CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202324Orig1s000

MEDICAL REVIEW(S)

CLINICAL TEAM LEADER REVIEW OF NDA

NDA 202324

DRUG INLYTA® (axitinib) tablets for oral administration

APPLICANT Pfizer, Inc.

PROPOSED INDICATION INLYTA is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

REVIEW PRIORITY Standard

DATE RECEIVED April 14, 2011

DATE COMPLETED January 11, 2012

PDUFA DATE February 14, 2012

Table of Contents

PRODUCT INFORMATION 4
REGULATORY HISTORY 4
CLINICAL TRIALS 6
PIVOTAL RANDOMIZED PHASE 3 TRIAL 6
Trial Design 6
Eligibility 7
Objectives 7
Treatment 8
Demographics 9
Efficacy 12
Progression-Free Survival **12**
PFS in United States Subpopulation **14**
Interim Overall Survival Analysis **15**
Final Overall Survival Analysis **16**
Objective Response **17**
Response Duration **18**
Safety 19
Exposure **19**
Deaths **20**
Discontinuations Due to Adverse Events **21**
Notable Adverse Events **23**
Safety Summary **27**
ONCOLOGY DRUGS ADVISORY COMMITTEE 27
LABELING 28
CONCLUSION 28
RECOMMENDATION 28

Table of Tables

Table 1 Approved Targeted Drugs for Advanced RRC 5
Table 2 Pivotal Phase 3 RC Study A4061032 and Supportive Phase 2 Studies A4061012, A4061035, and A4061023: Summary of Efficacy Results (Full Analysis Set) 6
Table 3 Demographic and Baseline Characteristics by Treatment; Full Analysis Set 9
Table 4 Summary of Disease Characteristics and Prior Treatment 10
Table 5 Interim Overall Survival Analysis 15
Table 6 Final Overall Survival Analysis 16
Table 7 Best Overall Response by Treatment and Stratification 17
Table 8 Exposure 19
Table 9 Summary of Axitinib Dose Escalations and Reductions 19
Table 10 Summary of Deaths by Treatment: Safety Analysis Set 20
Table 11 Discontinuations Due to Adverse Events 21
Table 12 Overall Summary of Treatment-Related Adverse Events by 23
Table 13 Summary of Adverse Events by Treatment, MedDRA Preferred Term, and Maximum CTCAE Grade Experienced by ≥5% of Patients: Safety Analysis Set 23
Table 14 Hypertension 24
Table 15 Adverse Events Related to Hyperthyroidism and Hypothyroidism 25
Table 16 Bleeding Events 25
Table 17 Arterial Thrombotic Events 26
Table 18 Venous Thrombotic Events 26
Table 19 Laboratory Adverse Events > 10% in Either Arm 27

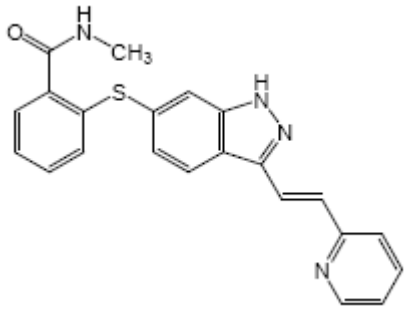
Table of Figures

Figure 1: Structural Formula of Axitinib 4
Figure 2 Progression-Free Survival ITT IRC Analysis 12
Figure 3 Kaplan-Meier Curve of Progression-Free Survival by Treatment and Prior Sunitinib-Containing Regimen; IRC Assessment 13
Figure 4 Kaplan-Meier Curve of Progression-Free Survival by Treatment and Prior Cytokine-Containing Regimen; IRC Assessment 13
Figure 5 PFS in United States Subpopulation 14
Figure 6 Interim Overall Survival Analysis 15
Figure 7 Final Overall Survival Analysis 16

PRODUCT INFORMATION

Axitinib is chemically designated as *N*-methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol- 400 6-ylsulfanyl]-benzamide. The molecular formula is $C_{22}H_{18}N_4OS$, and the molecular weight is 386.47 Daltons. The structural formula is shown in Figure 1.

Figure 1: Structural Formula of Axitinib



applicant figure

REGULATORY HISTORY

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 was granted in April 2008 with caveat that improvements in the primary endpoint of PFS must be both clinically and statistically significant.

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]

applicant table

CLINICAL TRIALS

As shown in Table 2, the NDA is supported by a pivotal randomized Phase 3 trial and 3 single arm Phase 2 trials.

Table 2 Pivotal Phase 3 RC Study A4061032 and Supportive Phase 2 Studies A4061012, A4061035, and A4061023: Summary of Efficacy Results (Full Analysis Set)

