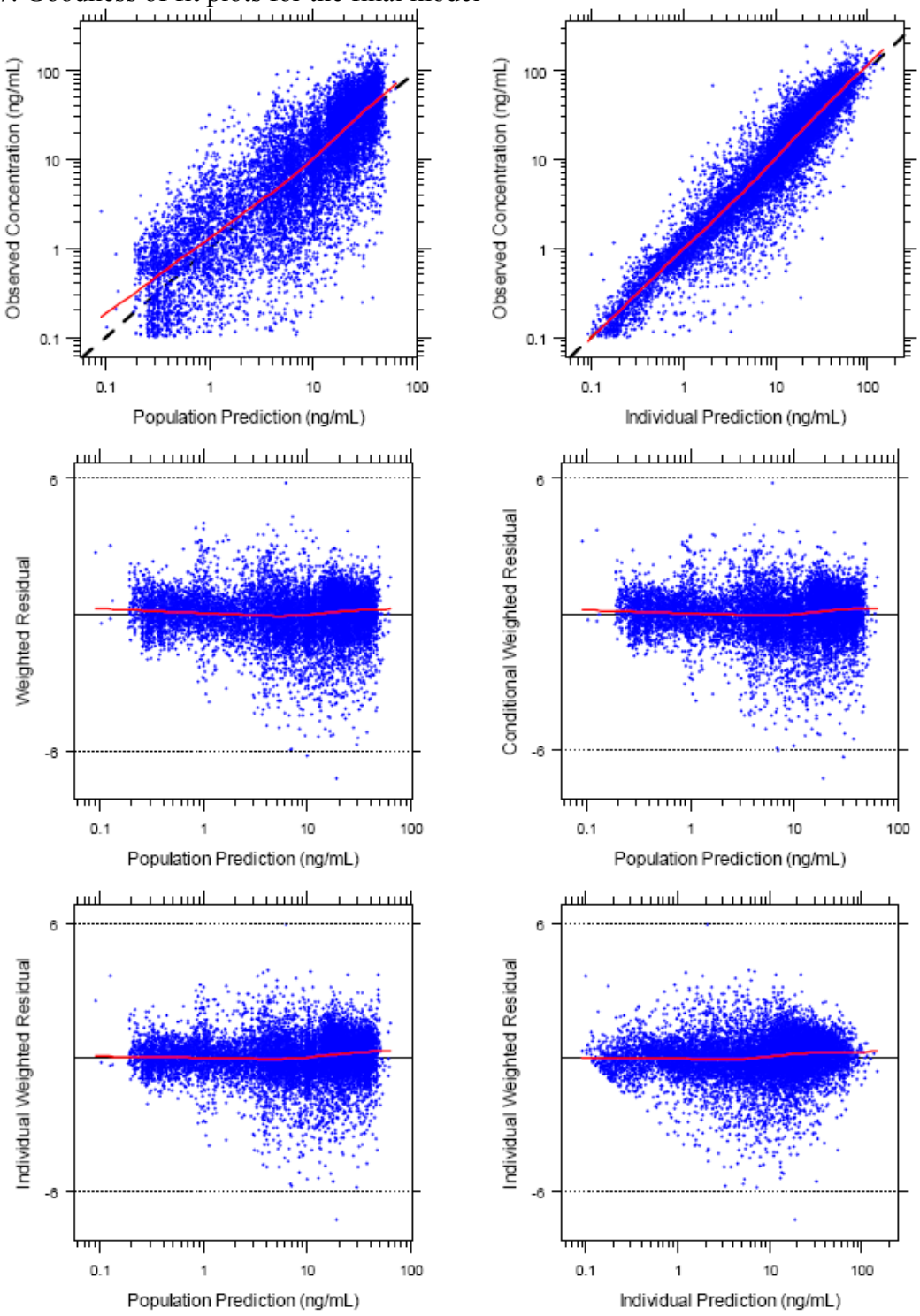
Table 2: Parameter estimates for Base, full and final model

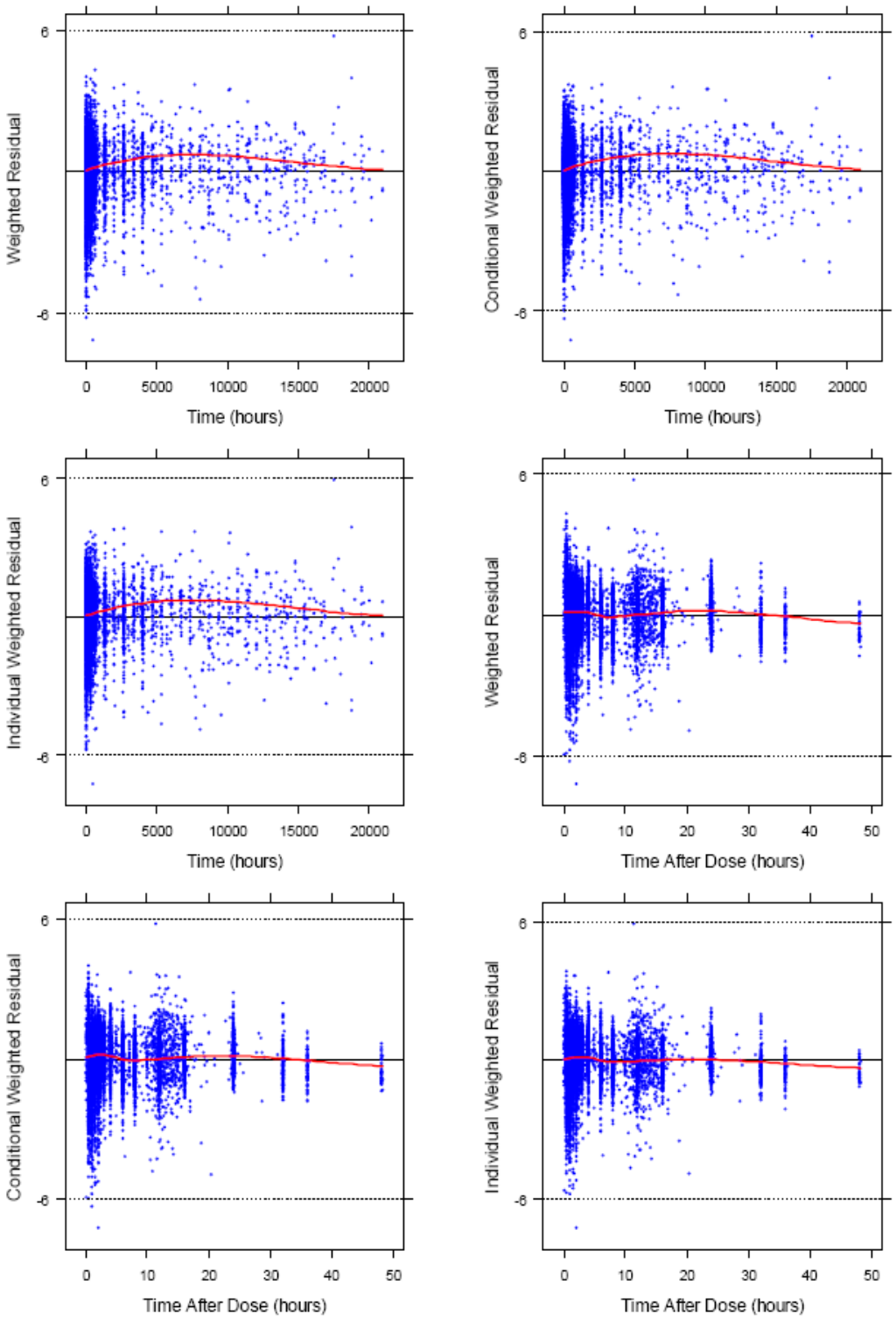
	Base Model				Full Model				Final Model			
MOF	2499.461				2363.398				2392.011			
Change from Base	0				-136.063				-107.450			
Parameter	**Estimate**	**%SE**	**95% CI[a]**		**Estimate**	**%SE**	**95% CI[a]**		**Estimate**	**%SE**	**95% CI[a]**	
CL (L/h)	13.7	11%	11.0	17.0	15.0	11%	12.2	18.5	14.6	8.5%	12.4	17.2
Age>60 effect on CL	--				-0.253	18%	-0.345	-0.161	-0.213	26%	-0.320	-0.106
Smoking effect on CL[b]	--				0.865	42%	0.155	1.57	1.02	44%	0.144	1.90
Japanese effect on CL	--				-0.278	21%	-0.393	-0.163	-0.249	25%	-0.370	-0.128
Other-Asian effect on CL	--				-0.188	26%	-0.285	-0.0912	--			
Solid Tumor effect on CL	--				0.405	47%	0.0287	0.781	--			
AST effect on CL	--				-0.103	45%	-0.194	-0.0119	--			
Vc (L)	47.7	9.2%	39.8	57.1	47.2	8.3%	40.1	55.6	47.3	6.2%	41.9	53.4
Weight effect on Vc	--				0.835	13%	0.642	1.09	0.778	14.0%	0.591	1.02
Q (L/h)	4.26	5.7%	3.81	4.76	4.00	8.1%	3.41	4.69	4.00	4.7%	3.65	4.39
Vp (L)	470	13%	366	604	400	9.0%	335	477	393	16%	285	542
ka for fed subjects (1/h)	0.481	5.4%	0.432	0.535	0.483	6.1%	0.428	0.545	0.482	4.8%	0.439	0.529
Fasting effect on ka	1.97	15%	1.40	2.54	1.96	15%	1.39	2.53	1.97	13%	1.46	2.48
tlag (h)	0.455	0.42%	0.451	0.459	0.454	0.41%	0.450	0.458	0.454	0.41%	0.450	0.458
F for fed subjects, Form IV	0.466	9.5%	0.387	0.561	0.455	8.7%	0.384	0.540	0.457	6.6%	0.402	0.520
Fasting effect on F, Form IV	0.309	15%	0.218	0.400	0.330	14%	0.242	0.418	0.330	13%	0.243	0.417
Form XLI effect on F	-0.133	23%	-0.192	-0.0736	-0.121	26%	-0.182	-0.0597	-0.121	24%	-0.179	-0.0630
CL ω^2	0.403	9.0%	0.338	0.481	0.333	11%	0.271	0.410	0.359	9.4%	0.299	0.432
CL ω · 100% (%CV)	*63.5%*				*57.7%*				*59.9%*			
CL-Vc ω (covariance)	0.225	12%	0.170	0.280	0.198	21%	0.116	0.280	0.200	14%	0.146	0.254
Vc ω^2	0.197	14%	0.150	0.259	0.167	24%	0.104	0.267	0.158	17%	0.113	0.220
Vc ω · 100% (%CV)	*44.4%*				*40.9%*				*39.7%*			
Q ω^2	0.599	19%	0.413	0.870	0.780	16%	0.574	1.06	0.754	15%	0.561	1.01
Q ω · 100% (%CV)	*77.4%*				*88.3%*				*86.8%*			
Vp ω / Q ω	1.25	18%	0.887	1.76	1.39	14%	1.07	1.81	1.37	11%	1.10	1.71
ka ω^2	0.601	12%	0.476	0.759	0.583	13%	0.451	0.753	0.593	12%	0.472	0.744
ka ω · 100% (%CV)	*77.5%*				*76.4%*				*77.0%*			
Residual error SD-oral	0.582	2.0%	0.559	0.606	0.582	2.0%	0.559	0.606	0.582	2.0%	0.559	0.606
Residual error SD- IV	0.333	17%	0.240	0.462	0.336	12%	0.264	0.427	0.335	16%	0.244	0.461

