CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202324Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 25, 2012
From	John R. Johnson, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202324
Applicant	Pfizer, Inc.
Date of Submission	April 14, 2011
PDUFA Goal Date	February 14, 2012
Proprietary Name / Established (USAN) names	INLYTA (Axitinib)
Dosage forms / Strength	Tablets 1 mg and 5 mg
Proposed Indication(s)	INLYTA is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).
Recommended:	Approval

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1. Introduction

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR)-1, VEGFR-2, and VEGFR-3. The Applicant requests approval for the treatment of patients with advanced renal cell carcinoma (RCC) regardless of whether the patients have had prior chemotherapy. However, all of the patients in their only randomized trial have had prior chemotherapy. Other issues are that there is only one randomized trial, that the Axitinib effect on the primary endpoint, progression-free survival (PFS), is modest and that the modest PFS effect is not reflected by any favorable effect on overall survival. Axitinib toxicity is similar in severity to other approved drugs for this indication, but the toxicity profile is different. Another issue is that most of the Axitinib effect on PFS was in the prior cytokine subgroup. Most patients in the United States will have had prior sunitinib instead of prior cytokines.

Provide an overview of the basic regulatory and scientific facts of the application and, in particular, an explanation of what issues this review will consider in greater detail.

2. Background

THE FOLLOWING IS EXCERPTED FROM THE MEDICAL OFFICER REVIEW

Il-2 and INF alpha are approved for treatment of advanced renal cell cancer (RCC). More recently the 6 targeted drugs in Table 1 were approved. Table 1 shows for each targeted drug the patient population studied and the efficacy results. The only drug shown to improve overall survival is Temserolimus in poor risk treatment naïve patients. An SPA for Axitinib for treatment of advanced RCC was granted in April 2008 with caveat that improvements in the primary endpoint of PFS must be both clinically and statistically significant.

Renal cell carcinoma (RCC) is the seventh leading cancer type in men and the eighth leading cancer type in women, with an estimated total of 58,240 new cases and 13,040 deaths due to RCC in 2010.[i] Localized RCC can be treated with surgery with excellent long-term survival results. However, the prognosis for patients with locally advanced or metastatic disease remains poor, with median overall survival prior to the introduction of Surgery and traditional chemotherapy have not played a role in advanced or metastatic RCC, as their use has not been shown to affect survival in this population. Cytokines such as interferon-α (IFN-α) and interleukin-2 (IL-2) have response rates ranging from 7% to 23%,[ii,iii] and high-dose IL-2 has been shown to induce durable complete responses in approximately five percent of treated patients.[iv] However, the toxicity associated with both of these agents has diminished their use, especially with the newer agents that have been developed in the last decade.

In the past six years, the treatment options for patients with advanced RCC have increased from IFN-α and IL-2 to six new agents with two different modes of actions: vascular endothelial growth factor receptor (VEGF-R) inhibitors sorafenib, sunitinib, and pazopanib

and VEGF antibody bevacizumab; and mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus (Table 1).

Table 1 Approved Targeted Drugs for Advanced RRC

	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]

3. CMC/Device

- **Drug Substance**

  In the CMC review by Jean Tang entered into DARRTS on 12/12/11 there were 8 deficiencies. The following is excerpted from the CMC reviewed entered into DARRTS on 1/24/12.

  ## Recommendations

  A. Recommendation and Conclusion on Approvability

  The application is recommended for APPROVAL with respect to CMC

  Include the following language in the action letter:
  Based on the provided stability data, an expiration dating period of 36 months is granted
  for the drug product when stored at 20-25°C (68-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

  B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

  The method and method validation data used to detect (b) (4) and (b) (4) level in Drug Substance will be provided post-approval.

- **Drug Product**

  In the CMC review by Amit Mitra entered into DARRTS on 12/12/11 there were 5 deficiencies. The following is excerpted from the CMC reviewed entered into DARRTS on 1/24/12.

  ## Recommendations

  A. Recommendation and Conclusion on Approvability

  The application is recommended for approval with respect to CMC.
  Include the following language in the action letter:
  Based on the provided stability data, an expiration dating period of 36 months is granted for the drug product when stored at 20-25°C (68-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

- **General Product Quality Considerations**

THE FOLLOWING IS EXCERPTED FROM THE CHEMISTRY REVIEW

Overall Recommendation: The development and validation results for the analytical sections involved in this NDA are acceptable

- **Biopharmaceutics Review**

THE FOLLOWING IS EXCERPTED FROM THE BIOPHARMACEUTICS REVIEW

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.

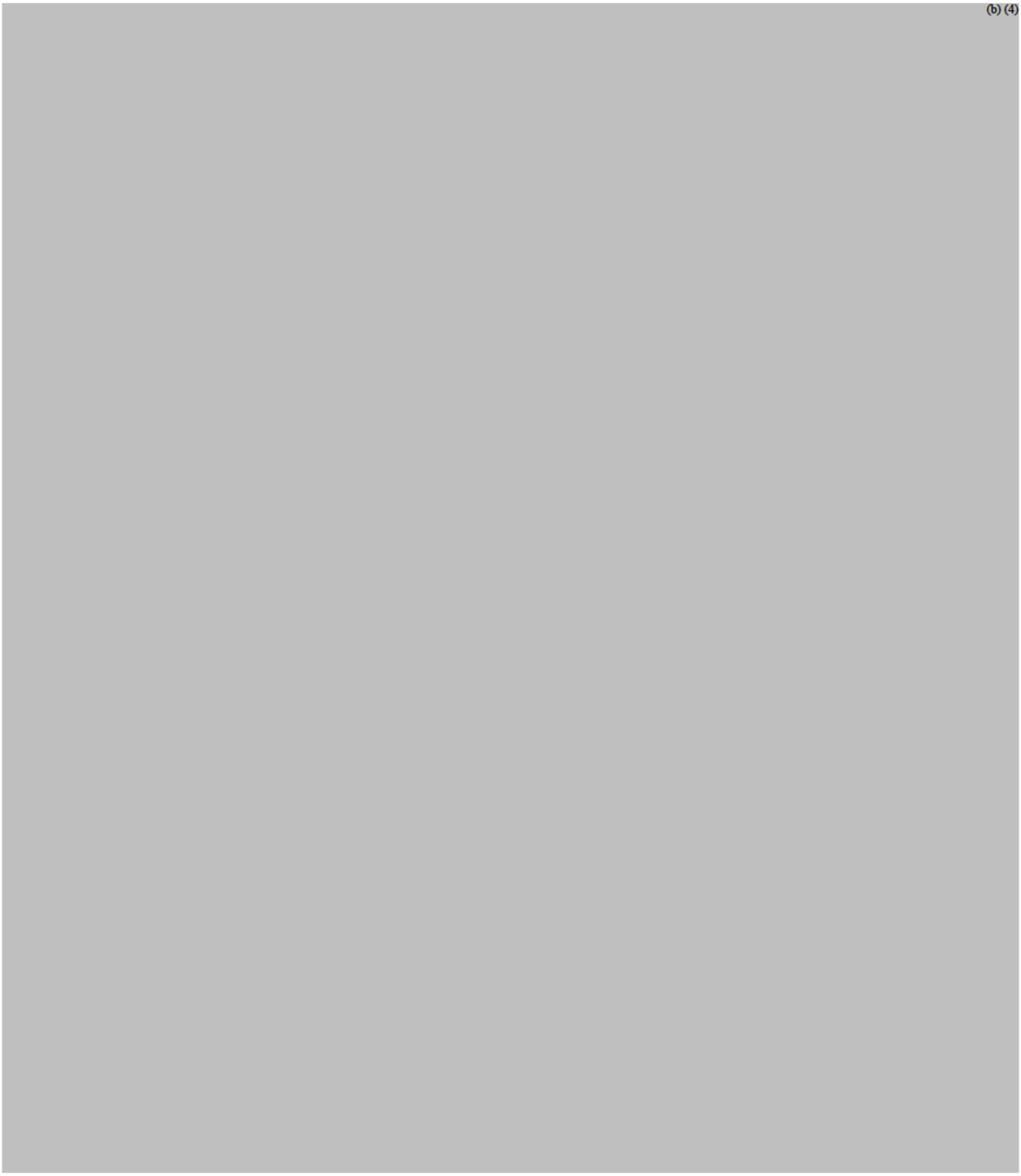
- **Biostatistics Review**

THE FOLLOWING IS EXCERPTED FROM THE BIOSTATISTICS REVIEW

Conclusions and Recommendation
In conclusion, we made the following comments:

I Analytical QbD

(b) (4)



(b) (4)

- **Facilities review/inspection**

  Approved 12/4 11.

- **Environmental Assessment Or Claim Of Categorical Exclusion**

THE FOLLOWING IS EXCERPTED FROM THE CHEMISTRY REVIEW

> The applicant stated that EIC is below 1 ppb (b) (4) and requested a categorical exclusion based according to 21CFR §25.31(b) without the EIC calculation. Therefore, the applicant was requested to provide calculation to show that the EIC is below 1 ppb to justify the EA waiver request. In an amendment, the provided the calculation for EIC (b) (4) which is below the less than 1 ppb required for granting the waiver. Therefore, no further information is necessary.

4. Nonclinical Pharmacology/Toxicology

THE FOLLOWING IS EXCERPTED FROM THE PHARMACOLOGY/TOXICOLOGY REVIEW

Non-clinical pharmacology and toxicology studies to support axitinib NDA 202324 for the treatment of renal cell carcinoma after failure of one prior systemic therapy were reviewed by Anwar Goheer, PhD, Alexander H. Putman, Ph.D., and Robeena Aziz, MPH, Ph.D. Information included studies conducted with orally administered axitinib investigating the drug's pharmacology, toxicokinetics and ADME, safety pharmacology, general toxicology (mouse and dog), and genetic toxicity (*in vivo* and *in vitro*). Reproductive and developmental toxicology studies were conducted in mice to assess the effects of axitinib on fertility and embryo-fetal development. The studies cited in the review consist primarily of original research studies conducted by the applicant.

Pharmacology studies submitted to the NDA support that axitinib is a kinase inhibitor which binds to and inhibits the activity of multiple receptor tyrosine kinases including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2 and VEGFR-3.

The most common adverse reactions observed with axitinib in patients (≥20% according to Highlights section of the label) were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decrease, vomiting, asthenia, and constipation.

Safety pharmacology studies conducted with axitinib in mice, rats and dogs identified the potential for increased systolic blood pressure and decreased heart rate. In repeat-dose studies, toxicities in bone and teeth, spleen and thymus (in mice), and elevated cholesterol and triglycerides (in dogs) were not observed clinically, but may be relevant to patient risk under certain circumstances. Toxicities were observed throughout the gastrointestinal tract in mice and dogs.

Axitinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human lymphocyte chromosome aberration assay. However, axitinib was genotoxic in the *in vivo* mouse bone marrow micronucleus assay. Kinetochore staining results from the *in vivo* micronucleus assay indicated that the increases in micronucleated polychromatic erythrocytes were due to an aneugenic mechanism.

Axitinib may impair reproductive function and fertility in males and females. In repeat-dose toxicology studies in mice and dogs, findings in the male reproductive tract were observed in the testes/epididymis at exposures approximately equivalent to and lower than patient exposure, respectively. Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to exposure in patients.

In a fertility study in mice, axitinib did not affect mating or fertility rate when administered to males at any dose tested. Reduced fertility and embryonic viability were observed in female mice at all doses tested. Doses in this study resulted in systemic exposures greater than exposures in patients.

Axitinib is embryotoxic, fetotoxic, and teratogenic to mice, at exposures lower than human exposures at the recommended human starting dose. During a fertility and early embryonic development study, axitinib administered to female mice prior to mating and through the first week of pregnancy caused an increase in post-implantation loss. In an embryo-fetal developmental toxicity study, pregnant mice received oral axitinib twice daily during the period of organogenesis. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformations (cleft palate) and variations in skeletal ossification (interfrontal ossification sites, incomplete ossification of the supraoccipitals). A no effect level for adverse embryo-fetal effects was not identified in this study. The potential benefit of axitinib in pregnant women in this patient population may outweigh the potential risk to the developing fetus. Therefore, Pregnancy Category D is recommended for the use of axitinib in this patient population.

Recommendations: I concur with Drs. Goheer's, Putman's and Aziz's

conclusion that pharmacology and toxicology data support the approval of NDA 202324 for axitinib. There are no outstanding nonclinical issues that would preclude the approval of axitinib for the proposed indication.

5. Clinical Pharmacology/Biopharmaceutics

THE FOLLOWING IS ABSTRACTED FROM THE CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW.

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 Tmax ranges between .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.

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.

6. Clinical Microbiology

THE FOLLOWING IS ABSTRACTED FROM THE PRODUCT QUALITY MICROBIOLOGY REVIEW

A. Recommendation on Approvability – The recommendation is to approve this submission from a quality microbiology standpoint.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Formulated powders are (b) (4) film coated and packaged. This is a nonsterile drug product.

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – NA

7. Clinical/Statistical- Efficacy

A single RCT was submitted, comparing the PFS of patients with mRCC receiving axitinib vs. sorafenib following failure of one prior systemic first-line regimen containing 1 or more of the following: sunitinib, bevacizumab + IFN, temsirolimus, or cytokine(s). Patients were randomized one to one to receive axitinib was 5 mg twice daily (BID) administered orally with food or sorafenib administered orally without food at a starting dose of 400 mg BID. Subjects

who tolerated axitinib with no related adverse events above CTCAE Grade 2 for a consecutive 2 week period were recommended to have their dose increased by one dose level to 7 mg BID and subsequently to a maximum of 10 mg BID (unless the subject's blood pressure BP was >150/90 mm Hg or the subject was receiving antihypertensive medication). For treatment related Grade 4 non-hematologic or hematologic toxicity, the axitinib dose was interrupted and restarted at one lower dose level as soon as improvement to CTCAE Grade 2 or less occurred. Dose reduction below 2 mg BID were not to be implemented prior to discussion with the Sponsor. When dose reduction was necessary to manage sorafenib-related adverse drug reactions, the sorafenib dose was reduced to 400 mg once daily (QD). If additional dose reduction was required, sorafenib was reduced to a single 400 mg dose every other day.

Progression-Free Survival

The primary efficacy endpoint was PFS as determined by an independent radiology review committee (IRC).