Study Number(N)	Assessment Method	ORR % (95% CI)	PFS (months) Median (95% CI)	DR (months) Median (95% CI)	OS (months) Median (95% CI)
Pivotal Phase 3 RCC Study A4061032					
Overall population					
Axitinib (361)	Blinded IRC	19.4 (15.4, 23.9)	6.7 (6.3, 8.6)	11.0 (7.4, NE)	NE (15.9, NE)*
Sorafenib (362)	Blinded IRC	9.4 (6.6, 12.9)	4.7 (4.6, 5.6)	10.6 (8.8, 11.5)	18.9 (18.0, NE)*
HR or RR Axitinib:Sorafenib		2.056 (1.408, 3.003)	0.665 (0.544, 0.812)	NA	1.008 (0.774, 1.313)
Sunitinib-refractory subgroup					
Axitinib (194)	Blinded IRC	11.3 (7.2, 16.7)	4.8 (4.5, 6.4)	11.0 (5.2, NE)	15.2 (12.2, NE)
Sorafenib (195)	Blinded IRC	7.7 (4.4, 12.4)	3.4 (2.8, 4.7)	11.1 (NE, NE)	18.0 (13.5, 20.7)
HR or RR Axitinib:Sorafenib		1.477 (0.792, 2.754)	0.741 (0.573, 0.958)	NA	1.070 (0.771, 1.485)
Cytokine-refractory subgroup					
Axitinib (126)	Blinded IRC	32.5 (24.5, 41.5)	12.1 (10.1, 13.9)	11.0 (7.4, NE)	NE
Sorafenib (125)	Blinded IRC	13.6 (8.1, 20.9)	6.5 (6.3, 8.3)	10.6 (5.9, 11.5)	NE
HR or RR Axitinib:Sorafenib		2.392 (1.434, 3.992)	0.464 (0.318, 0.676)	NA	0.744 (0.423, 1.307)
Bevacizumab –refractory subgroup					
Axitinib (29)	Blinded IRC	6.9 (0.8, 22.8)	4.2 (2.8, 6.5)	3.7 (NE, NE)	10.8 (9.2, NE)
Sorafenib (30)	Blinded IRC	3.3 (0.1, 17.2)	4.7 (2.8, 6.7)	NE	20.2 (10.7, 20.2)
HR or RR Axitinib:Sorafenib		2.029 (0. 2, 20.56)	1.147 (0.5683, 2.317)	NA	1.989 (0.732, 5.400)
Temsirolimus-refractory subgroup					
Axitinib (12)	Blinded IRC	41.7 (15.2, 72.3)	10.1 (1.5, 10.2)	5.6 (NE, NE)	NE (3.8, NE)
Sorafenib (12)	Blinded IRC	8.3 (0.2, 38.5)	5.3 (1.5, 10.1)	8.8 (NE)	8.0 (5.7, NE)
HR or RR Axitinib:Sorafenib		5 (0.704, 35.495)	0.511 (0.140, 1.865)	NA	0.652 (0.200, 2.128)
Supportive Phase 2 Cytokine-Refractory Advanced RCC					
A4061012 (52)	Investigator	44.2 (30.5, 58.7)	13.7 (9.7, 23.0)[b]	23.0 (20.9, NE)	29.9 (20.3, NE)
A4061035 (64)	Blinded IRC	50.0 (37.2, 62.8)	11.0 (9.2, 12.0)	11.5 (8.3, NE)	NA
	Investigator	54.7 (41.7, 67.2)	12.0 (9.2, 14.8)	12.8 (7.7, 15.5)	NA
Supportive Phase 2 Sorafenib-Refractory Advanced RCC					
A4061023 (62)	Investigator	22.6 (12.9, 35.0)	7.4 (6.7, 11.0)	17.4 (7.4, NE)	13.6 (8.4, 18.7)

Abbreviations: CI=confidence interval; DR=duration of response; HR=hazard ratio; IRC=independent review committee; NA=not available/not applicable, N = number of subjects randomized in Study A4061032 or treated in all other studies, NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RR=risk ratio

Data cut-off as of date 31 August 2011 for A4061032 and as per cut-off date of CSR for A4061012, A4061023, and A4061035.

*OS in Study A4061032 reflects immature results.

a Hazard ratio used for PFS. HR <1 indicates a reduction in HR in favor of axitinib; HR >1 indicates a reduction in HR in favor of sorafenib. Risk ratio is used for ORR. RR >1 indicated a higher likelihood of responding in the axitinib arm; RR <1 indicated a higher likelihood of responding in the sorafenib arm.

b Analyzed as a post-hoc efficacy endpoint applicant table

PIVOTAL RANDOMIZED PHASE 3 TRIAL

Trial Design

Patients were randomized in a 1:1 ratio to axitinib at a starting dose of 5 mg BID administered orally with food, or sorafenib at a starting dose of 400 mg BID administered orally without food.

Patients who tolerated axitinib (no related AEs above CTCAE Grade 2 for a consecutive 2-week period) were recommended to have their dose increased by 1 dose level to a maximum of 10 mg BID (unless the patient's BP was >150/90 mm Hg or the patient was

receiving antihypertensive medication). Axitinib could be decreased for toxicity to 3 mg BID and then 2 mg BID as necessary.
The sorafenib dose could be reduced to 400 mg once daily (QD) to manage sorafenib-related adverse drug reactions and then to a single 400 mg dose every other day, if further reduction was required.
Eligible subjects were stratified prior to randomization by baseline ECOG performance status (0 vs. 1) and prior systemic regimen: sunitinib-containing vs. bevacizumab-containing vs. temsirolimus containing vs. cytokine-containing.

Eligibility

Key eligibility criteria included histologically- or cytologically-confirmed diagnosis of RCC with a component of clear cell subtype, and with evidence of metastatic disease; one prior systemic first-line regimen for metastatic RCC; no evidence of uncontrolled hypertension; adequate organ function; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and a life expectancy of 12 weeks.

Objectives

The primary objective of this study was to compare 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).

The secondary objectives were to
- Compare the OS of patients in each arm;
- Compare the ORR of patients in each arm;
- Evaluate the safety and tolerability of axitinib;
- Estimate the duration of response (DR) of patients in each arm.

Treatment

Treatment was administered continuously in 4-week cycles. In Arm A, the starting dose of axitinib was 5 mg twice daily (BID) administered orally with food. (b) (4) tablets of axitinib were used in the study. In Arm B, sorafenib was administered orally without food at a starting dose of 400 mg BID. In both arms, doses were to be taken as close to 12 hours apart as possible and at approximately the same times each day. 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). The clinical judgments of the treating physician were to be exercised when titrating the axitinib dose.

Except for hypertension and proteinuria, a dose reduction to one lower dose level to 3 mg BID and subsequently to a minimum of 2 mg BID was recommended in subjects experiencing axitinib-related Grade 3 non-hematologic toxicity.

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 reductions below 2 mg BID were not to be implemented prior to discussion with the Sponsor. In Arm B, 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.

Demographics

Treatment groups are reasonably balanced for demographic and disease characteristics as shown in Tables 3 and 4.