[a] Confidence interval is calculated as estimate·exp(± 1.96 %SE/100), or for quantities that can be positive or negative (covariate parameters and covariances), as estimate ± 1.96 SE, to allow the interval to span 0.
Source Data: ePharmacology Artifact ID Numbers 3604999 (base), 3605062 (full), 3605065 (final) and 3606870 (table)

(Source: PMAR-00079 report, page 55, table 15)

Figure 7. Goodness of fit plots for the final model





(Source: PMAR-00079 report, page 148-149)

Reviewer's Comments:
The population PK analysis and results provided by the sponsor are acceptable. Sponsor followed a thorough approach in developing and validating the population PK model, evaluating and interpreting the effect of relevant covariates. The reviewer agrees with the sponsor's conclusion that there was no clinically relevant effect of age, race, gender, mild to severe renal impairment, CYP2C19 and UGT1A1 genotype status on PK of axitinib. For further details please refer to pmar-00075 and pmar-00079 study report.

3.2 Exposure-Response Analysis for Safety

3.2.1 Objectives

To conduct the exposure-response relationship for selected safety endpoints (diarrhea, fatigue, hand-foot syndrome, hypertension, proteinuria, stomatitis).

3.2.2 Methods

Separate analysis was carried out for all the four trials mentioned below.

- **Study A4061012**, a Phase 2, single-arm, open-label, multi-center study of axitinib in patients (US) with mRCC whose disease had failed one prior cytokine-based therapy. Data available from 52 patients.
- **Study A4061023**, a Phase 2, single-arm, open-label, multi-center study of axitinib in patients (US) with advanced RCC whose disease had failed at least one prior treatment with sorafenib; most patients had additionally received prior treatment with sunitinib and/or other agents. Data available from 62 patients.
- **Study A4061035**, a Phase 2, single-arm, open label, multi-center study of axitinib in patients (Japanese) with mRCC whose disease had failed one prior cytokine-based therapy as first line. Data available from 34 patients.
- **Study A4061032**, a 2-arm, randomized, open-label, multi-center Phase 3 study of axitinib versus sorafenib in patients with advanced RCC after failure following one prior systemic first-line regimen containing one or more of the following agents: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s). Data available from 55 patients.

Logistic regression analysis was conducted to establish relationship between exposure and the safety endpoints. The final estimated posthoc PK parameters from the population PK model were used to calculate individual subject predicted measures of exposure. Various exposure measures, including dose or AUC over the previous day, week, month, and study, were screened by testing their correlation with the highest AE Grade by patient.

3.2.3 Conclusions

The results showed that for each AE, the previous day measures, AUC before the adverse event provided the best correlation. For AE Grade ≥ 1, only stomatitis and diarrhea showed exposure-AE relationships ($p<0.05$) across all three phase 2 studies. In study A4061035, the results showed significant relationships for all AEs with last AUC and last dose, except for hypertension. In all three phase 2 studies, there was no significant relationship between axitinib

exposure and hypertension possibly because of compensatory treatment and/or selection bias only patients who did not have AE > Grade 2 increase in blood pressure could have their dose escalated.

Of the safety endpoints assessed for A4061032, the best correlation of AE Grade ≥ 1 with axitinib exposure was observed for diarrhea, fatigue, and hand-foot syndrome although these were not statistically significant.

Reviewer's Comments:

- *Sponsor performed exposure-response analysis for safety separately for all the four clinical trials. Since there are few patients in the phase 2 trials and only 55 patients from the pivotal trial with PK data, reviewer pooled the data from the phase 3 trial and three phase 2 trials to perform the exposure-safety analysis for hypertension, proteinuria, fatigue and diarrhea. Multivariate logistic regression analysis was also performed to adjust for confounding factors such as baseline ECOG, patient type, age, weight and baseline blood pressure.*
- *Sponsor did not find significant relationship between exposure and hypertension most likely because they performed logistic regression analysis separately for all the studies. It is important to note that the p-value for slopes for the exposure-hypertension logistic regression analysis (phase 2 trials) ranged from 0.07 to 0.09 with a trend depicting that hypertension increased with increased exposure. When reviewer pooled all the data for exposure-hypertension analysis, it was observed that the relationship was significant.*
- *Furthermore, the sponsor did the analysis for AE grade ≥ 1. Reviewer conducted exposure-safety analysis with AE grade ≥ 3in addition to AE grade ≥ 1.*

4 Reviewer's Analysis

4.1 Exposure-Response Analysis for Safety

4.1.1 Objectives

To perform the exposure-response relationship for hypertension, proteinuria, fatigue and diarrhea by pooling the data from the three phase two and one phase 3 trial and to assess if the proposed dose modification scheme proposed by the sponsor is appropriate to manage hypertension and proteinuria.

4.1.2 Methods

Data from the three phase 2 trials and a phase 3 trial was pooled to perform the exposure-response analysis for safety endpoints. Consistent with the sponsor's analysis, AUC observed before the adverse event was utilized as the exposure variable.

4.1.3 Datasets

The datasets utilized for the analysis are summarized below.

Study Number	Name	Link to EDR
A4061012, A4061023, A4061035	txemae.xpt	\\cdsesub1\evsprod\NDA202324\0000\m5\datasets\pmar-00080\analysis
	bpcont.xpt	
	endpnt.xpt	
A4061032	txemae.xpt	\\cdsesub1\evsprod\NDA202324\0005\m5\datasets\pmar-00140\analysis\datasets
	bpcont.xpt	
	endpnt.xpt	

4.1.4 Software

SAS 9.2 and TIBCO Spotfire S-Plus 8.1were used for analyses.

4.1.5 Model

The relationship between probability of adverse events and axitinib exposures was modeled using logistic regression. Multivariate regression analysis was also conducted to examine if exposure was significantly associated with adverse events after adjusting for potential confounding factors like baseline ECOG, age, patient type, baseline blood pressure.

4.1.6 Results

Exposure related increase in adverse events was observed for all grade diarrhea, hypertension, fatigue and proteinuria. The results for the univariate and multivariate analysis for these adverse events are provided in Table 3.

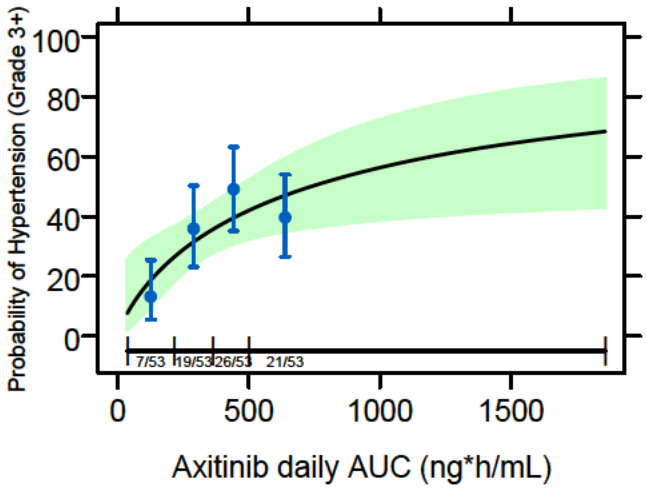
Table 3: Parameter estimates for univariate and multivariate logistic regression for all grade adverse events

Adverse Event (All grade)	Slope (P-value) for AUC/100 Univariate	Slope (P-value) for AUC/100 Multivariate*
Hypertension	0.27 (P=0.0002)	0.29 (P=0.0008)
Proteinuria	0.29 (P<0.0001)	0.28 (P=0.0002)
Fatigue†	0.30 (P<0.0001)	0.32 (P<0.0001)
Diarrhea	0.35 (P<0.0001)	0.36 (P<0.0001)

* Adjusted for baseline ECOG, patient type, age and baseline systolic blood pressure
† Also adjusted for weight apart from ECOG, patient type, age and baseline systolic blood pressure

Exposure-response analysis was also conducted for grade ≥ 3 adverse events. However, due to lesser proportion of patients experiencing grade 3 or higher proteinuria, fatigue or diarrhea, a significant relationship could not be established. For grade ≥ 3 hypertension, the relationship was statistically significant (P=0.005) with a slope of 0.17 for AUC/100 (Figure 8). AUC/100 ng*h/ml was a significant predictor of grade ≥ 3 hypertension (slope=0.15, P=0.03) after accounting for baseline ECOG, patient type, age and baseline blood pressure in a multivariate logistic model.

Figure 8. Exposure dependent increase in grade ≥ 3 hypertension



4. 2 PHARMACOGEMOMICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202324
Submission Date	14 April 2011
Applicant Name	Pfizer
Generic Name	Axitinib
Proposed Indication	Advanced renal cell carcinoma
Primary Reviewer	Rosane Charlab Orbach, Ph.D.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H.

1 Background

Axitinib is an oral vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3 tyrosine kinase inhibitor (TKI). It inhibits the auto-phosphorylation of VEGFR-1, 2 and 3 with IC50 at picomolar levels in vitro, and has approximately 10-fold lower potency toward inhibition of platelet-derived growth factor receptors (PDGFR) alpha and beta and the stem cell factor receptor KIT. Based on in vitro data, axitinib is metabolized by polymorphic drug metabolizing enzymes (primarily CYP3A, and to a lesser extent CYP2C19, CYP1A2 and UGT1A1), and is also a substrate of polymorphic transporters. During development, FDA requested an analysis of the correlation of UGT1A1 genotype with safety and efficacy in addition to exposure for axitinib (b) (4) In conjunction with FDA request, DNA samples for candidate pharmacogenetic analyses were collected in several early phase studies and in the pivotal study (axitinib arm only) as part of the axitinib clinical development program.