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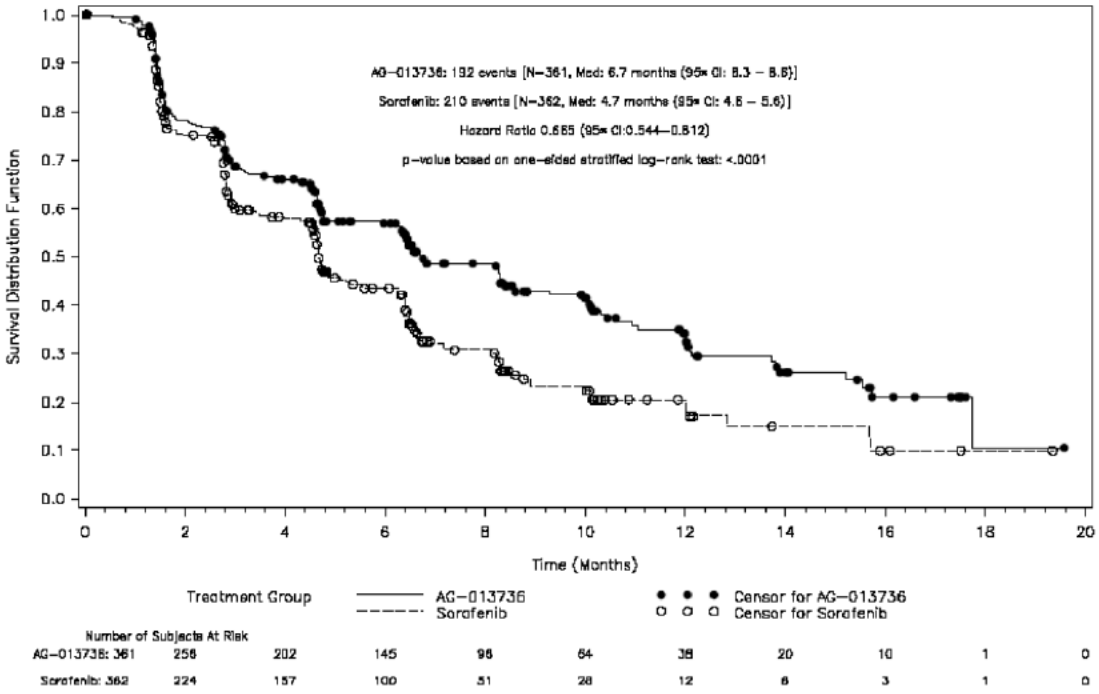
Figure 1 Progression-Free Survival ITT IRC Analysis



applicant figure

As shown in Figure 1, the ITT IRC PFS analysis demonstrates an axitinib advantage with HR=0.655 (95% CI=0.544—0.812), stratified Log Rank p<0.0001, axitinib median PFS 6.7 months and sorafenib median PFS 4.7 months.

As shown in Figure 2 and Figure 3, most of the PFS benefit comes from the subgroup with prior cytokine treatment. PFS benefit is much less in the subgroup with prior sunitinib treatment. Most patients in the United States will have had prior sunitinib treatment.

On the other hand, as shown in Figure 4, an unplanned subgroup PFS analysis in the U.S population shows an axitinib benefit with stratified HR =0.613 (95% CI 0.401-0.938), p=0.0115 Log Rank, one-sided, axitinib median PFS 6.7 months and sorafenib median PFS 3.5 months.

Figure 2 Kaplan-Meier Curve of Progression-Free Survival by Treatment and Prior Sunitinib-Containing Regimen; IRC Assessment

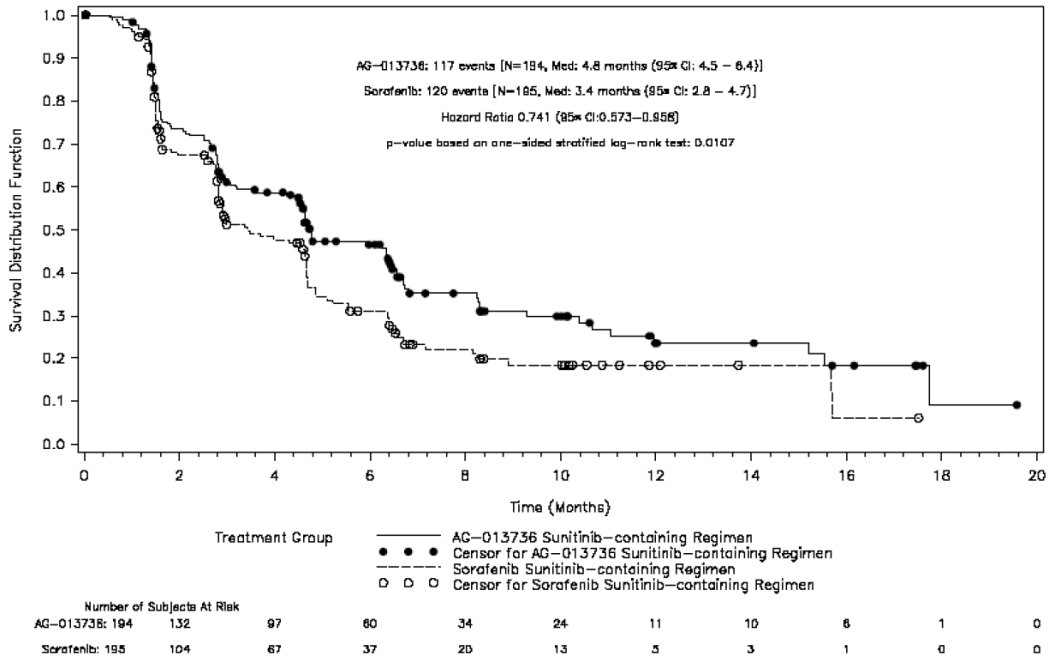


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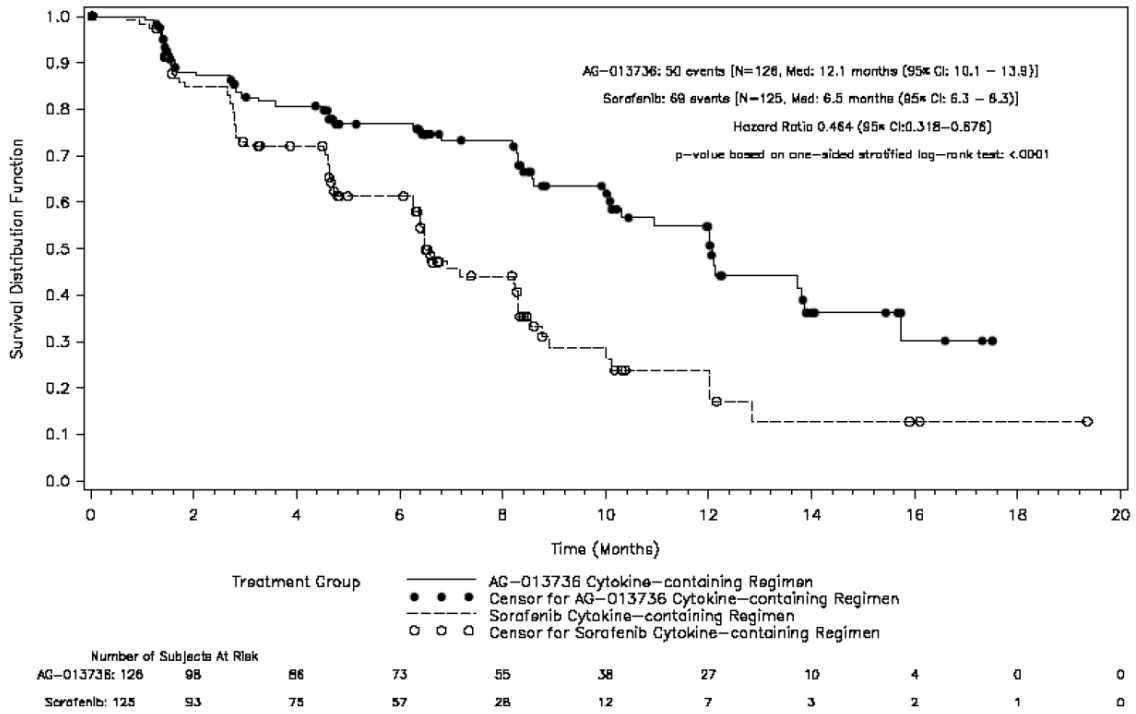
Figure 3 Kaplan-Meier Curve of Progression-Free Survival by Treatment and Prior Cytokine-Containing Regimen; IRC Assessment