Table 3 Demographic and Baseline Characteristics by Treatment; Full Analysis Set

Variable		Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Age, years	Mean (SD)	59.7 (10.5)	60.0 (10.1)
	Median	61.0	61.0
	Minimum, maximum	20, 82	22, 80
	N	361	362
Age (years)	<65	238 (65.9)	238 (65.7)
	≥65	123 (34.1)	124 (34.3)
Sex	Male	265 (73.4)	258 (71.3)
	Female	96 (26.6)	104 (28.7)
Race	White	278 (77.0)	269 (74.3)
	Black	1 (0.3)	4 (1.1)
	Asian	77 (21.3)	81 (22.4)
	Indian Subcontinent Asian	11 (3.0)	13 (3.6)
	Southeast Asian	1 (0.3)	0
	Japanese	26 (7.2)	29 (8.0)
	Korean	11 (3.0)	16 (4.4)
	Chinese	28 (7.8)	23 (6.4)
	Other	5 (1.4)	8 (2.2)
	Mulatto	1 (0.3)	0
	Hispanic	3 (0.8)	8 (2.2)
	Mixed	1 (0.3)	0
Weight (kg)	Mean (SD)	76.6 (18.4)	77.9 (19.2)
	Median	74.8	73.9
	Minimum, maximum	36.9, 154.0	37.5, 182.8
	N	361	360
Height (cm)	Mean (SD)	170.5 (9.8)	169.8 (9.1)
	Median	171.0	170.0
	Minimum, maximum	140.0, 195.0	144.2, 198.0
	N	360	359
ECOG performance status[a]	0	195 (54.0)	200 (55.2)
	1	162 (44.9)	160 (44.2)
	>1	1 (0.3)	0
Geographic region	North America	88 (24.4)	98 (27.1)
	Europe	187 (51.8)	170 (47.0)
	Asia	73 (20.2)	79 (21.8)
	Other	13 (3.6)	15 (4.1)
MSKCC risk group[b]	Favorable	158 (43.8)	148 (40.9)
	Intermediate	199 (55.1)	210 (58.0)
	Poor	4 (1.1)	4 (1.1)

applicant table

Countries included in each geographic region are as follows: Asia: China, India, Japan, Korea, Singapore, and Taiwan; European Union: Austria, Germany, France, Great Britain, Greece, Ireland, Italy, Poland, Russia, Slovakia, Spain, and Sweden; North America: Canada and United States; and Other: Australia and Brazil.

Abbreviations: ECOG = Eastern Cooperative Oncology Group, kg = kilogram, mg = milligram, MSKCC = Memorial Sloan-Kettering Cancer Center, N = number of patients, n = number of patients meeting specified criteria, SD = standard deviation

a ECOG Performance Status was taken from case report forms and was the last measure obtained before dosing.

b MSKCC risk groups were derived using the following 4 risk factors: high lactate dehydrogenase (>1.5 × upper limit of normal), low serum hemoglobin (less than the lower limit of normal), high corrected serum calcium (>10 mg/dL), and absence of prior nephrectomy.

Table 4 Summary of Disease Characteristics and Prior Treatment

Page 1 of 2			
Variable		**Axitinib N=361**	**Sorafenib N=362**
Time since initial histopathological diagnosis; weeks	n	361	362
	Mean (SD)	183.6 (213.1)	179.1 (197.1)
	Median	100.6	102.2
	Minimum, maximum	(0.1, 1219.6)	(0.9, 1096.6)
Time since metastatic diagnosis; weeks	n	360	362
	Mean (SD)	97.3 (108.8)	85.2 (87.0)
	Median	58.6	61.5
	Minimum, maximum	(1.1, 752.7)	(1.1, 882.7)
Histological classification; n (%)	Clear cell	355 (98.3)	359 (99.2)
	Other	1 (0.3)	0
	Not reported	5 (1.4)	3 (0.8)
Current stage; n (%)	Stage III	39 (10.8)	40 (11.0)
	Stage IV	322 (89.2)	322 (89.0)
Prior surgery for primary diagnosis (excluding nephrectomy); n (%)	None	154 (42.7)	149 (41.2)
	Unresected	4 (1.1)	7 (1.9)
	Resected	145 (40.2)	136 (37.6)
	Biopsy	74 (20.5)	85 (23.5)
	Partially resected	18 (5.0)	29 (8.0)
	Not found	4 (1.1)	5 (1.4)
	Not reported	8 (2.2)	10 (2.8)
Previous radiotherapy; n (%)	No	286 (79.2)	289 (79.8)
	Yes	75 (20.8)	73 (20.2)
	Neoadjuvant	2 (0.6)	1 (0.3)
	Adjuvant	12 (3.3)	16 (4.4)
	Palliative	62 (17.2)	57 (15.7)
Previous surgery for nephrectomy; n (%)	No	34 (9.4)	31 (8.6)
	Yes	327 (90.6)	331 (91.4)
	Unresected	3 (0.8)	1 (0.3)
	Resected	312 (86.4)	320 (88.4)
	Partially resected	19 (5.3)	13 (3.6)
	Not found	1 (0.3)	2 (0.6)
	Not reported	5 (1.4)	2 (0.6)
Best response to prestudy systemic therapy; n (%)	Complete response	3 (0.8)	3 (0.8)
	Partial response	65 (18.0)	73 (20.2)
	Stable disease	153 (42.4)	132 (36.5)
	Progressive disease	120 (33.2)	134 (37.0)
	Unknown	20 (5.5)	18 (5.0)

Page 2 of 2			
Variable		**Axitinib N=361**	**Sorafenib N=362**
Procedure used to document prestudy progression[a]	Conventional CT scan	22 (6.1)	15 (4.1)
	Spiral CT scan	320 (88.6)	324 (89.5)
	X-ray	11 (3.0)	10 (2.8)
	MRI scan	10 (2.8)	9 (2.5)
	Bone scan	41 (11.4)	32 (8.8)
	Histopathologically	0	1 (0.3)
	Other	8 (2.2)	17 (4.7)
Metastatic site; n (%)	Bone	119 (33.0)	107 (29.6)
	Pleural effusion	18 (5.0)	18 (5.0)
	Lung	274 (75.9)	292 (80.7)
	Lymph node	209 (57.9)	202 (55.8)
	Ascites	2 (0.6)	5 (1.4)
	Liver	102 (28.3)	103 (28.5)
	Pancreas	8 (2.2)	10 (2.8)
	Spleen	14 (3.9)	10 (2.8)
	Adrenal	77 (21.3)	60 (16.6)
	Kidney	81 (22.4)	77 (21.3)
	Pelvis	11 (3.0)	4 (1.1)
	Peritoneum	26 (7.2)	30 (8.3)
	Other	139 (38.5)	130 (35.9)

applicant table

Abbreviations: CT = computed tomography, N = number of patients, n = number of patients meeting specified criteria, SD = standard deviation