The sponsor claims in the proposed label that CYP2C19 and UGT1A1 gene variants do not impact exposure (excerpt from annotated label below).

(b) (4)

The purpose of this review is to determine whether: 1) polymorphisms in genes involved in axitinib disposition are associated with clinically relevant variability in axitinib pharmacokinetics ($AUC_{0\text{-}inf}$) as measured in a pooled analysis of phase 1 data; and 2) UGT1A1 genotype is associated with variable axitinib efficacy or toxicity in the pivotal efficacy study.

2 Submission Contents Related to Genomics

Data from 11 phase I clinical studies in healthy volunteers (Studies A4061003, A4061004, A4061006, A4061007, A4061018, A4061021, A4061026, A4061033, A4061036, A4061037, and A4061047) were used by the sponsor to perform a meta-analysis (Pharmacokinetic Meta-Analysis Statistical Report; MM080381) of the association between genetic polymorphisms in metabolizing enzymes (CYPs and UGTs) and transporters with axitinib exposure ($AUC0_{0\text{-}inf}$).

The sponsor also evaluated the effect of UGT1A1*28 and CYP2C19 genotype on axitinib pharmacokinetics (PMAR-00075) by population pharmacokinetic (PopPK) analysis of pooled data from 10 phase I healthy volunteer studies (all of the above without A4061003).

In addition, 296 patients from the axitinib arm of the pivotal study A4061032 were genotyped for UGT1A1 variants in a substudy to assess correlations between safety and efficacy endpoints and UGT1A1 genotype. Blood samples for genotyping were not collected for patients in the sorafenib arm.

***Table 1*: Studies for which DNA was analyzed for axitinib disposition polymorphisms**

Study	Design	Number of subjects (N)*
Healthy volunteer studies phase 1 studies		
A4061003	Open-label, single dose, mass balance study of ^{14}C labeled axitinib in healthy male subjects	8
A4061004	Single-blind, randomized, 2-way crossover drug interaction study with ketoconazole	35
A4061006	Open-label food-effect study assessing the effect of a high-fat, high-calorie meal and fasting on axitinib PK	42
A4061007	Open-label, 2-way crossover, absolute bioavailability study comparing axitinib PK after intravenous and oral administrations	16
A4061018	Randomized, open-label, crossover relative bioavailability study to evaluate different oral formulations of axitinib	40
A4061021	Open-label, randomized, 2-sequence, 3-period crossover bioequivalence study to compare (b) (4) tablets	40
A4061026	Open-label, 2-period, 2-treatment crossover drug interaction study with rifampin	40
A4061033	Open-label, randomized, 4-sequence, 4-period, crossover, relative bioavailability study	56
A4061036	Open-label, parallel-group study in subjects with normal and mild to moderate hepatic impairment	24
A4061037	Open-label, randomized, 4-sequence, 4-period, crossover relative bioavailability study	20
A4061047	Open-label, randomized, 2-sequence, 4-period crossover bioequivalence study	68
Total		**389**
Cancer Patient phase 3 study		
A4061032	Randomized, open-label, multicenter, multinational study	**723**

Source: Modified from sponsor's table 1- PMAR-00075 and sponsor's table 1- Listing of All Completed Clinical Studies. * Note: Not all of the sponsor's candidate gene variants were assayed in all patients. See Table 2 for details.

A summary of the sponsor's meta-analytical and PopPK methods can be found at the Study MM080831 and Sponsor's Pharmacokinetic Meta-Analysis Statistical Reports, and Population Modeling Analysis Report (PMAR)-00075.

3 Key Questions and Summary of Findings

3.1 Question 1?

Are there clinically relevant differences in axitinib exposures based on drug metabolizing or transporter gene variations that require dose adjustments?

No. No robust associations with a number of gene variants and PK variability were observed. CYP2C19 poor metabolizers (PMs) exhibited nominally higher axitinib concentrations than extensive metabolizers (EMs). Subjects with polymorphisms in ABCB1 also exhibited different axitinib concentrations. Despite these differences, axitinib can be titrated based on tolerability; therefore, a priori dose adjustment based on genotype is not warranted based on the currently available data.

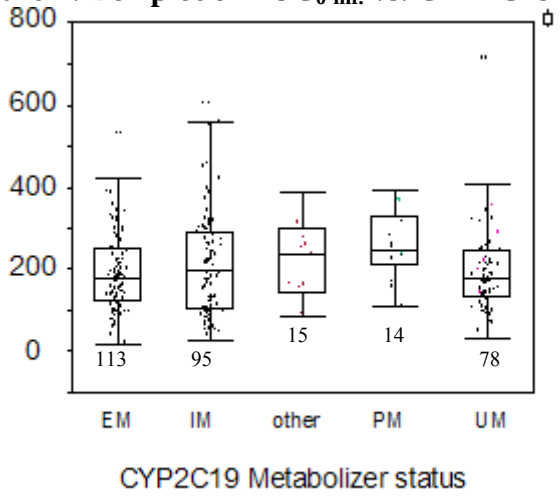
3.1.1 Overview of Sponsor's Analyses

There is substantial inter-subject variability (~70%) in exposures following axitinib dose of 5 mg bid. Pharmacogenetic analyses were performed by the sponsor to evaluate whether this observed pharmacokinetic variability is, in part, a result of polymorphisms in drug disposition genes. CYP2C19 and UGT1A1 genotypes were evaluated as covariates in PopPK analysis. In addition, disposition gene polymorphisms were evaluated using a fixed effects meta-analysis. The sponsor's methodology (e.g., selection of variants, genotyping methods, haplotype assignment, phenotype assignment) was appropriate except where noted below. No deviations from the Hardy-Weinberg equilibrium that affected the reviewer interpretation were noted.

3.1.2 CYP2C19

CYP2C19*2, CYP2C19*3, CYP2C19*17 alleles were assessed. Genotype-derived phenotypes were then assigned to subjects by the sponsor as follows: **7** UMs (*17/*17); 14 PMs (*X/*X, where X = null allele [*2 or *3]); and 294 EMs (overall number of subjects =315). EMs were classified as anyone who was not a UM or PM per the sponsor's internal practice. While the UM and PM categories are properly assigned and represent the extreme of the phenotypic spectrum, the EM category, as assigned by the sponsor, includes both wild-type subjects and subjects heterozygous for null alleles (*2 and *3). These individuals are typically designated as IMs in conventional pharmacogenetic designations. In the reviewer's opinion, *1/*17 should also be included in the UM category, *1/*X should be designated as IM, and *17/*X should be designated as "Other" since the phenotypic consequences of having 1 gain-of-function and 1 null allele are unknown. The reviewer reassigned accordingly for analysis (Figure 1).

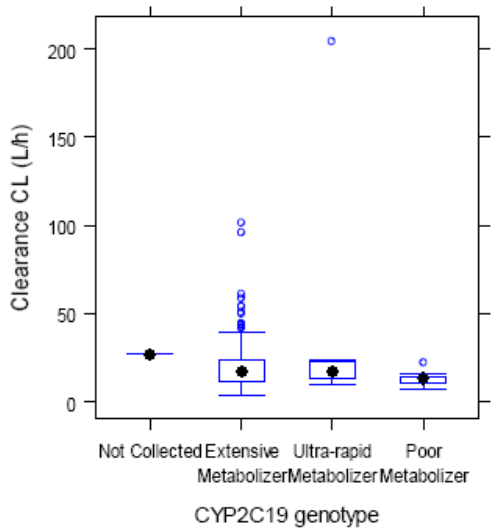
***Figure 1*: Box plot of $AUC_{0\text{-inf.}}$ vs. CYP2C19 metabolizer categories**



According to the sponsor's meta-analysis, there was no statistically significant correlation between selected genetic polymorphisms in CYP2C19 and axitinib AUC $_{0\text{-inf}}$ after multiplicity adjustment. However, a nominal difference in AUC between CYP2C19 EMs and PMs (95%CI 5-50% higher $AUC_{0\text{-inf}}$ in CYP2C19 PMs) was noted. Significant overlap was observed across phenotype groups (Figure 1). The small numbers of subjects in some of these phenotypic categories and lack of comprehensive genotyping make it difficult to assess whether the finding in PMs is spurious or represents a biologically real difference in axitinib PK. It is also not clear whether PK differences by genotype exist for doses other than 5 mg BID. Since axitinib may be titrated based on tolerability, a priori dose adjustment based on CYP2C19 genotype is not necessary based on the data available at this time.

In addition to the sponsor's meta-analysis, the sponsor evaluated CYP2C19 variants in PopPK analysis of pooled data from 10 healthy volunteer phase 1 studies (n=337). In this analysis, 312 subjects were categorized as EMs, 8 as UMs and 15 as PMs, Tested CYP2C19 variants were not considered to be a significant covariate on axitinib clearance (CL) based on sponsor analysis, although CL did appear to be reduced in CYP2C19 PMs compared with other groups (Figure 2). For details of this analysis, refer to Pharmacometrics review.

***Figure 2*: Axitinib clearance by CYP2C19 phenotype.**



Source: Sponsor's figure 12 - summary of clinical pharmacology

3.1.3 Additional Findings from Sponsor's Meta-Analysis

According to the sponsor's meta-analysis, there was not statistically significant correlation between selected genetic polymorphisms in CYP3A4, CYP3A5, UGT1A1, ABCB1, ABCG2, and SLCO1B1 and axitinib AUC $_{0\text{-inf}}$ after multiplicity adjustment (Tables 2 and 3). Of note, the genotype analyses were conducted over many years, and not every gene was assessed in each of the 11 healthy volunteer studies. Conclusive results could not be drawn for gene variants for which a limited number of patients were assayed (e.g., ABCB1, ABCG2, SLCO1B1).