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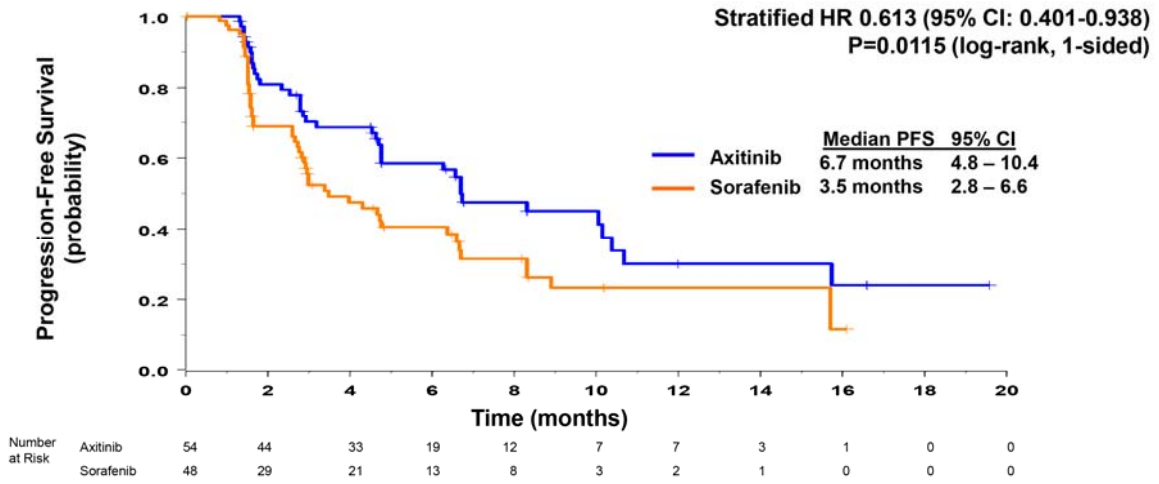
PFS in United States Subpopulation

Figure 4 PFS in United States Subpopulation



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Final Overall Survival Analysis

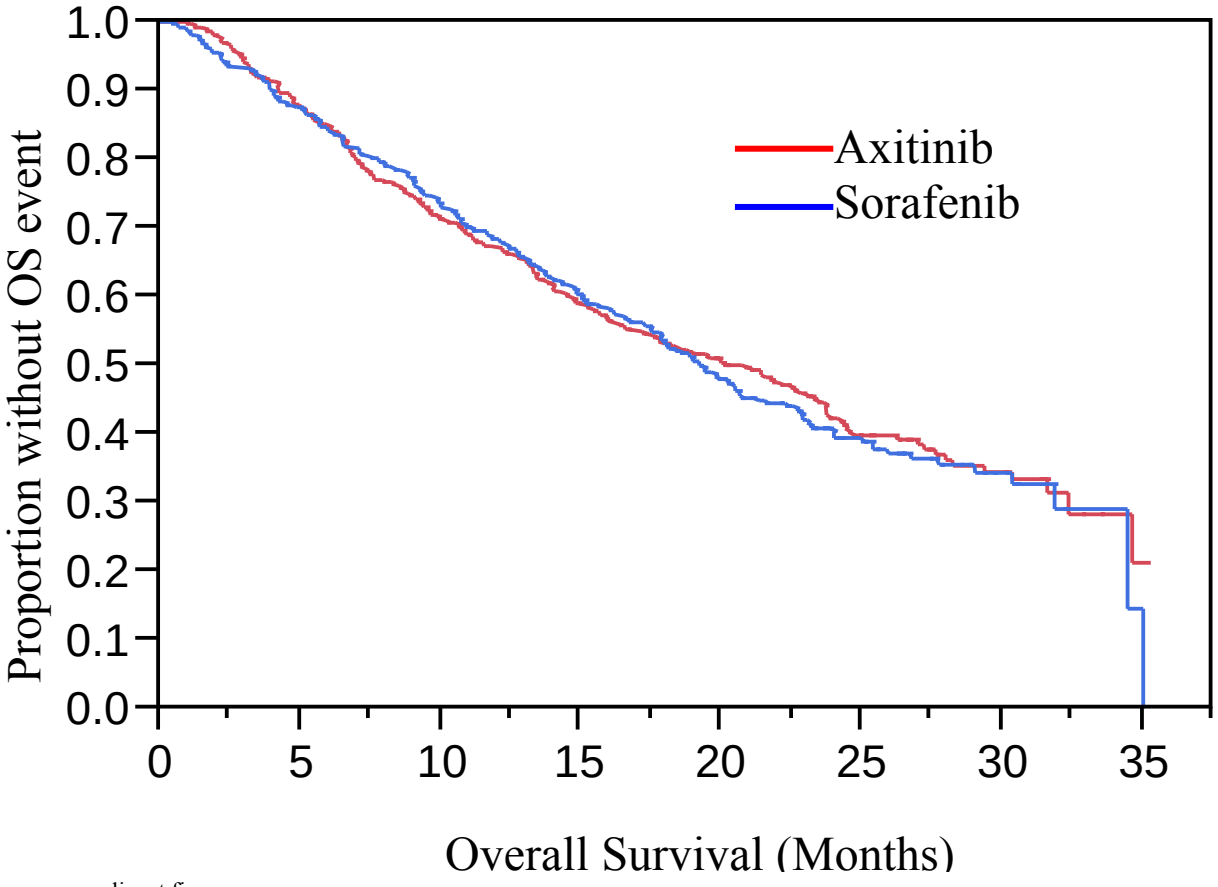
As shown in Table 2 and Figure 5, there was no axitinib effect on final overall survival. There was no crossover to the other treatment after progression

Table 2 Final Overall Survival Analysis

	Axitinib N=361	**Sorafenib N=362**
Deaths (%)	210 (58.2)	213 (358.8)
Median OS in months (95% CI)	20.1 (16.7, 23.4)	19.4 (17.5, 21.6)
Hazard Ratio (95% CI)	0.97 (0.8-1.17)	
P-value	0.37	

applicant table

Figure 5 Final Overall Survival Analysis



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Objective Response

Table 3 Best Overall Response by Treatment and Stratification Factor; Stratified Analysis; IRC Assessment