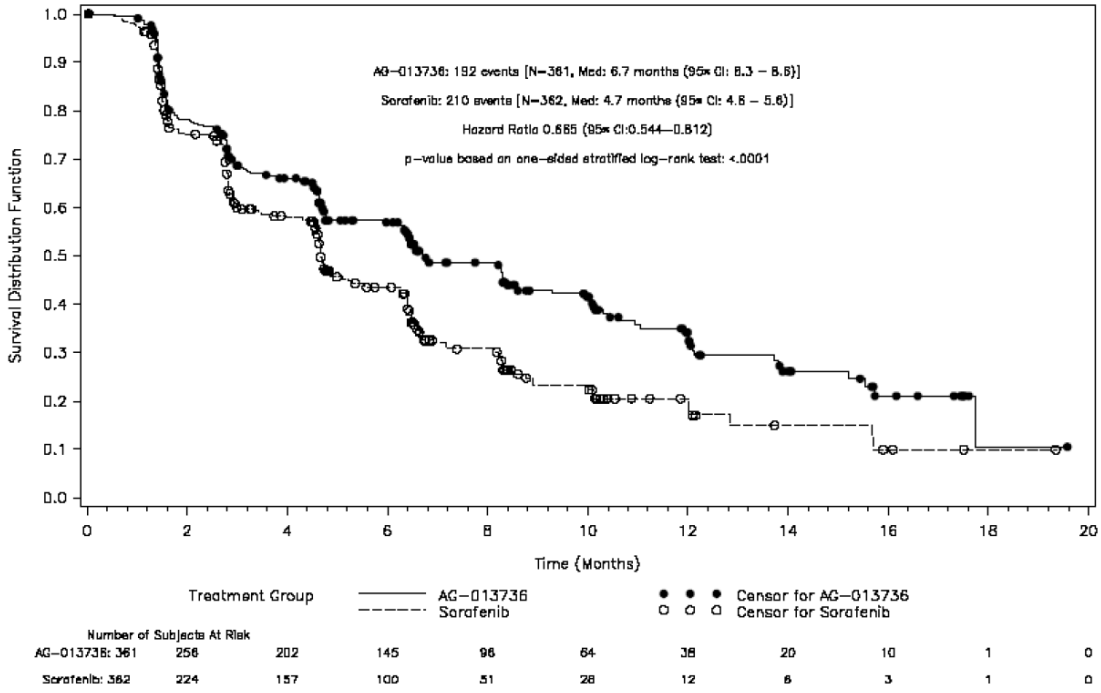
[a] Protocol Amendment 3 (dated 10 February 2009) removed the requirement for documentation of progressive disease with prestudy scans

Efficacy

Progression-Free Survival

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

Figure 2 Progression-Free Survival ITT IRC Analysis



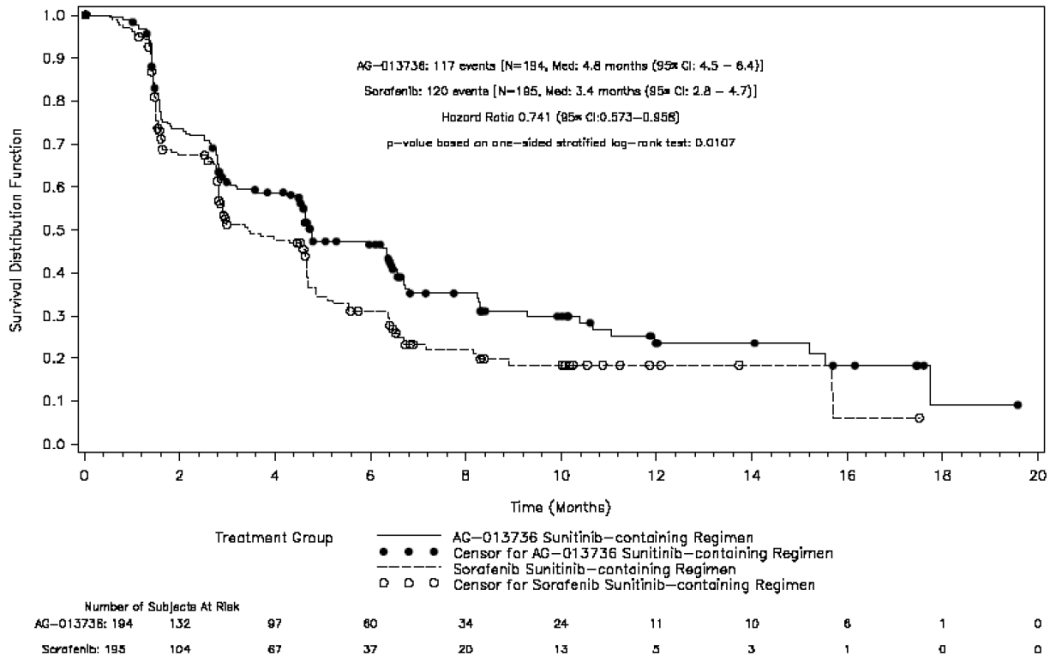
applicant figure

As shown in Figure 2, 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 3 and Figure 4, 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.