***Table 2*: Polymorphisms used in the meta-analysis, and the total number of healthy volunteers evaluated for these polymorphisms**

Polymorphisms	Number of subjects
CYP3A4*1B	45
UGT1A*6	76
CYP3A5 (*3 and *6)	315
UGT1A1*28	293
UGT1A*60	222
UGT1A*93	222
ABCB1(G2677T/A)	145
ABCB1(C3435T)	145
ABCG2(C421A)	139
SLCO1B1(T521C)	145

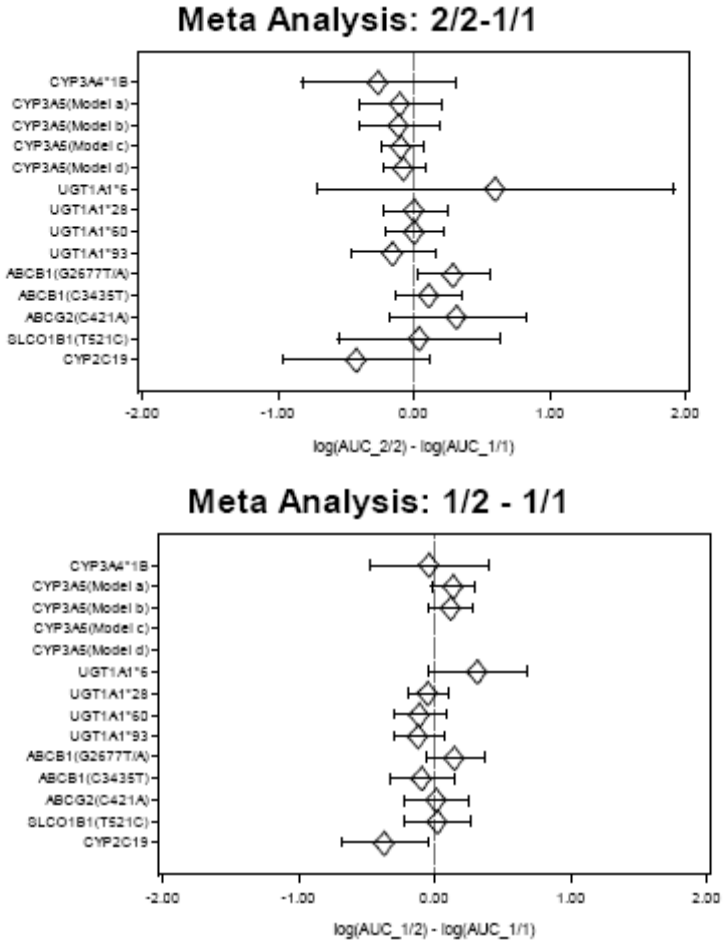
***Table 3*: Fixed effects meta-analysis for each gene polymorphism**

Genotype	F Value	p-Value	Adjusted p-Value*
*CYP3A4*1B*	0.49	0.62	1.00
CYP3A5 (Model a)	1.82	0.16	0.99
CYP3A5 (Model b)	1.46	0.23	1.00
CYP3A5 (Model c)	1.40	0.24	1.00
CYP3A5 (Model d)	0.90	0.34	1.00
*UGT1A1*6*	1.81	0.17	1.00
*UGT1A1*28*	0.26	0.77	1.00
*UGT1A1*60*	0.89	0.41	1.00
*UGT1A1*93*	1.12	0.33	1.00
ABCB1(G2677T/A)	2.36	0.10	0.59
ABCB1(C3435T)	1.31	0.27	1.00
ABCG2(C421A)	0.79	0.45	1.00
SLCO1B1(T521C)	0.02	0.98	1.00
CYP2C19	2.61	0.07	0.45

Source: Sponsor's table 3 - Pharmacokinetic Meta-Analysis Statistical Report

Additional exploratory analyses were conducted by the sponsor to assess the potential correlation between genotype and exposure. Forest plots showing the genetic effect estimates and confidence intervals from the fixed effects meta-analysis based on all studies with available genotype data are displayed in Figure 3. For most gene polymorphisms/studies (except CYP3A5, UGT1A1*28 and CYP2C19), two contrasts (log ratios) were analyzed (2/2 with 1/1 and 1/2 with 1/1). For CYP3A5, contrasts were computed depending on the model. For Models a and b, "fully expressed – not expressed" and "intermediately expressed – not expressed" were computed; for models c and d, "expressed – not expressed" was computed; for UGT1A1*28, two contrasts "7/7 – 6/6" and "6/7 – 6/6" were computed; for CYP2C19, two contrasts "UM – PM" (plot on the top and "EM – PM" (plot on the bottom) were computed. UGT1A1*6 2/2 genotype had only one subject and results were not reliable. For ABCB1 (G2677T/A), AUC of the two genotypes 2/2 and 1/1 were statistically significantly different ($P<0.05$; 95% confidence that $AUC_{0\text{-inf}}$ 2/2 was 2% to 76% higher than $AUC_{0\text{-inf}}$ 1/1). Of note, CYP1A2 polymorphisms were not assessed by the sponsor. CYP1A2 haplotypes have been associated with increased activity due to induction of expression. The phenotype is only observed in the presence of inducers such as smoking or heavy coffee intake. The effect of smoking status was evaluated using PopPK analysis, which suggested a higher clearance in active smokers. However, just 3% of the dataset was of active smokers (refer to Pharmacometrics review). The sponsor indicated that the effect of smoking will be further characterized in future studies.

Figure 3: **Forest plots with estimates and CI for the difference between genotypes 2/2 -1/1 (top) and 1/2-1/1 (bottom) for each gene**



Source: Sponsor's figure 1- Pharmacokinetic Meta-Analysis Statistical Report

3.1.4 Additional PopPK Analyses

The potential effect of selected polymorphisms in UGT1A1 and CYP2C19 in the axitinib pharmacokinetic variability was evaluated using PopPK analysis of pooled data from 10 healthy volunteer phase 1 studies (n=337). Data regarding CYP2C19 were presented in section 3.1.2 above. Genotyping for UGT1A1 *28 was conducted using a Sequenom MassArray assay developed at Pfizer. The number of subjects with UGT1A1 genotype is indicated in Table 4. An "unknown" category was assigned. UGT1A1 promoter polymorphisms other than TA6 and TA7 (e.g. TA5 or TA8) were assigned to the category "other" (Figure 4).

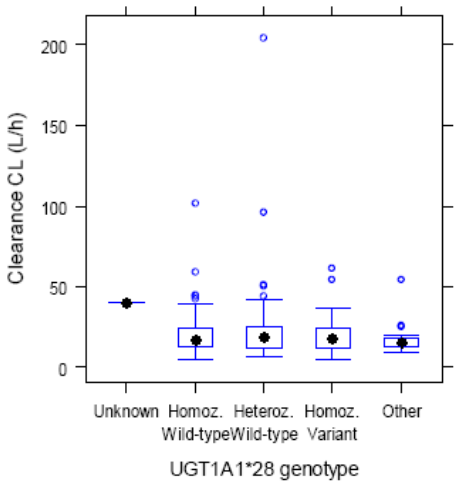
The UGT1A1*28 polymorphism was not considered to be a significant covariate on axitinib clearance (CL) based on sponsor analysis (Figure 4), which was reproduced by the Pharmacometrics reviewer. For details of this analysis, refer to Pharmacometrics review.

***Table 4*: Counts of included genotype data by study**

Study	N	UGT1A1 *28		
		Homozygous Wild-type	Heterozygous	Homozygous Variant
A4061004	32	14	14	3
A4061006	41	21	13	6
A4061007	16	7	4	4
A4061018	20	9	9	1
A4061021	40	18	14	7
A4061026	40	23	13	4
A4061033	54	27	18	6
A4061036	8	4	4	0
A4061037	20	8	6	1
A4061047	66	42	12	3
Total	337	173	107	35

Source: Sponsor's table 8, PMAR-00075.

***Figure 4:* Axitinib clearance by genotype (UGT1A1*28)**



Source: Sponsor's figure 12 - summary of clinical pharmacology

3.2 Question 2?

Is there a conclusive correlation between UGT1A1 genotype and efficacy or safety?

No. There was no plausible correlation between UGT1A1*28 status and improved outcomes or higher incidence of adverse events. This is consistent with the lack of influence of UGT1A1 variants on axitinib PK.

3.2.1 Efficacy and Safety Endpoints According to UGT1A1 Genotype

The sponsor assessed whether there is a potential association between UGT1A1 genotype, efficacy and adverse events in the pivotal study A4061032. Alleles evaluated included UGT1A1*6, *27, *60,*93 (TaqMan Allelic Discrimination Assay) and UGT1A1*28 (Fragment Analysis Genotyping). Other axitinib disposition genes were not assessed. UGT1A1 genotyping was only performed in the treatment arm. For the UGT1A1 TA repeat polymorphism, patients

with 6 (UGT1A1*1, wild-type) or 7 (UGT1A1*28, variant) TA repeats comprised >99% of the total observed alleles; 3 patients carrying 5 or 8 TA repeats were excluded from the analysis. 293 patients were thus included in the efficacy analyses. The *28 allele frequencies were in Hardy-Weinberg equilibrium, as assessed by the reviewer. Median event time and a 2-sided 95% CI were provided for efficacy endpoints (e.g., PFS) for the UGT1A1 genotype categories (6/6, 6/7 and 7/7). Descriptive tabulation of AE data in relation to UGT1A1 genotype for the UGT1A1 polymorphisms was provided according to system organ class for all AEs, as well as for SAE and Grade 3/4 subsets.

***Table 5*: Progression-Free Survival by UGT1A1*28 genotype**

Progression-Free Survival Parameter	Axitinib Treatment Arm; *UGT1A1* Genotype (Number of TA Repeats)		
	TA_6/TA_6 (**1/*1*) N=146	TA_6/TA_7 (**1/*28*) N=113	TA_7/TA_7 (**28/*28*) N=34
Progression status; n (%)			
Patient did not progress or die due to any cause while on-study; n (%)	62 (42.47)	56 (49.56)	13 (38.24)
Patient observed to have progressed or died due to any cause while on-study; n (%)	84 (57.53)	57 (50.44)	21 (61.76)
Progression-free survival time (months)			
Quartiles (95% confidence interval)			
25%	2.3 (1.5, 2.8)	2.8 (1.6, 4.6)	2.8 (1.4, 6.3)
50%	6.3 (4.5, 6.7)	8.6 (6.4, 13.9)	8.3 (2.9, 12.0)
75%	12.1 (10.1, NE)	17.7 (13.9, 17.7)	12.1 (8.3, 15.5)

Source: Sponsor's table 39, full clinical study report, protocol A4061032)

There was no consistent correlation between the presence of the *28 allele and progression status (Table 5), or between UGT1A1*28, UGT1A1*6, UGT1A1*27, UGT1A1*60 and UGT1A1*93 polymorphisms and the incidence of AEs (not shown). These neutral findings are consistent with the observation that UGT1A1 variants did not affect axitinib concentrations in a clinically meaningful way (see Sections 3.1.3 and 3.1.4).