Best Overall Response Parameter	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Overall stratified analysis (n)	361	362
Patients with baseline assessment	360 (99.7)	359 (99.2)
Patients with measureable disease at baseline	350 (97.0)	349 (96.4)
Best overall response		
Complete response	0	0
Partial response	70 (19.4)	34 (9.4)
Stable disease (≥20 weeks)	96 (26.6)	77 (21.3)
Stable disease (<20 weeks)	84 (23.3)	120 (33.1)
Progressive disease	78 (21.6)	76 (21.0)
Not assessed	0	0
Indeterminate	22 (6.1)	42 (11.6)
Overall confirmed objective response rate (CR + PR)	70 (19.4)	34 (9.4)
95% exact CI[a]	15.4%-23.9%	6.6%-12.9%
Treatment comparison (axitinib vs sorafenib)		
Risk ratio[b]	2.056	
95% CI of risk ratio[b]	1.408-3.003	
P-value[c]	0.0001	
Stratification category: prior sunitinib-containing regimen (n)	194	195
Patients with baseline assessment	194 (100)	195 (100)
Patients with measureable disease at baseline	188 (96.9)	189 (96.9)
Best overall response		
Complete response	0	0
Partial response	22 (11.3)	15 (7.7)
Stable disease (≥20 weeks)	49 (25.3)	26 (13.3)
Stable disease (<20 weeks)	53 (27.3)	70 (35.9)
Progressive disease	51 (26.3)	51 (26.2)
Not assessed	0	0
Indeterminate	13 (6.7)	27 (13.8)
Overall confirmed objective response rate (CR + PR)	22 (11.3)	15 (7.7)
95% exact CI[a]	7.2%-16.7%	4.4%-12.4%
Treatment comparison (axitinib vs sorafenib)		
Risk ratio[b]	1.477	
95% CI of risk ratio[b]	0.792-2.754	
P-value[d]	0.1085	

Best Overall Response Parameter	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Stratification category: prior cytokine-containing regimen (n)	126	125
Patients with baseline assessment	126 (100)	123 (98.4)
Patients with measureable disease at baseline	123 (97.6)	120 (96.0)
Best overall response		
Complete response	0	0
Partial response	41 (32.5)	17 (13.6)
Stable disease (≥20 weeks)	39 (31.0)	44 (35.2)
Stable disease (<20 weeks)	20 (15.9)	33 (26.4)
Progressive disease	16 (12.7)	15 (12.0)
Not assessed	0	0
Indeterminate	7 (5.6)	11 (8.8)
Overall confirmed objective response rate (CR + PR)	41 (32.5)	17 (13.6)
95% exact CI[a]	24.5%-41.5%	8.1%-20.9%
Treatment comparison (axitinib vs sorafenib)		
Risk ratio[b]	2.392	
95% CI of risk ratio[b]	1.434-3.992	
P-value[d]	0.0002	

applicant table

Abbreviations: CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, IRC = Independent Review Committee, N = number of patients, n = number of patients meeting prespecified criteria, PR = partial response

a Using exact method based on F-distribution.

b Risk ratio and CI based on the Mantel-Haenszel estimator; risk ratio is adjusted for same stratification factors as Cochran-Mantel-Haenszel test.

c For the overall stratified analysis, the p-value was from a 1-sided Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior treatment.
d P-value is from a 1-sided Cochran-Mantel-Haenszel test stratified by ECOG performance status.

Response Duration

Based on blinded IRC assessment, the median DR in the axitinib arm was 11 months (95% CI [7.4, not estimatable]) compared with 10.6 months in the sorafenib arm (95% CI [8.8, 11.5]). Based on blinded IRC assessment, the median DR in the prior sunitinib-containing regimen in the axitinib arm was 11.0 months (95% CI [5.2, not estimatable]) compared with 11.1 months in the sorafenib arm (95% CI [not estimatable, not estimatable]). Based on blinded IRC assessment, the median DR in the prior cytokine-containing regimen in the axitinib arm was 11.0 months (95% CI [7.4, not estimatable]) compared with 10.6 months in the sorafenib arm (95% CI [5.9, 11.5]).

Discuss the background of the clinical program, highlighting agreements with the Sponsor prior to NDA submission, and subsequent review issues such as those regarding endpoints, number of trials, other departures from standard clinical evaluations, adverse events, risk/benefit, etc. Include the basic design of the efficacy studies, qualitative issues, key tables and figures that are intended to appear in the clinical sections of labeling. Even if there are no major issues, provide a brief overview of these critical aspects of the basis for the regulatory action being recommended. Greater detail should be provided if notable issues or findings exist or if other final documentation in the action package is lacking.

- Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.

- Includes discussion of notable efficacy issues both resolved and outstanding

8. Safety

The submitted Safety Database is satisfactory. No special safety measures are needed other than the usual post marketing safety monitoring.

Exposure

As shown in Table 8, the median number of days on treatment was axitinib 196 and sorafenib 152. The median relative dose intensity was axitinib 98.6% and sorafenib 91.7%. There was dose reduction in 30.6% of axitinib patients and 52.1% of sorafenib patients. There was dose interruption in 76.9% of axitinib patients and 80.3% of sorafenib patients.

Table 4 Exposure

	Axitinib N = 359	Sorafenib N = 355
Number of Days on Treatment Median	196	152
Total Cumulative Dose Median	1896 mg	89600 mg
Number of patients with dose escalation (%)	132 (36.8)	NA
Dose Per Day Median	Planned: 10 mg 9.9 mg	Planned: 800 mg 773.9 mg
Relative Dose Intensity (%) Median	98.6	91.7
Number of patients with dose reduction (%)	110 (30.6%)	185 (52.1%)
Number of patients with dose interruption (%) Reason AE Other	276 (76.9%) 194 (54%) 202 (56.3)	285 (80.3%) 224 (63.1%) 183 (51.5%)

from medical officer review

Table 5 Summary of Axitinib Dose Escalations and Reductions

Axitinib dose levels	**Axitinib N=359 n (%)**
Total daily dose < 6 mg 6-8 mg 10 mg 12-14 mg 20 mg	 30 (8.4) 58 (16.2) 139 (38.7) 60 (16.7) 71 (19.8)
Number of patients escalated and then reduced	71 (19.8)

modified from medical officer review

Deaths

Table 10 shows a summary of deaths by treatment. Deaths while on study drug or within 28 days of study drug discontinuation were 9.7% for axitinib and 6.5% for sorafenib.

Table 6 Summary of Deaths by Treatment: Safety Analysis Set

Summary of Deaths	**Axitinib N=359 n (%)**	**Sorafenib N=355 n (%)**
Patients who died	113 (31.5)	109 (30.7)
Patients who died on-study[a]	35 (9.7)	23 (6.5)
Disease under study	28 (7.8)	15 (4.2)
Study treatment toxicity[b]	0	2 (0.6)
Coagulation deranged possibly due to sorafenib/Fragmin or tumor necrosis	0	1 (0.3)
GI bleed sorafenib	0	1 (0.3)
Unknown	2 (0.6)	3 (0.8)
Other	5 (1.4)	3 (0.8)
Acute cerebrovascular accident	1 (0.3)	0
Disease progression	0	1 (0.3)
Duodenal ulcer hemorrhage	0	1 (0.3)
GI hemorrhage and possible intra-abdominal bleed at site of kidney tumor	1 (0.3)	0
General weakness	1 (0.3)	0
Pulmonary embolus	1 (0.3)	0
Sepsis	1 (0.3)	0
Stroke	0	1 (0.3)
Patients who died during follow-up[c]	78 (21.7)	86 (24.2)
Disease under study	65 (18.1)	72 (20.3)
Study treatment toxicity	0	0
Unknown	3 (0.8)	7 (2.0)
Other	10 (2.8)	7 (2.0)
Acute renal failure and acute myocardial infarction	1 (0.3)	0
Brain hemorrhage	0	1 (0.3)
Cardio-respiratory failure in the course of disease progression	1 (0.3)	0
Disease progresion[d]	0	1 (0.3)
Disease progression[d]	1 (0.3)	1 (0.3)
Hypoxic respiratory failure	0	1 (0.3)
Interstitial lung disease	1 (0.3)	0
Massive intrapulmonary and intrabronchial bleeding	1 (0.3)	0
Pneumonia	0	1 (0.3)
Progression disease	1 (0.3)	0
Progressive disease	3 (0.8)	0
Pseudomonas bronchopneumonia	0	1 (0.3)
Respiratory hemorrhage	1 (0.3)	0
Sepsis	0	1 (0.3)

Data in this table are from the Notice of Death case report form page. Data cutoff date: 31 August 2010.
Abbreviations: AE = adverse events, CRF = case report form, GI = gastrointestinal, N = number of patients, n = number of patients fitting specified criteria

[a] On-study deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.