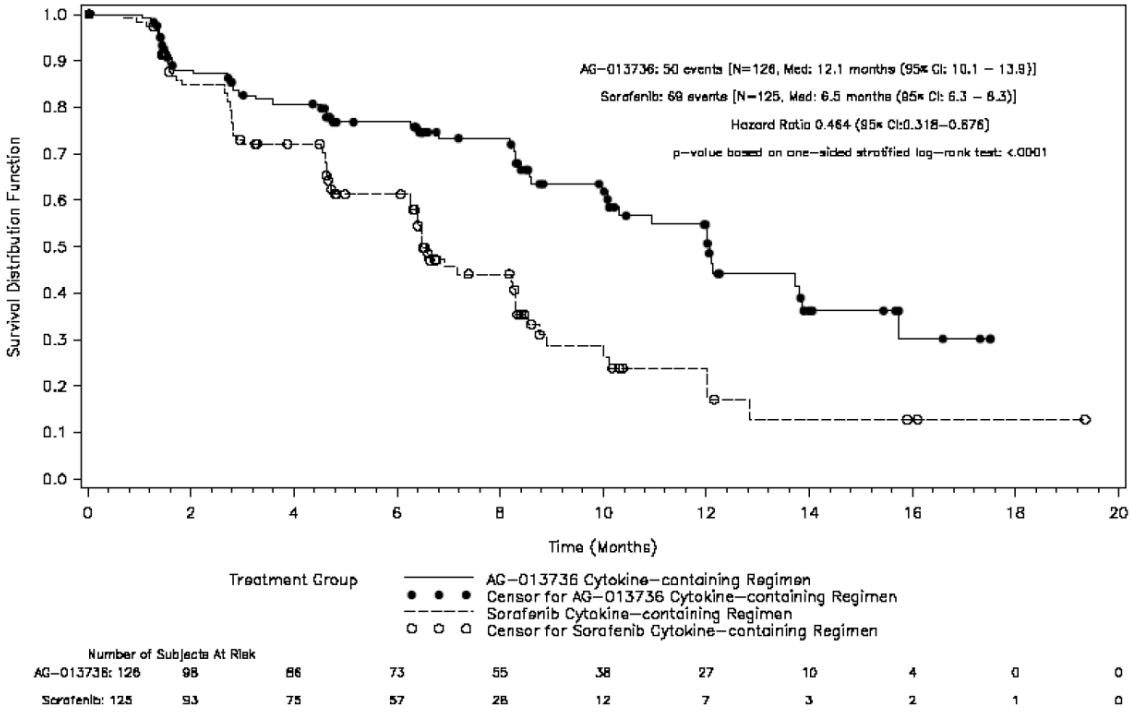
On the other hand, as shown in Figure 5, an unplanned subgroup PFS analysis in the U.S population shows an axitinib benefit with stratified HR =0.613 (95% CI 0.401-0.938), p=0.0115 Log Rank, one-sided, axitinib median PFS 6.7 months and sorafenib median PFS 3.5 months.

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



applicant figure

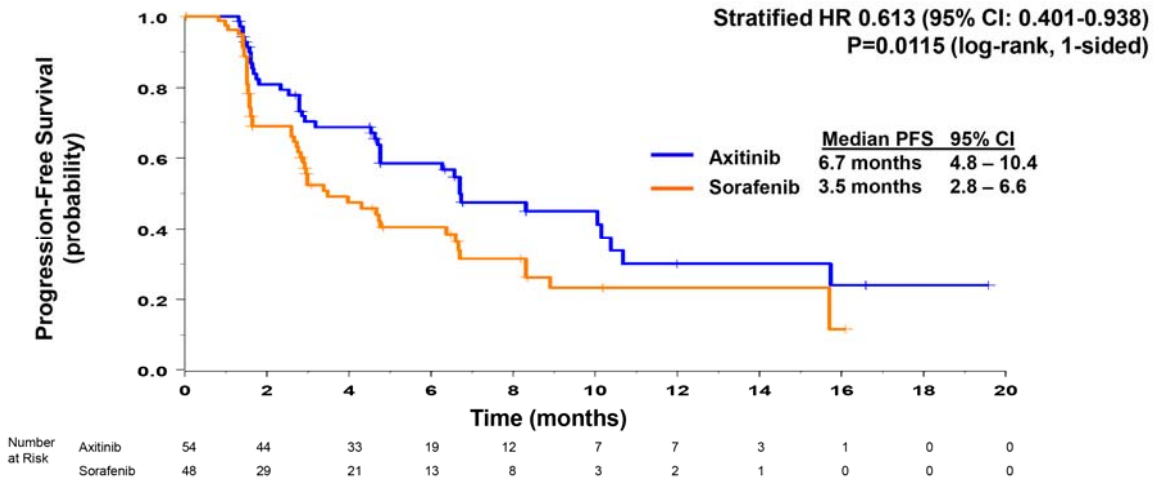
Figure 4 Kaplan-Meier Curve of Progression-Free Survival by Treatment and Prior Cytokine-Containing Regimen; IRC Assessment



applicant figure

PFS in United States Subpopulation

Figure 5 PFS in United States Subpopulation



applicant figure

Interim Overall Survival Analysis

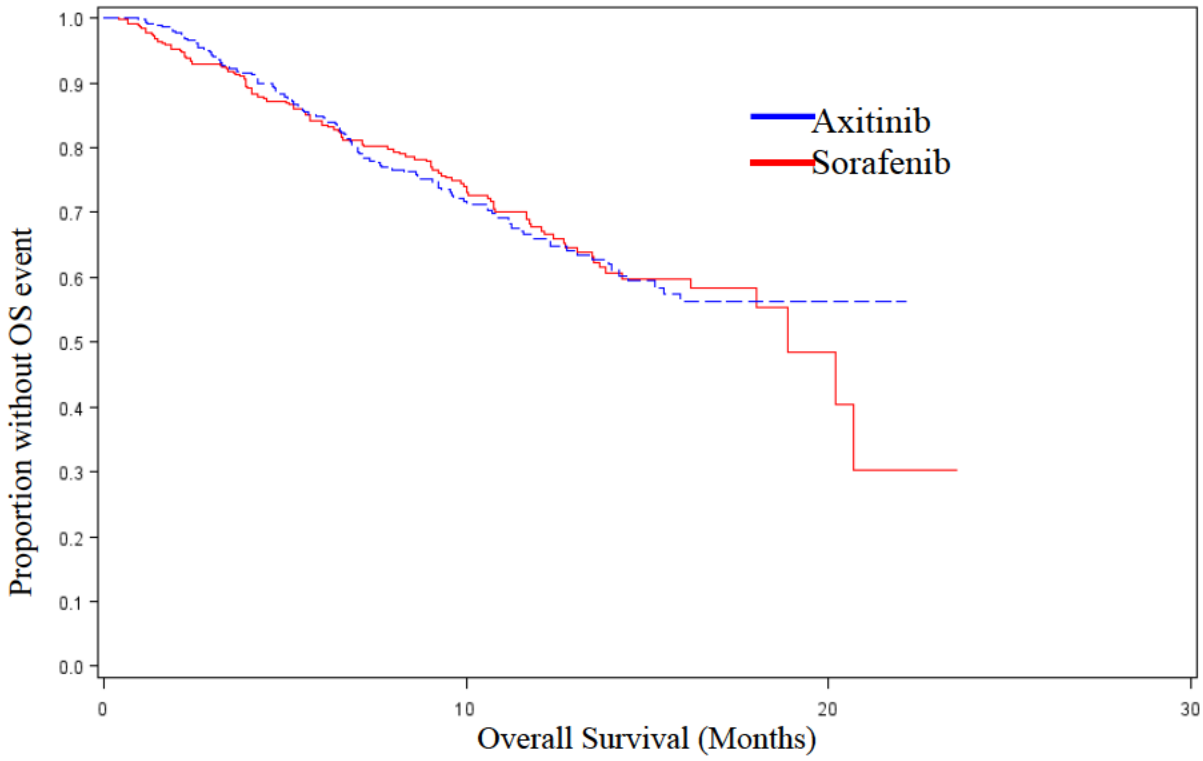
As shown in Table 5 and Figure 6, there was no axitinib effect on interim overall survival. There was no crossover to the other treatment after progression.