4 Summary and Conclusions

1. The sponsor performed pharmacogenetic analyses of axitinib PK using pooled analysis of 11 phase 1 studies and PopPK analysis of 10 phase 1 studies.
2. Several candidate genes were assessed. Only a fraction of subjects enrolled in the phase 1 studies were assayed for all the gene variants of interest. The most complete dataset was for CYP2C19 and UGT1A1 variants.
3. CYP2C19*2, CYP2C19*3, CYP2C19*17 alleles were assessed. The reviewer reassigned genotype-derived phenotypes in a way different from the sponsor. Irrespective of the phenotype assignment method, there did not seem to be a clinically meaningful difference in axitinib exposure. Since axitinib may be titrated based on tolerability, *a priori* dose adjustment based on CYP2C19 genotype is not necessary based on the data available at this time.
4. Tested UGT1A1 polymorphisms were not significantly associated with axitinib clearance. Additionally, UGT1A1 variants were not consistently associated with incidence of AEs or efficacy rates in the pivotal efficacy trial. These neutral findings are consistent with the observation that UGT1A1 variants did not affect axitinib concentrations in a clinically meaningful way.

5. Conclusive results could not be drawn for gene variants for which a limited number of subjects were assayed (e.g., ABCB1, ABCG2, SLCO1B1).

5 Recommendations

5.1 Post-marketing studies

None.

5.2 Label Recommendations

See integrated Office of Clinical Pharmacology review for detailed labeling recommendations.

Rosane Charlab Orbach, Ph.D.
Reviewer, Genomics Group, OCP

Issam Zineh, Pharm.D., M.P.H.
Associate Director, Genomics Group, OCP

4.3 NDA FILING AND REVIEW FORM

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202324**	**Brand Name**	**Inlyta®**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Axitinib**
Medical Division	**Oncology**	**Drug Class**	**Tyrosine kinase inhibitor**
OCP Reviewer	**Sarah Schrieber, Pharm.D.**	**Indication(s)**	Advanced renal cell carcinoma.
OCP Team Leader	**Qi Liu , Ph.D.**	**Dosage Form**	1 mg and 5 mg tablets
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**	**Dosing Regimen**	5 mg twice daily
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**		
Pharmacogenomics Reviewer	**Rosane Charlab-Orbach, Ph.D.**		
Pharmacometrics Team Leader	**Issam Zineh, Pharm.D.**		
Date of Submission	**4/16/11**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Pfizer**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**6**		**Plasma: AGOT00, AGOT01, AGOT04, AGOT07,AGOT09 Urine: AGOT02**
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**A4061003**
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		**PDM-017,**
Plasma protein binding:	**X**	**2**		**PDM-017, 8216659 (AAG)**
Pharmacokinetics -				
Healthy Volunteers-				
single dose:	**X**	**4**		**A4061050 (PK); A4061004 and A4061026 (DDI); A4061036 (hepatic)**
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**3**		**Solid tumor: A4061044, RCC: A4061046, A4061032**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**3**		**A4060010 (5-30mg), A4061044, A4061050 (5-10mg)**
fasting / non-fasting multiple dose:	**X**	**2**		**A4060010 (10-40mg), A4061019 (2-10mg)**
Drug-drug interaction studies -				

In-vivo effects on primary drug:	**X**	**3**		**A4061004 (ketoconazole); A4061026 (rifampin); A4060010 (rabeprazole)**
In-vivo effects of primary drug:	**X**	**1**		**A4061019 (paclitaxel)**
In-vitro:	**X**	**9**		**PDM-020 (CYP inh), PDM-039 (CYP inh), 764-05388 (CYP ind), 111529 (transporter substrate), 055543 (Pgp inh), 301040127 (UGT1A1 inh), 154709 (GastroPLUS Pgp), 190355 (SymCYP validation), 161413 (SymCYP 1A2, 2C8)**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		**A4061036 in normal, mild, and moderate**
PD - QT Study:	**X**	**1**		**A4061004**
Phase 2:	**X**	**7**		**Solid tumor: A4060010, A4061022, A4061044 RCC: A4061035 NSCLC: A4061011 Thyroid: A4061014 Melanoma: A4061015**
Phase 3:	**X**	**1**		**A4061032**
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**		**RCC: A4061012, A4061023 and A4061035**
Phase 3 clinical trial:	**X**	**1**		**RCC: A4061032**
Population Analyses -				
Data rich:	**X**	**15**		**Healthy: A4061004, A4061006, A4061007, A4061018, A4061021, A4061026, A4061033, A4061036, A4061037, A4061047, A4061050, A4061053 Solid tumor: A4060010, A4061022, A4061044**
Data sparse:	**X**	**6**		**Solid tumor: A4060010, A4061044 RCC: A4061012, A4061023, A4061035, A4061032**
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		**A4061007** (b) (4)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**A4061033 (fed,** (b) (4) **),**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**4**		**A4061046 (fed,** (b) (4) **), A4061052 (1 mg x 5 vs 5 mg x 1), A4061021** (b) (4)
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**A4061053 (Form XLI), A4061006** (b) (4)
Bio-waiver request based on BCS				
BCS class				

Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**11**		**UGT1A1 and CYP2C19 in Healthy: A4061004, A4061006, A4061007, A4061018, A4061021, A4061026, A4061033, A4061036, A4061037, A4061047** **RCC: A4061032**
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**28**		

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/s/

SARAH J SCHRIEBER
01/17/2012
This review supercedes & replaces the Dec 20, 2011 review; the OCP DCP5 director signature is included in this review.

NITIN MEHROTRA
01/17/2012

CHRISTINE E GARNETT
01/17/2012

ROSANE CHARLAB ORBACH
01/17/2012

ISSAM ZINEH
01/17/2012

QI LIU
01/17/2012

NAM ATIQUR RAHMAN
01/17/2012

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-324	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	4/13/2011		
Division:	Division of Oncology Products	**Secondary Signature:** Sandra Suarez Sharp, Ph.D.	
Sponsor:	Pfizer	**Biopharmaceutics Lead:** Angelica Dorantes, Ph.D.	
Trade Name:	INLYTA	**Date Assigned:**	4/13/2011
Generic Name:	Axitinib	**Date of Review:**	12/12/2011
Indication:	Treatment of advanced renal cell carcinoma (RCC)	**Type of Submission:** Original New Drug Application	
Formulation/strengths:	Immediate Release (IR) Film-Coated Tablet/1 mg and 5 mg		
Route of Administration:	Oral		

SUMMARY:

This is a 505(b)(1) New Drug Application for an immediate release tablet containing 1 mg and 5 mg of axitinib, indicated for the treatment of advanced renal cell carcinoma (RCC). This submission has Quality by Design elements for drug substance and drug product manufacturing.

The Biopharmaceutics review for this NDA is focused on:

- The evaluation and acceptability of the proposed dissolution methodology and acceptance criterion for axitinib;
- The evaluation of the Biopharmaceutics data supporting the proposed design space for axitinib film coated tablets.

A. Applicant's Proposed Dissolution Method and Acceptance Criterion

The proposed dissolution method is:

- Apparatus: Rotating Paddle (USP <711> Apparatus 2)
- Rotation speed: 75 rpm
- Dissolution medium: 0.01 N HCl
- Volume of dissolution medium: 900 mL
- Dissolution medium temperature: 37 ± 0.5°C

The proposed acceptance criterion is: (b) (4).

The dissolution method has adequate discriminating power, and therefore is deemed acceptable. The proposed dissolution acceptance criterion is considered too permissive and unable to screen for batches that may be inequivalent.

The following dissolution acceptance criterion is recommended: Q = (b) (4) at 30 minutes. This specification was set based on: 1) The mean in-vitro dissolution profiles for the 1 mg and 5 mg strengths at release and under long term (36 months) stability studies, and 2) The results from BA/BE study A4061033 which indicates that the axitinib product made with (b) (4) API particle size may not be bioequivalent to the proposed axitinib product made with (b) (4) API particle size. The Applicant accepted the FDA's recommended dissolution acceptance criterion at a teleconference dated December 5, 2011.

B. The Role of Dissolution on the Development of the Design Space for Axitinib Film Coated Tablets

The proposed commercial axitinib tablets are manufactured (b) (4) using equipment commonly available in the pharmaceutical industry.

Multivariate, univariate experimentation and engineering models were utilized to generate the operating knowledge space and establish the design space. The key or critical quality attributes associated with the axitinib proposed commercial formulation are product uniformity of dosage units (Key Quality Attribute, KQA), dissolution (KQA) and photo-stability (Critical Quality Attribute, CQA).

(b) (4)

During the review cycle, the ONDQA review team advised the Applicant to conduct f2 testing to demonstrate equivalent performance (clinical relevance) of product batches manufactured within the proposed design space. The Applicant responded (b) (4) . The Biopharmaceutics review team considers the Applicant's use of (b) (4) as not acceptable because the proposed drug product does not meet the criteria set forth in ICH Q6A (b) (4)

The uncertainty created by the lack of data (e.g dissolution profile comparisons) demonstrating clinical relevance throughout the proposed design space was communicated to the ONDQA review team as "the design space being not acceptable from a Biopharmaceutics perspective". The ONDQA review team concluded that from a CMC perspective the control strategy implemented would ensure consistent product quality. Nevertheless, the Applicant was recommended to conduct f2 testing for any movements outside the NOR and within the proposed design space. The Applicant accepted the FDA recommendations at a teleconference dated December 5, 2011,

This reviewer also had concerns that the proposed (b) (4) design space would provide adequate dissolution of axitinib and communicated this to the Applicant during the review cycle. The Applicant responded that (b) (4) However the ONDQA review team later on communicated to the Applicant that their proposed design space (b) (4) was not acceptable and advised the Applicant to establish target values for the process parameters to ensure the formation of axitinib (b) (4). At a teleconference on December 5, 2011, the Applicant agreed on further reviewing this recommendation. No update on this issue has been received as of December 9, 2011.

RECOMMENDATION:

1. Axitinib 1 mg and 5 mg tablets are recommended for approval from a Biopharmaceutics standpoint.
    - The following dissolution method and acceptance criterion for the 1 mg and 5 mg strength tablets have been agreed upon with the Applicant on a teleconference dated December 5, 2011:
        i. Dissolution method: Apparatus II, 75 rpm agitation rate, 900 mL media volume, 37 °C, 0.01 N HCl (pH 2.2) medium.
        ii. Dissolution acceptance criterion: Q= (b) (4) at 30 minutes.

2. The Applicant's design space for axitinib tablets is questionable from a Biopharmaceutics standpoint since the submitted data provides insufficient evidence supporting consistent *in vivo* performance of drug product manufactured within the ranges of the proposed design space.
    - The FDA's recommendation accepted by the Applicant on a teleconference dated December 5, 2011 to conduct f2 testing for any movements outside the NOR and within the proposed design space may alleviate this uncertainty provided an action is taken to ensure consistent quality throughout the drug product marketing phase for those instances were f2 fails.