[b] The reason for death was collected on the AE CRF (see Table 45) and on the Notice of Death CRF (table above). Therefore the categorization of death differed. For axitinib, on the Notice of Death CRF, 3/4 deaths related to axitinib were captured under 'Other' (1 each due to GI hemorrhage, general weakness, and sepsis) and 1/4 deaths were captured under 'Disease under study'. For sorafenib, on the Notice of Death CRF, 2/3 deaths due to sorafenib were captured under 'Study treatment toxicity' and 1/3 deaths were captured under 'Disease under study'.

[c] Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.

[d] 'Disease progression' and 'disease progresion' were both listed.

applicant table

Discontinuations Due to Adverse Events

Table 11 shows the discontinuations due to adverse events by treatment group. Axitinib had 9.7% of patients discontinued due to adverse events and sorafenib had 13%.

Table 7 Discontinuations Due to Adverse Events

	Axitinib N=359	Sorafenib N=355
Any Adverse Event	35 (9.7%)	46 (13%)
Disease progression	11	4
Fatigue	4	1
Transient ischemic attack	3	0
Asthenia	2	3
Pleural effusion	2	1
Decreased appetite	2	0
Palmar-plantar erythrodysaesthesia syndrome	1	4
Dyspnea	1	2
Anemia	1	1
Vomiting	1	1
Retinal vein thrombosis	1	0
Ascites	1	0
Blood creatinine increased	1	0
Hypoglycemia	1	0
Altered state of consciousness	1	0
Cerebral hemorrhage	1	0
Dyspnea exertional	1	0
Pneumothorax	1	0
Hypertension	1	0
Diarrhea	0	3
Nausea	0	2
Erythema multiforme	0	2
Rash	0	2
Angina pectoris	0	1
Myocardial infarction	0	1
Duodenal ulcer hemorrhage	0	1
Enterocolitis	0	1
Gastrointestinal hemorrhage	0	1
Periodontitis	0	1
Upper gastrointestinal hemorrhage	0	1
Cholangitis	0	1
Hepatic function abnormal	0	1
Sepsis	0	1
Fall	0	1
Blood bilirubin increased	0	1

Weight decreased	0	1
Renal cell carcinoma	0	1
Hemiparesis	0	1
Hyperaesthesia	0	1
Ischemic stroke	0	1
Renal failure acute	0	1
Pruritus	0	1
Pruritus generalized	0	1
Rash generalized	0	1
Hemorrhage	0	1

from medical officer review

Table 8 Overall Summary of Treatment-Related Adverse Events by Treatment: Safety Analysis Set

Adverse Event Parameter	Axitinib n (%)	Sorafenib n (%)
Patients evaluable for AEs[a]	359	355
No. of AEs	2630	2389
Patients with AEs	325 (90.5)	336 (94.6)
Patients with serious AEs	44 (12.3)	43 (12.1)
Patients with Grade 3 or 4 AEs[b]	177 (49.3)	188 (53.0)
Patients with Grade 5 AEs[b]	4 (1.1)	3 (0.8)
Patients discontinued treatment due to AEs	14 (3.9)	29 (8.2)
Patients with dose reduction of treatment due to AEs	92 (25.6)	70 (19.7)
Patients temporarily discontinued due to AEs	168 (46.8)	195 (54.9)

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients fitting specified criteria, No. = number
a MedDRA (version 13.1) coding dictionary applied.
b CTCAE Grade Version 3.0. applicant table

Table 9 Summary of Adverse Events by Treatment, MedDRA Preferred Term, and Maximum CTCAE Grade Experienced by ≥5% of Patients: Safety Analysis Set

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Preferred Term[a]	Axitinib N=359				Sorafenib N=355			
	Grade 3[b] n (%)	Grade 4[b] n (%)	Grade 5[b] n (%)	Total[c] n (%)	Grade 3[b] n (%)	Grade 4[b] n (%)	Grade 5[b] n (%)	Total[c] n (%)
Any AE	181 (50.4)	21 (5.8)	34 (9.5)	342 (95.3)	182 (51.3)	36 (10.1)	24 (6.8)	347 (97.7)
Diarrhea	37 (10.3)	1 (0.3)	0	197 (54.9)	23 (6.5)	3 (0.8)	0	189 (53.2)
Hypertension	55 (15.3)	1 (0.3)	0	145 (40.4)	38 (10.7)	1 (0.3)	0	103 (29.0)
Fatigue	39 (10.9)	2 (0.6)	0	140 (39.0)	17 (4.8)	1 (0.3)	0	112 (31.5)
Decreased appetite	16 (4.5)	1 (0.3)	1 (0.3)	123 (34.3)	13 (3.7)	0	0	101 (28.5)
Nausea	8 (2.2)	1 (0.3)	0	116 (32.3)	4 (1.1)	0	0	77 (21.7)
Dysphonia	0	0	0	111 (30.9)	0	0	0	48 (13.5)
Palmar-plantar erythrodysesthesia syndrome	18 (5.0)	0	0	98 (27.3)	57 (16.1)	0	0	181 (51.0)
Weight decreased	8 (2.2)	0	0	89 (24.8)	5 (1.4)	0	0	74 (20.8)
Vomiting	11 (3.1)	1 (0.3)	0	85 (23.7)	3 (0.8)	0	0	61 (17.2)
Asthenia	16 (4.5)	2 (0.6)	1 (0.3)	74 (20.6)	8 (2.3)	1 (0.3)	0	50 (14.1)
Constipation	4 (1.1)	0	0	73 (20.3)	3 (0.8)	0	0	72 (20.3)
Hypothyroidism	1 (0.3)	0	0	69 (19.2)	0	0	0	29 (8.2)
Cough	3 (0.8)	0	0	55 (15.3)	2 (0.6)	0	0	59 (16.6)
Stomatitis	5 (1.4)	0	0	54 (15.0)	1 (0.3)	0	0	44 (12.4)
Mucosal inflammation	5 (1.4)	0	0	55 (15.3)	2 (0.6)	0	0	44 (12.4)
Arthralgia	5 (1.4)	2 (0.6)	0	54 (15.0)	5 (1.4)	0	0	39 (11.0)
Dyspnea	6 (1.7)	2 (0.6)	1 (0.3)	53 (14.8)	7 (2.0)	2 (0.6)	1 (0.3)	43 (12.1)
Abdominal pain	7 (1.9)	1 (0.3)	0	51 (14.2)	3 (0.8)	0	0	38 (10.7)
Back pain	9 (2.5)	0	0	50 (13.9)	6 (1.7)	0	0	46 (13.0)
Headache	2 (0.6)	0	0	50 (13.9)	0	0	0	40 (11.3)
Pain in extremity	1 (0.3)	1 (0.3)	0	45 (12.5)	2 (0.6)	0	0	48 (13.5)
Rash	1 (0.3)	0	0	45 (12.5)	14 (3.9)	0	0	112 (31.5)
Proteinuria	11 (3.1)	0	0	39 (10.9)	6 (1.7)	0	0	26 (7.3)
Dysgeusia	0	0	0	38 (10.6)	0	0	0	29 (8.2)
Dry skin	0	0	0	36 (10.0)	0	0	0	38 (10.7)
Dyspepsia	0	0	0	36 (10.0)	0	0	0	8 (2.3)