Table 5 Interim Overall Survival Analysis

	Axitinib N=361	**Sorafenib N=362**
Deaths (%)	113 (31.2)	110 (30.4)
Median OS in months (95% CI)	NR (15.9, NR)	18.9 (18, NR)
Hazard Ratio (95% CI)	1.009 (0.77-1.31)	
P-value	0.53	

applicant table

Figure 6 Interim Overall Survival Analysis



applicant figure

Final Overall Survival Analysis

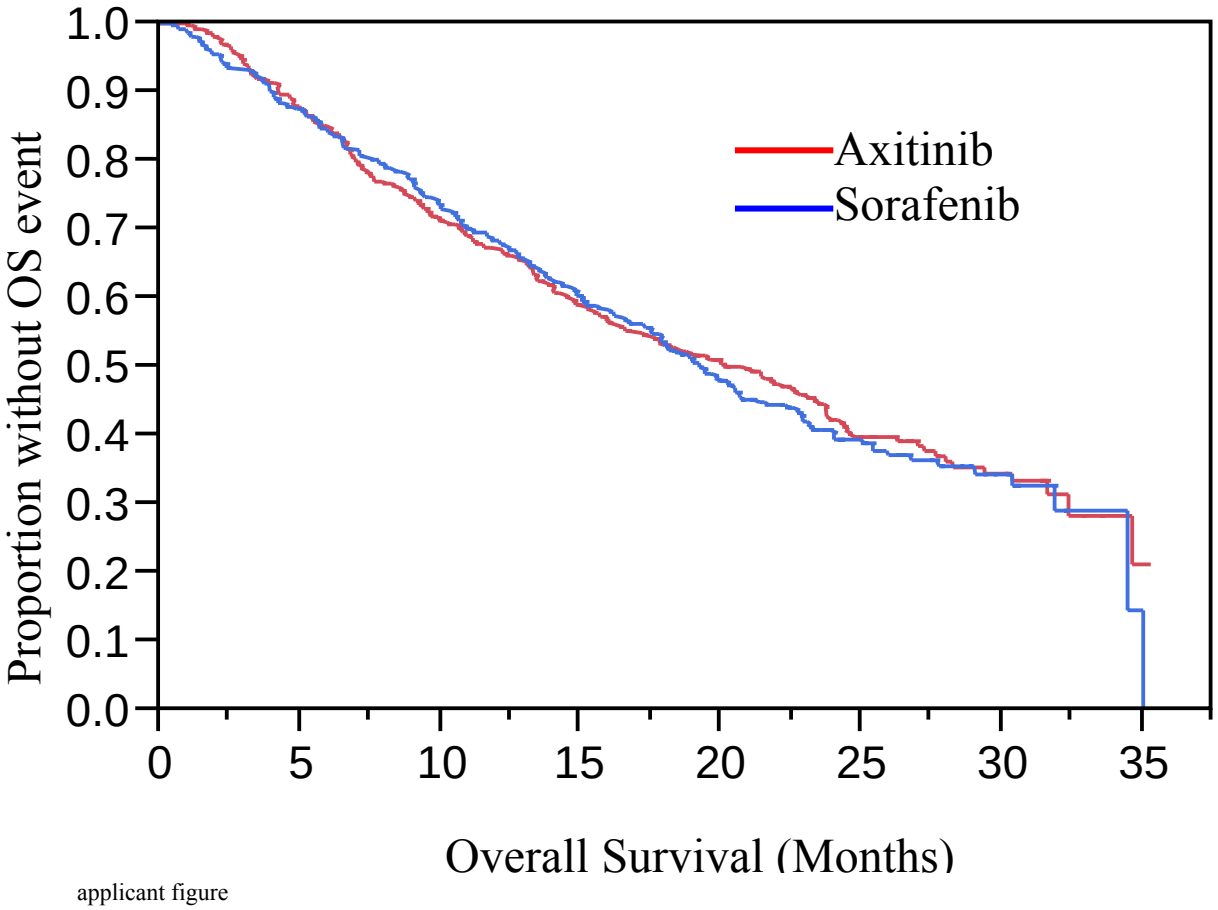
As shown in Table 6 and Figure 7, there was no axitinib effect on final overall survival. There was no crossover to the other treatment after progression

Table 6 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 7 Final Overall Survival Analysis



applicant figure

Objective Response

Table 7 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]).

Safety

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 8 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	276 (76.9%)	285 (80.3%)
AE	194 (54%)	224 (63.1%)
Other	202 (56.3)	183 (51.5%)

from medical officer review

Table 9 Summary of Axitinib Dose Escalations and Reductions

Axitinib dose levels	**Axitinib N=359 n (%)**
Total daily dose	
< 6 mg	30 (8.4)
6-8 mg	58 (16.2)
10 mg	139 (38.7)
12-14 mg	60 (16.7)
20 mg	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 10 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 11 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 12 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 13 Summary of Adverse Events by Treatment, MedDRA Preferred Term, and Maximum CTCAE Grade Experienced by ≥5% of Patients: Safety Analysis Set

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 14 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 15 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 16 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 17 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 18 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 19 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

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

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

ONCOLOGY DRUGS ADVISORY COMMITTEE

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.

LABELING

See revised labeling by the FDA review team.

CONCLUSION

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. 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

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.

John R. Johnson, M.D.