3. The Applicant should maintain a maximum film coat percentage of (b) (4).
    - At a teleconference on December 5, 2011, the Applicant stated that they will further review FDA's recommendation. As of December 9, 2011, the Applicant has not provided agreement on this recommendation or proposed a maximum film coat percentage

Kareen Riviere, PhD
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Sandra Suarez Sharp, PhD
Senior Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

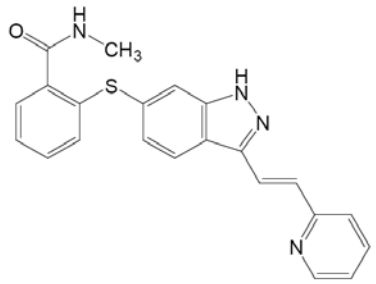
cc: Angelica Dorantes, Ph.D.

BIOPHARMACEUTIC INFORMATION:

1. Background

The chemical structure of axitinib is shown in Figure 3.2.S.1.2-1.

Figure 3.2.S.1.2-1. Axitinib Structure



Axitinib is designated as a BCS Class II drug substance (low solubility, high permeability). The aqueous solubility of axitinib is presented in Table 3.2.S.1.3-1. The solubility of axitinib is higher under low pH gastric conditions. As pH increases, the solubility has a decaying profile. With a pKa of 4.8, Axitinib is a weak base and will exist predominantly as a neutral molecule (> 98%) at pH 6.5. There is minimal solubility above the pKa. The absolute bioavailability of oral Axitinib is 58%.

Table 3.2.S.1.3-1. Aqueous Solubility of Axitinib

Aqueous Solution	Solubility (microgram/mL)
Water pH 7.5	0.2
0.1N HCl, pH 1.1	1841
0.06N HCl pH 1.7	320
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 2.2	75
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 2.9	12
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 3.7	2.3
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 4.0	1.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 4.4	0.5
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 5.2	0.3
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 6.0	0.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 7.0	0.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 7.8	0.2

The Applicant formulated axitinib in several orally administered dosage forms and an intravenous solution during different phases of clinical development. The dosage forms used in the clinical trials include tablets, intravenous solution (b) (4)

Table 3.2.P.2.2-3 summarizes the composition of the axitinib tablets used in clinical trials and commercial formulation and shows that the commercial and clinical formulations have the same composition. Several BA/BE studies (refer to section 2: Bioequivalence studies) were conducted to bridge among several CMC changes done throughout the development of the drug product (b) (4)

Table 3.2.P.2.2-3 Composition of 1 mg, 5 mg, and 10 mg Axitinib Immediate Release Tablets Used in Clinical Studies and Commercial Formulation

Components (mg)										
Formulation Description	(b) (4)									
Formulation ID Number	D0400960/ D0400647/ S01308AA	D0400962/D0400648	PD AG013736-01	D0602467	D0602468	D0703554, D0703558	D0703783	D0804373	D0703784	D0804373	D0703784
Strength	(b) (4)									1 mg	5 mg
Axitinib1										1.000	5.000
Lactose Monohydrate (b) (4	(b) (4)										
Microcrystalline Cellulose											
Croscarmellose Sodium (b) (4											
Magnesium Stearate (b) (4											
Opadry® II Red 32K15441 (b) (4											
Shape	(b) (4)									Oval	Triangular
Debossing										"Pfizer"/ "1 XNB"	"Pfizer"/ "5 XNB"

(b) (4) Grey boxes – Not applicable

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(b) (4)

Axitinib 1 mg and 5 mg (b) (4) red iron oxide film coated tablets (b) (4) were prepared (b) (4). The 1 mg tablet is oval shaped while the 5 mg tablet is triangular shaped.

As seen in Table 3.2.P.1-1 and Table 3.2.P.1-2, the composition of axitinib 1 mg and 5 mg tablets are qualitatively but not quantitatively similar.

Reviewer Comments:
Although the axitinib 1 mg and 5 mg tablets are not quantitatively similar in composition, the Applicant has demonstrated that axitinib 1 mg and 5 mg tablets are bioequivalent through the conduct of in vivo studies (refer to section 2).

Table 3.2.P.1-1 Composition of 1 mg Axitinib Film Coated Tablets

Component	Function	Reference to Standard	Theoretical Unit and/or Formula (mg)
Axitinib	Active	Pfizer	1.000[1]
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph. Eur.,JP	(b) (4)
Lactose Monohydrate		NF, Ph. Eur.,JP	
Croscarmellose Sodium		NF, Ph. Eur.,JP	
Magnesium Stearate		NF, Ph. Eur.,JP	
(b) (4)			
Film Coat			
Opadry® II Red 32K15441		Pfizer[3]	
(b) (4)		USP, Ph. Eur., JP	
Total Finished Tablet			

Table 3.2.P.1-2 Composition of 5 mg Axitinib Film Coated Tablets

Component	Function	Reference to Standard	Theoretical Unit and/or Formula (mg)
Axitinib	Active	Pfizer	5.000[1]
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph. Eur.,JP	(b) (4)
Lactose Monohydrate		NF, Ph. Eur.,JP	
Croscarmellose Sodium		NF, Ph. Eur.,JP	
Magnesium Stearate		NF, Ph. Eur.,JP	
(b) (4)			
Film Coat			
Opadry® II Red 32K15441		Pfizer[3]	
(b) (4)		USP, Ph. Eur., JP	
Total Finished Tablet			

For more details on the drug product manufacturing aspects of axitinib tablets, refer to Dr. Amit Mitra's CMC review.

2. Bioequivalence (BE) Studies

Table 1 from Section 2.7.1.4.1 Appendix A provides a tabular summary of bioavailability and bioequivalence data for Axitinib 1 mg and 5 mg tablets.

Section 2.7.1.4.1 Appendix A, Table 1 Tabular Summary of Axitinib Bioavailability and Bioequivalence Studies

Protocol No.	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	$AUC_{0\text{-last}}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
A4061021	To establish the BE of the axitinib (b) (4) (b) (4) tablet to the axitinib (b) (4) tablet in the fasted state	Design: OL, R, single dose, 2-sequence, 3 period, crossover, HV Subjects: 40 Sex: 38 M/2 F Mean Age (min/max): 33.4 (18-54) years Evaluated for: PK: 40 Safety: 40	Axitinib 5-mg tablet (b) (4) (b) (4) Route: oral; Dose Regimen: single dose)					
			(b) (4) Formulation	199 (39)	207 (36)	46.6 (42)	1.7 (1.0-3.02)	7.4 (87)
			(b) (4) Formulation	193 (46)	200 (44)	44.7 (53)	1.7 (1.02-3.0)	6.0 (53)
			Statistical Comparison – Geometric LS Mean Ratio % (90% CI)					
				(b) (4)				
			C_{max}	93.9 (81.3, 108)				
			$AUC_{0\text{-}\infty}$	97.9 (89.2, 107)				

Protocol No.	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	$AUC_{0\text{-last}}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
A4061063	To establish the BE of test 5-mg tablets of axitinib polymorph Form XLI to reference 5-mg tables of axitinib polymorph Form IV under fed conditions	Design: OL, R, single dose, 2-sequence, 4-period, crossover, replicate design, with 7 day washout, HV Subjects: 42 Sex: 42 M/0 F Mean Age (min/max): 29.9 (21 - 45) years Evaluated for: PK: 42 Safety: 42	Axitinib 5-mg polymorph Form IV vs Axitinib 5-mg polymorph Form XLI tablets in the fed state (Route: oral; Dose Regimen: single dose)					
			Commercial Form XLI FCIR tablet (Test)	216 (40)	220 (40)	43.0 (33)	3.25 (1.50-4.01)	3.36 (33)
			Form IV FCIR tablet (Reference)	242 (38)	246 (38)	49.0 (28)	3.00 (1.00-5.00)	3.02 (33)
			Statistical Comparison - Geometric Mean Ratio % (90% CI)					
				Form XLI/Form IV				
			C_{max}	86.5 (81.5, 91.9)				
			$AUC_{0\text{-}\infty}$	87.8 (83.4, 92.4)				

Protocol No.	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	$AUC_{0\text{-last}}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
A4061052	To establish the BE of five 1-mg FCIR tablets (test treatment) vs one 5-mg tablet (reference treatment) (b) (4) (b) (4) in the fasted state	Design: OL, R, 4-period, 2-sequence crossover, replicate study, HV Subjects: 60[a] Sex: 60 M/0 F Mean Age (min/max): 30.6 (21-44) years Evaluated for: PK: 59 Safety: 59	Reference: one 5-mg FCIR tablet of axitinib (b) (4) (b) (4) Test: Five 1-mg FCIR tablets of axitinib (b) (4) (Route: oral; Dose Regimen: replicate dosing)					
			5 x 1 mg (test)	285 (45)	289 (46)	65.1 (41)	1.75 (1.00-3.51)	3.81 (37)
			1 x 5 mg (reference)	265 (40)	270 (39)	63.3 (41)	1.75 (1.00-3.25)	3.85 (38)
			Statistical Comparison – Geometric LS Mean Ratio % (90% CI)					
				5 x 1 mg Form XLI/1 x 5mg Form XLI				
			C_{max}	104 (95.8, 112)				
			$AUC_{0\text{-}\infty}$	106 (98.8, 113)				

According to the Applicant, BE was demonstrated (b) (4) The 5 mg tablet used in pivotal Phase 3 study A4061032 is identical (b) (4) to the proposed commercial formulation 5 mg tablet. Finally, BE was demonstrated between one 5 mg tablet and five 1 mg proposed commercial formulation tablets in Study A4061052. These BA/BE studies are being reviewed by OCP.

Figure 3.2.P.2.2-4 summarizes the bioequivalence outcomes for Axitinib 1 mg and 5 mg tablets.

Figure 3.2.P.2.2-4 Bioequivalence Outcomes for 1 mg and 5 mg Axitinib Tablets

(b) (4)

3. Dissolution Method

Development

The Applicant investigated the effect of apparatus, agitation speed, and media on dissolution profiles. The Applicant's purpose for the dissolution testing was for quality control purposes at product release and stability testing.

The proposed dissolution method:

- Apparatus: Rotating Paddle (USP <711> Apparatus 2)
- Rotation speed: 75 rpm
- Dissolution medium: 0.01 N HCl
- Volume of dissolution medium: 900 mL
- Dissolution medium temperature: 37 ± 0.5°C

Table 3.2.P.2.2-13 summarizes the dissolution test conditions studied during dissolution development.