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, n = number of patients fitting specified criteria
a MedDRA (version 13.1) coding dictionary applied.
b CTCAE Grade Version 3.0.
c Total of all CTCAE Grade events.
modified applicant table

Notable Adverse Events

Hypertension

Table 10 Hypertension

Preferred Term[a]	Axitinib N=359				Sorafenib N=355			
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Accelerated hypertension	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Blood pressure increased	3 (0.8)	1 (0.3)	0	0	3 (0.8)	2 (0.6)	0	0
Hypertension	145 (40.4)	55 (15.3)	1 (0.3)	0	103 (29.0)	38 (10.7)	1 (0.3)	0
Hypertensive crisis	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, n = number of patients meeting prespecified criteria, No. = number

a MedDRA (version 13.1) coding dictionary applied. applicant table.

Thyroid Events

In the axitinib arm 95 (26.5%) patients and in the sorafenib arm 48 (13.5%) patients started or increased their dose of existing thyroid medications after the first dose of study drug.

Table 11 Adverse Events Related to Hyperthyroidism and Hypothyroidism

Preferred Term[a]	Axitinib N=359				Sorafenib N=355			
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
Hyperthyroidism	0	0	0	4 (1.1)	1 (0.3)	0	0	4 (1.1)
Hypothyroidism	1 (0.3)	0	0	69 (19.2)	0	0	0	29 (8.2)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, n = number of patients meeting prespecified criteria, No. = number, SOC = system organ class
a MedDRA (version 13.1) coding dictionary applied. applicant table

Bleeding Events

Table 12 Bleeding Events

	Axitinib N=359		Sorafenib N=355	
	All Grades (%)	Gr 3-5 (%)	All Grades (%)	Gr 3-5 (%)
Gastrointestinal Tract Hemorrhages	16 (4.5)	2 (<1)	12 (3.4)	7 (2)
Anal	1	0	0	0
Duodenal Ulcer	0	0	1	1
Gastric	1	1	0	0
Gastrointestinal	1	0	3	3
Hemorrhoidal	3	0	0	0
Lower gastrointestinal	1	1	1	1
Rectal	8	0	5	0
Retroperitoneal	0	0	1	1
Tongue	1	0	0	0
Upper gastrointestinal	0	0	1	1
Epistaxis	22 (6.1)	0	15 (4.2)	0
Hematuria	12 (3.3)	1 (<1)	7 (2)	0
Hemoptysis	9 (2.5)	1 (<1)	16 (4.5)	2 (<1)
Cerebral Hemorrhage	1 (<1)	1 (<1)	0	0
Urinary Tract Hemorrhage	1 (<1)	0	2 (<1)	0
Urethral Hemorrhage	0	0	1 (<1)	0
Gingival Bleeding	4 (1.1)	0	8 (2.3)	0
Pharyngeal Hemorrhage	1 (<1)	0	0	0

Pulmonary Hemorrhage	0	0	2 (<1)	1 (<1)
Respiratory Tract Hemorrhage	0	0	2 (<1)	0
Hemorrhage	4 (1.1)	0	4 (1.1)	1 (<1)
Hematoma	0	0	1 (<1)	0
Periorbital Hematoma	0	0	2 (<1)	0

from medical officer review

Arterial Thrombotic Events

Table 13 Arterial Thrombotic Events

	Axitinib N=359		**Sorafenib N=355**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Myocardial infarction	0	0	2 (<1)	1 (<1)
Retinal artery occlusion	1 (<1)	1 (<1)	0	0
Cerebral ischemia	0	0	1 (<1)	1 (<1)
Ischemic stroke	0	0	1 (<1)	1 (<1)
Transient ischemic attack	3 (<1)	3 (<1)	0	0

from medical officer review

Venous Thrombotic Events

Table 14 Venous Thrombotic Events

	Axitinib N=359		**Sorafenib N=355**	
	All Gr (%)	Gr 3-5 (%)	All Gr (%)	Gr 3-5 (%)
Retinal vein occlusion	1 (<1)	1 (<1)	0	0
Retinal vein thrombosis	1 (<1)	1 (<1)	0	0
Pulmonary embolism	7 (1.9)	7 (1.9)	2 (<1)	2 (<1)
Deep vein thrombosis	2 (<1)	2 (<1)	0	0
Jugular vein thrombosis	1 (<1)	0	0	0
Subclavian vein thrombosis	1 (<1)	0	0	0
Thrombosis	1 (<1)	0	0	0
Venous thrombosis	1 (<1)	0	0	0

from medical officer review

Laboratory Adverse Events > 10% in Either Arm

Table 15 Laboratory Adverse Events > 10% in Either Arm

	Axitinib N=359		Sorafenib N=355	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
ALT Increased	72 (21.8)	2 (<1)	68 (21.7)	7 (2.2)
ALP Increased	100 (29.8)	5 (1.5)	107 (33.5)	5 (1.6)
AST Increased	67 (20.2)	2 (<1)	77 (24.8)	5 (1.6)
Bicarbonate decreased	156 (49.8)	1 (<1)	142 (48.8)	0
Creatinine Increased	184 (54.8)	0	130 (40.9)	4 (1.3)
Hypercalcemia	100 (29.8)	1 (<1)	72 (22.6)	0
Hyperglycemia	93 (27.6)	7 (2.1)	72 (22.6)	5 (1.6)
Hyperkalemia	60 (18)	12 (3.6)	46 (14.6)	11 (3.5)
Hypernatremia	58 (17.1)	3 (<1)	41 (12.9)	3 (<1)
Hypoalbuminemia	50 (14.8)	1 (<1)	56 (17.6)	2 (<1)
Lipase increased	90 (26.6)	16 (4.7)	146 (45.7)	47 (14.7)
Amylase Increased	84 (24.9)	6 (1.8)	104 (32.6)	5 (1.6)
Hypoglycemia	39 (13.1)	2 (<1)	29 (9.1)	1 (<1)
Hyponatremia	68 (18.9)	17 (4.8)	53 (14.9)	14 (3.9)
Hypophosphatemia	51 (14.2)	8 (2.2)	166 (46.8)	55 (15.5)
Hypocalcemia	44 (12.2)	7 (1.9)	101 (28.4)	10 (2.8)
Hemoglobin Decreased	111 (34.7)	2 (<1)	163 (51.6)	12 (3.8)
Lymphocytes Decreased	130 (36.2)	18 (5)	145 (40.8)	21 (5.9)
Platelets Decreased	54 (15)	1 (<1)	53 (14.9)	1 (<1)
White blood cells Decreased	38 (10.6)	0	55 (15.5)	1 (<1)

from medical officer review

Safety Summary

The severity of toxicity of axitinib is similar to that of other drugs approved for this indication. However, the toxicity profile is different.

Hypertension, dysphonia, and hypothyroidism are more frequent for axitinib than sorafenib.

Hand-foot syndrome, rash, and alopecia are more frequent for sorafenib than axitinib.