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

/s/

JOHN R JOHNSON
01/11/2012

CLINICAL REVIEW

Application Type	NME
Application Number(s)	202324
Priority or Standard	Standard
Submit Date(s)	04/13/2011
Received Date(s)	04/14/2011
PDUFA Goal Date	02/14/2012
Division / Office	OHOP/DOP1
Reviewer Name(s)	Amy McKee, M.D.
Review Completion Date	01/09/2012
Established Name	axitinib
(Proposed) Trade Name	Inlyta
Therapeutic Class	Tyrosine kinase inhibitor
Applicant	Pfizer, Inc.
Formulation(s)	oral
Dosing Regimen	5 mg BID
Indication(s)	Second-Line Therapy for Metastatic Renal Cell Cancer

Template Version: March 6, 2009

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 8

1.1 Recommendation on Regulatory Action 8
1.2 Risk Benefit Assessment 8
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 8
1.4 Recommendations for Postmarket Requirements and Commitments 9

2 INTRODUCTION AND REGULATORY BACKGROUND 9

2.1 Product Information 9
2.2 Tables of Currently Available Treatments for Proposed Indication 9
2.3 Availability of Proposed Active Ingredient in the United States 11
2.4 Important Safety Issues With Consideration to Related Drugs 11
2.5 Summary of Presubmission Regulatory Activity Related to Submission 11
2.6 Other Relevant Background Information 12

3 ETHICS AND GOOD CLINICAL PRACTICES 15

3.1 Submission Quality and Integrity 15
3.2 Compliance with Good Clinical Practices 15
3.3 Financial Disclosures 16

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 17

4.1 Chemistry Manufacturing and Controls 17
4.2 Clinical Microbiology 17
4.3 Preclinical Pharmacology/Toxicology 17
4.4 Clinical Pharmacology 17
4.4.1 Mechanism of Action 17
4.4.2 Pharmacodynamics 17
4.4.3 Pharmacokinetics 18

5 SOURCES OF CLINICAL DATA 19

5.1 Tables of Studies/Clinical Trials 19
5.2 Review Strategy 19
5.3 Discussion of Individual Studies/Clinical Trials 19

6 REVIEW OF EFFICACY 27

Efficacy Summary 27
6.1 Indication 27
6.1.1 Methods 27
6.1.2 Demographics 27
6.1.3 Subject Disposition 29
6.1.4 Analysis of Primary Endpoint(s) 29
6.1.5 Analysis of Secondary Endpoints(s) 33

6.1.6 Other Endpoints 36
6.1.7 Subpopulations 36
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 37
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 38
6.1.10 Additional Efficacy Issues/Analyses 38

7 REVIEW OF SAFETY 39

Safety Summary 39
7.1 Methods 40
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 40
7.1.2 Categorization of Adverse Events 41
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 42
7.2 Adequacy of Safety Assessments 43
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 43
7.2.2 Explorations for Dose Response 46
7.2.3 Special Animal and/or In Vitro Testing 46
7.2.4 Routine Clinical Testing 46
7.2.5 Metabolic, Clearance, and Interaction Workup 46
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 46
7.3 Major Safety Results 46
7.3.1 Deaths 46
7.3.2 Nonfatal Serious Adverse Events 52
7.3.3 Dropouts and/or Discontinuations 52
7.3.4 Significant Adverse Events 54
7.3.5 Submission Specific Primary Safety Concerns 59
7.4 Supportive Safety Results 59
7.4.1 Common Adverse Events 59
7.4.2 Laboratory Findings 63
7.4.3 Vital Signs 63
7.4.4 Electrocardiograms (ECGs) 64
7.4.5 Special Safety Studies/Clinical Trials 64
7.4.6 Immunogenicity 65
7.5 Other Safety Explorations 65
7.5.1 Dose Dependency for Adverse Events 65
7.5.2 Drug-Demographic Interactions 67
7.5.3 Drug-Disease Interactions 70
7.5.4 Drug-Drug Interactions 70
7.6 Additional Safety Evaluations 70
7.6.1 Human Carcinogenicity 70
7.6.2 Human Reproduction and Pregnancy Data 70
7.6.3 Pediatrics and Assessment of Effects on Growth 71
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 71

7.7 Additional Submissions / Safety Issues 71

8 POSTMARKET EXPERIENCE 71

9 APPENDICES 72

9.1 Labeling Recommendations 72
9.2 Advisory Committee Meeting 72
9.3 Literature Review/References 72

Table of Tables

Table 1: Currently Available Treatments for Advanced Renal Cell Carcinoma* 10
Table 2: Regulatory Milestones 12
Table 3: OSI Inspection Sites 16
Table 4: Clinical Studies in Support of NDA 202324 19
Table 5: Axitinib Dose Levels 21
Table 6: Patient Baseline Characteristics 28
Table 7: Prior Treatment 29
Table 8: Prior treatment in North America and Europe 29
Table 9: Patient Disposition 29
Table 10: Progression-free Survival by IRC 30
Table 11: Discordance between IRC and Investigators 31
Table 12: IRC versus Investigator Assessment of PFS 31
Table 13: Rates of Discordance between IRC Reviewers per Applicant 32
Table 14: Patients Censored for PFS 33
Table 15: Interim Overall Survival 34
Table 16: Final Overall Survival 35
Table 17: Progression-free Survival Stratified by Prior Treatment 36
Table 18: Protocol Deviations 39
Table 19: Summary of Axitinib Trials in Safety Analysis 41
Table 20: Incidence of Most Common Treatment-Emergent Adverse Events (>15%) in the ISS Database 42
Table 21: Exposure 43
Table 22: Summary of Axitinib Dose Escalations and Reductions 44
Table 23: Events Leading to Dose Modification (≥3 Patients on Either Arm) 44
Table 24: All Safety Population Deaths on A4061032 47
Table 25: All Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 28 Days of Last Dose on the Axitinib Arm 48
Table 26: All Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 28 Days of Last Dose on the Sorafenib Arm 50
Table 27: Deaths not Attributed to Disease Progression or TEAE 51
Table 28: Nonfatal Serious Adverse Events (≥1% on Either Arm) 52
Table 29: Reasons for Treatment Discontinuation per Applicant 53
Table 30: Discontinuations due to Adverse Events 53
Table 31: Bleeding Events 55
Table 32: Arterial Thrombotic Events 56
Table 33: Venous Thrombotic Events 57
Table 34: Hypertensive Adverse Events 58
Table 35: Grade 1-4 TEAEs (≥5% of Patients on Either Treatment Arm) 59
Table 36: Grade 3-4 TEAEs (≥1% of Patients on Either Arm) 61
Table 37: Laboratory Grade 1-4 Adverse Events in >10% in Either Arm 63
Table 38: Grade 1-4 Adverse Events by Age 68