Table 3.2.P.2.2-13 Summary of Axitinib Dissolution Profiles [a]

(b) (4)

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/s/

KAREEN RIVIERE
12/12/2011

SANDRA SUAREZ
12/12/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	202-324	**Reviewer:** Kareen Riviere	
Submission Date:	4/13/2011		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, Ph.D.	
Sponsor:	Pfizer	**Supervisor:** Patrick Marroum, Ph.D.	
Trade Name:	INLYTA	**Date Assigned:**	4/13/2011
Generic Name:	Axitinib	**Date of Review:**	June 24, 2011
Indication:	Treatment of advanced renal cell carcinoma (RCC)	**Type of Submission:** Original New Drug Application	
Formulation/strengths	Tablet/1 mg and 5 mg		
Route of Administration	Oral		

SUBMISSION:

This is a 505(b)(1) New Drug Application for an immediate release tablet containing 1 mg and 5 mg of Axitinib, indicated for the treatment of advanced renal cell carcinoma (RCC). This submission has Quality by Design elements for drug substance and drug product manufacturing.

BIOPHARMACEUTIC INFORMATION:

Axitinib has been formulated in several orally administered dosage forms and an intravenous solution during different phases of clinical development. The dosage forms used in the clinical trials include tablets, intravenous solutio (b) (4)

Axitinib is designated as a BCS II drug substance (low solubility, high permeability). The low solubility designation is based on its pH-dependent solubility. The high permeability designation is based on the human clinical data and rat Single Pass Intestinal Perfusion (SPIP) studies. The mean absolute oral bioavailability of Axitinib in healthy volunteers was determined as 58%.

(b) (4)

Proposed dissolution method and acceptance criterion:

- Apparatus: Rotating Paddle (USP <711> Apparatus 2)
- Rotation speed: 75 rpm
- Dissolution medium: 0.01 N HCl
- Volume of dissolution medium: 900 mL
- Dissolution medium temperature: 37 ± 0.5°C

The proposed acceptance criteria: (b) (4)

This submission includes a drug product development section; a dissolution development report with proposed dissolution specification and acceptance criterion; *in vivo* bioequivalence data demonstrating bioequivalence between five 1 mg tablets and one 5mg tablet (b) (4)

(b) (4)

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion for Axitinib.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 202-324 for filing purposes. We found this NDA filable from a Biopharmaceutics perspective. The sponsor has submitted a reviewable submission.

Kareen Riviere, PhD
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Angelica Dorantes, PhD
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc: Patrick Marroum, Ph.D.

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/s/

KAREEN RIVIERE
07/06/2011

ANGELICA DORANTES
07/06/2011

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 202324

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202324**	**Brand Name**	**Inlyta®**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Axitinib**
Medical Division	**Oncology**	**Drug Class**	**Tyrosine kinase inhibitor**
OCP Reviewer	**Sarah Schrieber, Pharm.D.**	**Indication(s)**	Advanced renal cell carcinoma.
OCP Team Leader	**Qi Liu , Ph.D.**	**Dosage Form**	1 mg and 5 mg tablets
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**	**Dosing Regimen**	5 mg twice daily
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**		
Pharmacogenomics Reviewer	**Rosane Charlab-Orbach, Ph.D.**		
Pharmacometrics Team Leader	**Issam Zineh, Pharm.D.**		
Date of Submission	**4/16/11**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Pfizer**
Medical Division Due Date	**12/20/11**	**Priority Classification**	**Standard**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**6**		**Plasma: AGOT00, AGOT01, AGOT04, AGOT07,AGOT09 Urine: AGOT02**
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**A4061003**
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		**PDM-017,**
Plasma protein binding:	**X**	**2**		**PDM-017, 8216659 (AAG)**
Pharmacokinetics -				
Healthy Volunteers-				
single dose:	**X**	**4**		**A4061050 (PK); A4061004 and A4061026 (DDI); A4061036 (hepatic)**
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**3**		**Solid tumor: A4061044, RCC: A4061046, A4061032**

Dose proportionality -				
fasting / non-fasting single dose:	**X**	**3**		**A4060010 (5-30mg), A4061044, A4061050 (5-10mg)**
fasting / non-fasting multiple dose:	**X**	**2**		**A4060010 (10-40mg), A4061019 (2-10mg)**
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**3**		**A4061004 (ketoconazole); A4061026 (rifampin); A4060010 (rabeprazole)**
In-vivo effects of primary drug:	**X**	**1**		**A4061019 (paclitaxel)**
In-vitro:	**X**	**9**		**PDM-020 (CYP inh), PDM-039 (CYP inh), 764-05388 (CYP ind), 111529 (transporter substrate), 055543 (Pgp inh), 301040127 (UGT1A1 inh), 154709 (GastroPLUS Pgp), 190355 (SymCYP validation), 161413 (SymCYP 1A2, 2C8)**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		**A4061036 in normal, mild, and moderate**
PD - QT Study:	**X**	**1**		**A4061004**
Phase 2:	**X**	**7**		**Solid tumor: A4060010, A4061022, A4061044 RCC: A4061035 NSCLC: A4061011 Thyroid: A4061014 Melanoma: A4061015**
Phase 3:	**X**	**1**		**A4061032**
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**		**RCC: A4061012, A4061023 and A4061035**
Phase 3 clinical trial:	**X**	**1**		**RCC: A4061032**
Population Analyses -				
Data rich:	**X**	**15**		**Healthy: A4061004, A4061006, A4061007, A4061018, A4061021, A4061026, A4061033, A4061036, A4061037, A4061047, A4061050, A4061053 Solid tumor: A4060010, A4061022, A4061044**
Data sparse:	**X**	**6**		**Solid tumor: A4060010, A4061044 RCC: A4061012, A4061023, A4061035, A4061032**
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		**A4061007** (b) (4)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**A4061033 (fed,** (b) (4) **),**

Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**4**		**A4061046 (fed, (b) (4) , A4061052 (1 mg x 5 vs 5 mg x 1), A4061021 (b) (4)**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**A4061053 (Form XLI), A4061006 (b) (4)**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**11**		**UGT1A1 and CYP2C19 in Healthy: A4061004, A4061006, A4061007, A4061018, A4061021, A4061026, A4061033, A4061036, A4061037, A4061047 RCC: A4061032**
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**28**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted	X			

	in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A.

Of note, the following information requests were sent to the sponsor on 5/9/11:

1. Please submit the paclitaxel method validation report 2100-404.
2. Population PK/PD study report PMAR-00140 (population pharmacokinetics and PK-PD analyses from study A4061032) could not be found in your submission. Please submit the report, relevant datasets and control streams or direct us to the location if you have already submitted it. The following are the general expectations for submitting pharmacometric data and models.
    a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
c. A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Sarah Schrieber, Pharm.D.	6-7-11
Clinical Pharmacology Reviewer	**Date**
Qi Liu, Ph.D.	6-7-11
Clinical Pharmacology Team Leader	**Date**

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

/s/

SARAH J SCHRIEBER
06/07/2011

QI LIU
06/08/2011

Initial Quality Assessment
Branch 2
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	202-324
Applicant:	Pfizer Inc. 10646 Science Center Drive San Diego, CA 92121
Authorizing US Agent:	N/A
Letter Date:	14 April, 2011
Stamp Date:	14 April, 2011
PDUFA Goal Date:	14 October, 2011 (priority)
Trade name:	Inlyta (proposed)
Established Name:	Axitinib
Dosage Form/Strength:	Tablet (1 mg and 5 mg)
Route of Administration:	Oral
Indication:	Advanced Renal Cell Carcinoma (RCC).
Regulatory Filing	For 505 (b) (1)
Related IND/NDA/DMF (Form 356h)	IND 63662, (b) (4)
Assessed by:	Haripada Sarker

	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:		x

Background Summary

This NDA introduces Axitinib, an immediate release tablet for oral administration containing 1 mg and 5 mg of drug substance. Axitinib, the drug substance, is a new molecular entity. Pfizer adopted Quality by Design (QbD) approach to develop Axitinib in accordance with ICH Q8, Q9 and Q10 using risk management approaches, prior knowledge and experimentation. The QbD approach includes DS and DP Manufacturing Process Development and Validation of Analytical Procedures. Applicant referred to various ICH forums to justify the proposed QbD approach utilized for this submission. This information is presented in an expanded section of the respective DS and DP CMC information. The following are some of the key interactions related to CMC.

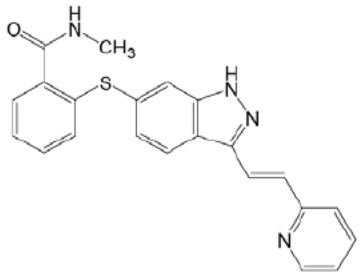
- June 19, 2008. Type-B, CMC specific meeting. Wide range of CMC issues are discussed, including DS starting material, QbD for analytical methods, DP stability plan, dissolution, and impurities.
- July 14, 2010. pre-NDA meeting mostly included non-CMC issues.

This NDA includes DS and DP quality information in eCTDQ format.

Drug Substance (DS)

The drug substance, axitinib is a white to light yellow powder, and the solubility of axitinib was higher in low pH media (> 1800 µg/ml at pH 1.1) but decreases rapidly across the pH range (0.2 µg/ml at pH 7.8). (b) (4) The DS is defined as BCS II (low solubility and high permeability) under the Biopharmaceutics Classification System (BCS).

Axitinib has no chiral center, but has a trans configuration at the olefinic double bond shown in the following Figure.



The DS proposed commercial process consists of (b) (4)

(b) (4)

Axitinib DS Manufacture, Analytical Testing and Release are performed at:
Pfizer Ireland Pharmaceuticals
Little Island
County Cork
Ireland

Control of DS is provided including the (b) (4)

A QbD approach was utilized to develop and optimize the manufacturing process and HPLC analytical method validation for Axitinib DS.

QbD in DS manufacturing process
Based on the quality target product profile (QTPP) and prior knowledge, Critical Quality Attributes (CQAs) were identified. The risk assessment was performed to determine the criticality and ranking of CQAs. Design of experiments (DOE) was performed to understand the input variables such as material attributes and process parameters and their relationship(s) with the proposed CQAs. The parameters that have higher probability of failure and a higher impact on CQA are designated as critical process parameters (CPPs) whereas the parameters which have low probability of failure but still have potential to impact CQA are designated as key process parameters (KPPs). CPP and KPP are used to define a proposed design space for axitinib drug substance. Non-critical process parameters (NCPP) which have low impact on CQAs are not included in the proposed design space. During the lifecycle of the product, NCPP will be managed under internal quality management system (IQS) of the applicant.