9. Advisory Committee Meeting

This NDA was presented to and discussed by the FDA Oncology Drugs Advisory Committee on December 7, 2011. There was one question posed to the Committee as follows.

Is the benefit:risk evaluation favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy? *[Voting Question] Yes, No, or Abstain*

The Committee vote was YES: 13, NO: 0, ABSTAIN: 0.

10. Pediatrics

THE FOLLOWING E-MAIL WAS RECEIVED ON 11/22/11 FROM GEORGE GREELEY, REGULATORY HEALTH PROJECT MANAGER, PEDIATRIC AND MATERNAL HEALTH STAFF

This email serves as confirmation of the review for Inlyta (Axitinib) conducted by the PeRC PREA Subcommittee on November 16, 2011.

The Division presented a full waiver in pediatric patients for the indication of advanced renal cell carcinoma because the disease/condition does not exist in children.

The PeRC agreed with the Division to grant a full waiver for this product.

11. Other Relevant Regulatory Issues

THE FOLLOWING IS ABSTRACTED FROM THE MEDICAL OFFICER REVIEW.

Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appears reasonable.

Compliance with Good Clinical Practices

The final protocol, all amendments and informed consent documentation for the Phase 3 trial supporting the indication were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centers participating in the study. The study was conducted after written approval was received from these bodies.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

Written informed consent was obtained before each patient entered the study (before initiation of protocol-specified activities). The investigators explained the nature, purpose, and risks of the study to each patient. Each patient was informed that he/she could withdraw from the study at any time and for any reason. Each patient was given sufficient time to consider the implications of the study before deciding whether to participate. Patients who chose to participate signed an informed consent document.

An independent, third-party Data Monitoring Committee (DMC) monitored the safety of patients on a periodic basis. The DMC determined whether the study should be terminated based on ongoing reviews of safety data. The DMC also evaluated interim efficacy data for potential recommendations about early termination due to futility based on observed results of the study.

DSI Inspections at Clinical Sites

Table 3 OSI Inspection Sites

Site # (Name, Address, Phone number, email, fax#)	Number of Subjects	Indication
Site 1106: Bernard Escudier Institut Gustave Roussy / Service d'Immunotherapie 39 53 rue Camille Desmoulins VILLEJUIF CEDEX 94805 FRANCE	19	Second-Line Therapy for Metastatic Renal Cell Cancer
Site 1062: Sergey A. Ivanov Radiology 86 Profsoyusnaya str. Moscow 117997 RUSSIAN FEDERATION	22	Second-Line Therapy for Metastatic Renal Cell Cancer
Site 1024: Dr. Robert John Motzer Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York NY 10065	15	Second-Line Therapy for Metastatic Renal Cell Cancer
Site 1087: Marc Dror Michaelson Massachusetts General Hospital Cancer Center 55 Fruit Street (Yawkey) Boston MA 02114	15	Second-Line Therapy for Metastatic Renal Cell Cancer

There were no issues with the conduct of the study and data audit at Sites 1062, 1024 and 1087 per the DSI investigators who conducted the inspections. There was a minor issue at Site 1106:

Excerpted below is the summary statement for this site deviation from the Clinical Inspection Summary:

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

Medical Officer Comment: As the deviation at Site 1106 is not a question of data integrity but rather documentation of an updated informed consent, this reviewer does not believe this affects the findings for the Phase 3 trial.

Financial Disclosures

Investigators who conducted the clinical trials supporting this NDA and who had no financial interests to disclose were submitted in the FDA form 3454. The disclosure was certified by D.

Stuart Sowder, Vice President-External Medical Communication for the applicant. Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA was submitted in the FDA form 3455. Thirty-three investigators in the key study supporting this NDA were found to have financial conflict of interest, either a proprietary interest or significant payments from or equity interest in the applicant. These investigators received payments as honoraria for speaking events, professional fees and consulting fees ranging from totals of $27,325 to $510,650. These investigators enrolled a total of 81 patients onto the Phase 3 trial, ranging from one to 15 patients at each site. While this represents slightly over 10% of the total patient population in the Phase 3 trial, it is unlikely that any single investigator could have influenced the efficacy results of the trial.

12. Labeling

- **Proprietary name**

  Accepted by DMEPA on 7/11/11.

  THE FOLLOWING IS EXCERPTED FROM THE DMEPA REVIEW

  The Proprietary Name Risk Assessment findings indicate that the proposed name, Inlyta, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proposed proprietary name, Inlyta, for this product at this time. DMEPA will notify the Applicant of this determination via letter.

- **DDMAC**

  THE FOLLOWING IS EXCERPTED FROM THE DDMAC REVIEW

  Reference is made to OPDP's review of the proposed PI dated December 21, 2011. Reference is also made to the Division of Medical Policy Program's (DMPP) review of the proposed PPI on January 3, 2012. Both reviews utilized the substantially complete version of the proposed PI dated December 20, 2011. DDTCP has reviewed DMPP's comments on the proposed PPI, and has no further comments from a promotional perspective at this time.

- **DMPP**

  THE FOLLOWING IS EXCERPTED FROM THE DDMP REVIEW

  In our review of the PPI we have:
  simplified wording and clarified concepts where possible
  ensured that the PPI is consistent with the prescribing information (PI)
  removed unnecessary or redundant information
  ensured that the PPI, meets the criteria as specified in FDA's Guidance for

Useful Written Consumer Medication Information (published July 2006)

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Axitinib should be approved for treatment of patients with advanced renal cell carcinoma (RCC) after failure of one first-line systemic therapy. Labeling should be revised as per the FDA review team. Standard post marketing safety monitoring is sufficient.

- **Risk Benefit Assessment**

I In a Phase 3 randomized controlled trial comparing axitinib with sorafinib in patients with progression after one prior treatment, axitinib was modestly superior to sorafinib for PFS with a HR=0.655 (95% CI=0.544—0.812), stratified Log Rank p<0.0001, axitinib median PFS 6.7 months and sorafenib median PFS 4.7 months. There was no survival effect. Patients were not crossed over to the other treatment after progression.

If sorafenib has PFS benefit in this setting, it should be added to the axitinib PFS benefit. However, there is no prospective randomized trial showing whether sorafenib has PFS benefit in this setting and, if so, the amount of such benefit.

Most of the axitinib PFS benefit is in the subgroup of patients with prior cytokine treatment. Most of the U.S. population will have had prior sutinitib. The PFS benefit in the prior sunitinib subgroup. On the other hand, an unplanned subgroup analysis in the U.S. patients in the Phase 3 trial showed a PFS benefit similar to the study as a whole.

The frequency and severity of adverse reactions was similar for axitinib and sorafenib. However, the adverse reaction profile was different. Hypertension, dysphonia, and hypothyroidism are more frequent for axitinib than sorafenib. Hand-foot syndrome, rash, and alopecia are more frequent for sorafenib than axitinib.

The Applicant requested axitinib full approval "for the treatment of patients with advanced renal cell carcinoma (RCC)". All patients in the randomized Phase 3 trial had one prior treatment for advanced renal cell carcinoma (RCC). FDA policy is that the indication is defined by the characteristics of the trial patients.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

THE FOLLOWING IS EXCERPTED FROM THE DRISK REVIEW

CONCLUSION

The applicant's proposal for labeling and routine pharmacovigilance is reasonable, and is consistent with other agents in the class used for the same indication.

RECOMMENDATIONS

Axitinib (Inlyta) can be approved without a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

  None

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/s/

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01/25/2012