For DS manufacturing, several graphical models describing the interaction of variables are provided to justify the proposed design space:

(b) (4)

(b) (4)

The applicant discusses the proposed control strategy to ensure the consistent production of the intended drug substance.

QbD in DS Analytical Method Validation

Pfizer presents a QbD approach for analytical methodology. The reversed phase HPLC assay/purity method for axitinib drug substance (b) (4) has been developed using science and risk-based approaches incorporating QbD principles. Several definitions are also provided to describe the QbD principles for analytical methods. While these terms are not found in the ICH guidelines, they are closely related to QbD terms and definitions currently described in ICH Q8, Q9, and Q10 for the drug substance and drug product manufacturing processes. Some of these terms are: Analytical Target Profile (ATP), critical method attribute, critical method parameter, Method Operable Design Region (MODR or Design Space), and Normal Operating Conditions (NOC). (b) (4)

(b) (4)

The proposed regulatory flexibility to implement the proposed post-approval changes will need to be evaluated.

DS Stability

The registration stability program consists of a formal program of three batches manufactured at Pfizer, Sandwich, UK using the commercial process, at commercial scale and 24 months stability data at 25°C/60 % RH and at the accelerated condition of 40°C/75% RH are provided. Information on the registration stability batches and the registration stability protocol are provided below. Supportive stability data also includes one batch of drug substance produced by (b) (4) for which stability testing has been completed through 24 months. A risk assessment study was performed to identify potential stability related quality attributes. Following is the stability testing protocol.

Table. Stability Testing Protocol

Storage Con	Interval (Months)							
	Initial	3	6	9	12	18	24	36
Initial/Release	A	---	---	---	---	---	---	---
40ºC/75%RH	---	C	B	---	---	---	---	---
25ºC/60%RH	---	C	B	C	A	C	A	A

Tests to be applied in accordance with the above protocol include:

A = Appearance, assay, purity, water content, crystal form by PXRD and microbial quality

B = Appearance, assay, purity, water content and crystal form by PXRD

C = Appearance, assay, purity and water content

Based on 24 months DS stability data, along with DS supporting stability data, a retest period of (b) (4) (b) (4) for axitinib DS is proposed when packaged in (b) (4)

Drug Product (DP)

Axitinib drug product information includes 2 different tablet strengths containing 1 and 5 mg of axitinib DS respectively. The 1 mg axitinib film coated tablets will be provided as red, film coated, oval shaped tablets debossed with "Pfizer" on one side and "1 XNB" on the other. The 5 mg axitinib film coated tablets will be provided as red, film coated, triangular shaped tablets debossed with "Pfizer" on one side and "5 XNB" on the other. The drug product is packaged in high density polyethylene (HDPE) bottles containing desiccant with induction seal and child-resistant closures (b) (4)

(b) (4) Following is the component and composition of DP.

Table. Composition of Axitinib 1 mg and 5 mg Tablets

Component	Function	Reference to Standard	1 mg Theoretical Unit and/or Formula	5 mg Theoretical Unit and/or Formula
Axitinib	Active	Pfizer	1.000 mg[1]	5.000 mg[1]
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph. Eur.,JP	(b) (4)	(b) (4)
Lactose Monohydrate		NF, Ph. Eur.,JP		
Croscarmellose Sodium		NF, Ph. Eur.,JP		
Magnesium Stearate		NF, Ph. Eur.,JP		
(b) (4)				
Film Coat				
Opadry® II Red 32K15441		Pharmaceutical[3]		
Total Finished Tablet				

Note: NF=National Formulary; USP=the United States Pharmacopeia; Ph.Eur. =the European Pharmacopeia; JP=Japanese Pharmacopeia

(b) (4)

All excipients are compendial and are tested and released in accordance with the specifications and methods described in the referenced pharmacopoeia. There are no novel excipients used in the manufacture of axitinib tablet. The commercial dosage strengths are differentiated by color and printing using globally acceptable components. No overages are indicated in the formulation for axitinib tablet.

Axitinib 1 and 5 mg tablets are manufactured (b) (4) The proposed DP manufacturing, testing and labeling site is as following;

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg,
Mooswaldallee 1
79090 Freiburg, Germany

Axitinib 1 and 5 mg tablets are controlled with Appearance, Identity (HPLC), Identity (UV), Assay (HPLC), Impurities (HPLC), Unspecified Degradation Products, Total Degradation Products, Dissolution (HPLC), and Uniformity of Dosage Units (weight variation). Acceptance criteria for release and the corresponding stability specification seem to be identical.

The proposed commercial container/closure systems for axitinib tablets consists of a HDPE bottle/closure system with desiccant (b) (4). These packaging configurations were studied in the DP registration stability program. The bottle sizes vary depending on the count of tablets.

A QbD approach was utilized to develop and optimize the manufacturing process and HPLC analytical method validation for Axitinib DP.

QbD in DP manufacturing process
Process optimization and design space establishment were achieved through risk assessment, multivariate and univariate studies with small scale development trials, modeling tools and knowledge gained from larger scale trials at the proposed commercial manufacturing site.

A series of initial studies were conducted to achieve the process optimization for enhancing manufacturing process control and screened key process parameters; the second study established the acceptable operating ranges of the unit operations; the third study confirmed and refined the design space. Following table summarizes the control strategy and linkage of the control parameters to the dependent key or critical quality attributes.

Table. Summary of the Axitinib Tablet Manufacturing Process Control Strategy

(b) (4)

Several pictorial models, graphs, and statistical methods are utilized to justify the design space. The non-critical quality attributes and process parameters are proposed to be controlled through the Applicant's internal quality systems.

QbD in DP Analytical Method Validation
Both QbD approaches for DP and DS analytical method validations appear similar. The results of the analytical method risk assessment were used to identify chromatographic method parameters for further experimentation. A statistical study using an experimental design approach was employed to

assess the potential effect these parameters may have on the reliability and precision of assay and purity measurements. (b) (4)

(b) (4)

DP Stability

Primary stability program consisting of axitinib immediate release film coated tablets packaged in HDPE bottles with desiccant (b) (4) has been completed up to 24 months at the long term storage condition of 30°C/75% RH and 6 months at the accelerated storage condition of 40°C/75% RH for 3 batches of 1 mg and 3 batches of 5 mg tablets and up to 18 months at 30°C/75% RH and 6 months at 40°C/75% RH for 1 batch of 1 mg tablets. In addition, photostability, and in-use studies were evaluated on one batch of each strength and tablet shape.

The analytical procedures used in the stability program are the same as the procedures described in Control of Drug Product with the exception of Appearance. Additionally, the non-product specific

analytical procedures, (b) (4) hardness, disintegration and microbial enumeration (USP <61>, Total Aerobic Microbial Count/Total Yeast and Mold Count were monitored on stability.

Based upon all the data presented in this stability summary a shelf life of 36 months stored at 25°C (77°C); excursions permitted between 15°C and 30°C (59°F to 86°F) is proposed.

Critical issues for review and recommendation

General Comments

a. The reviewers are encouraged to have open and frequent discussions (as necessary) with the applicant and the ONDQA QbD Lision committee related to the QbD approach used to develop the drug substance and drug product manufacturing and HPLC method development.
b. The reviewers are encouraged to be involved (either through participation or other means of communication) in any Pre-Approval Inspection (PAI) that may occur related to the drug substance or drug product.
c. The assigned reviewers need to check the development and pre-NDA meeting minutes where a wide range of QbD related issues are discussed.
d. EES information for drug substance and drug product needs to be re-examined for accuracy.

Critical Issues for Drug Substance

a. The acceptability of the starting materials should be determined as soon as possible.
b. Justification and rationale for conditions and ranges of the parameters outlined in the Regulatory Process Description (RPD) are provided. These should be evaluated based upon scientific rationale, demonstrated process understanding, and risk.
c. Close examination is needed to justify the MODR proposed for HPLC validation applied for DS assay and impurities both for approval and for post-approval management.
d. The formation, specifications, and control of the genotoxic or potential genotoxic impurities, which have been investigated, should be evaluated with close attention being paid to any risk management strategy proposed by the applicant.
e. Particle size distribution of DS may need to be controlled as a critical quality attribute.
f. Drug substance specifications and justifications should be evaluated for appropriateness based upon the scientific knowledge demonstrated in the NDA.
g. 24 months of stability data are presented in the NDA. However, Pfizer proposes a (b) (4) retest date.
h. The proposed strategy for post-marketing changes for DS manufacturing process and analytical method validation need to be justified based on the critical analyses of the QbD information.

Critical Issues for Drug Product

a. The appropriateness of the QbD approach along with the identification and justification of CQAs, and CPPs should be evaluated along with any proposed design spaces.
b. DP purity assessment ranges need to be justified by statistical analyses.
c. Drug product specifications, including dissolution and the timeline of Microbial Limit Tests, should be evaluated for appropriateness based on the QbD approach, process understanding, and justification.

d. [redacted] (b) (4)

e. 24 months of stability data are presented in the NDA. However, Pfizer proposes a 36 month expiry. Updated stability data (if any) need to be checked.

f. It should be noted that two different container closure system, HDPE bottles (60 [redacted] (b) (4) and 180 cc) [redacted] (b) (4) are used for the stability study.

g. A QbD approach, including the use of risk management tools, was used to develop the drug product, and design spaces are proposed for the manufacturing process. It is recommended that at least one assigned reviewer participates in the Pre-Approval Inspection of the drug product manufacturing site.

h. QbD approach, design space, and the continuous verification should be evaluated based on the potential impact on product quality, safety, and efficacy.

i. Check the DMF list for accuracy (see DMF Table below).

j. Close examination is needed to justify the MODR proposed for HPLC validation applied for DP assay and impurities both for approval and for post-approval management.

k. The strategy for post-marketing changes for DP manufacturing process and analytical method validation need to be justified based on the critical analyses of the QbD information.

Summary of DMFs information as follows.

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LOA Included
[redacted] (b) (4)			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √ √ √		Microbiology Pharm/Tox Biopharm Statistics (QbD) OCP/CDRH/CBER LNC DMEPA/ODS **EER** **EA**

Comments and Recommendations

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. A team approach, and more than one CMC reviewer is recommended for this NDA, since QbD approach is proposed in this application.

Haripada Sarker CMC Lead	June 6, 2011 Date
Janice Brown, CMC Lead for Sarah Pope Miksinski, Ph.D. Branch Chief	June 6, 2011 Date

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

/s/

HARIPADA SARKER
06/06/2011

JANICE T BROWN
06/07/2011