Table 39: Grade 3-4 Adverse Events by Age 68
Table 40: Grade 1-4 Adverse Events by Sex 69
Table 41: Grade 3-4 Adverse Events by Sex 70

Table of Figures

Figure 1: Structural Formula of Axitinib 9
Figure 2: Kaplan-Meier Plot of Progression-free Survival..... 30
Figure 3: Kaplan-Meier Plot of Interim Overall Survival..... 34
Figure 4: Kaplan-Meier Plot of Final Overall Survival..... 35
Figure 5: Forest Plot PFS Hazard Ratios in Subgroups (from applicant's CSR) 37
Figure 6: Exposure-Adverse Event Relationship..... 67

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the findings described in this clinical review of the new drug application for axitinib (NDA 202324), this reviewer recommends regular approval of axitinib for the following indication:

INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

1.2 Risk Benefit Assessment

The recommendation for approval is based mainly on the single, randomized clinical trial in which axitinib showed a statistically significant progression free survival (PFS) advantage over sorafenib in 723 patients with advanced renal cell carcinoma after failure of one prior systemic regimen.

A4061032 (AXIS) was a randomized, controlled, open-label, multicenter Phase 3 trial comparing axitinib to sorafenib as second-line systemic therapy in patients with metastatic renal cell carcinoma. Patients were randomized to receive either axitinib 5 mg po BID or sorafenib 400 mg po BID. The primary efficacy endpoint was PFS as assessed by an Independent Review Committee consisting of two blinded radiologists. The median PFS was 6.7 months (95% CI 6.3-8.4) for axitinib and 4.7 months (95% CI 4.6-5.6) for sorafenib, with a hazard ratio of 0.67 (95% CI 0.55-0.81). There was no difference in the final overall survival analysis between the two arms with a hazard ratio of 0.97 (95% CI 0.8-1.17).

The safety profile of axitinib is comparable to that of other drugs in the same class of small molecule inhibitors of the VEGF pathway in terms of the types of adverse events observed. Common adverse events include diarrhea, nausea, fatigue, asthenia, hypertension, dysphonia and dermatologic adverse events. Less common serious adverse events include arterial and venous thrombotic events, gastrointestinal perforation, bleeding events, hypothyroidism, proteinuria and reversible posterior leukoencephalopathy syndrome. There were no new signals for serious adverse events with axitinib that had not been previously identified for this class of drugs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

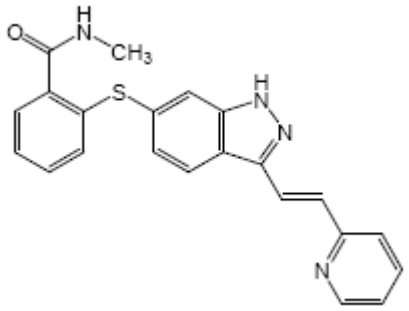
None.

2 Introduction and Regulatory Background

2.1 Product Information

Axitinib is chemically designated as *N*-methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-400 6-ylsulfanyl]-benzamide. The molecular formula is $C_{22}H_{18}N_4OS$, and the molecular weight is 386.47 Daltons. The structural formula is shown in Figure 1.

Figure 1: Structural Formula of Axitinib



2.2 Tables of Currently Available Treatments for Proposed Indication

Since 2005, six targeted agents have received marketing approval for the treatment of advanced RCC. The agents, type of trial and approval basis are noted in Table 1 below.

Table 1: Currently Available Treatments for Advanced Renal Cell Carcinoma*

Drug Name	Trial Type	Approval Date	Approval Basis	Survival Benefit?
Sorafenib	Randomized, double-blind, compared to placebo in patients with one prior systemic therapy†	December 2005 Full approval	PFS	No
Sunitinib	Two single-arm trials in patients with cytokine-refractory disease Randomized, double-blind, compared to IFN-α in previously untreated patients	January 2006 Accelerated approval February 2007 Full approval	ORR, DOR PFS	No No
Temsirolimus	Randomized, open-label, compared to IFN-α, in previously untreated patients with poor prognostic factors	May 2007 Full approval	OS (2nd PFS)	Yes
Everolimus	Randomized, double-blind, compared to placebo, in patients with RCC treated previously with sorafenib or sunitinib	March 2009 Full approval	PFS	No
Bevacizumab+ IFNα	Randomized, double-blind, compared to IFNα alone in previously untreated patients	July 2009 Full approval	PFS	No
Pazopanib	Randomized, double-blind, compared to placebo in treatment-naïve patients or patients (54%) with one prior cytokine regimen (46%)	October 2009 Full approval	PFS	No

*All of the above treatments are indicated for the treatment of advanced RCC with the exception of everolimus, which is indicated for the treatment of advanced RCC after failure of treatment with sunitinib or sorafenib. Interferon is not FDA-approved for the treatment of RCC. Interleukin-2 is approved for RCC based on response rates.
†Approximately 83% of patients had received cytokine therapy; the remaining 17% received chemotherapy or hormonal agents as prior therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Axitinib is not available in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

There are a multitude of products that target the vascular endothelial growth factor (VEGF) pathway, including an antibody to VEGF (bevacizumab) and small molecule inhibitors of the VEGF receptor (sunitinib, sorafenib and pazopanib). Bevacizumab has a box warning for gastrointestinal perforation, surgery and wound healing complications and hemorrhage. Sunitinib and pazopanib have box warnings for hepatotoxicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Major regulatory milestones along with key FDA recommendations prior to the NDA submission are summarized in Table 2.

Table 2: Regulatory Milestones

Milestone	Time	Key Regulatory Activities Related to Clinical Development
IND 63662 activated	December 2001	• No significant initial deficiencies
End-of-Phase 2 meeting	May 2007	• Randomized, Phase 3 trial in advanced RCC in second-line setting with sorafenib as comparator arm with blinded IRC-assessed primary efficacy endpoint discussed • Sponsor indicated second-line indication would be sought based on design of Phase 3 trial • FDA recommended overall survival as primary endpoint and discouraged interim analyses for efficacy based on progression-free survival
Special Protocol Assessment	January 2008	SPA denied based on all of the following: PFS as primary endpoint, potential interim efficacy analyses by the DMC, inadequate case report forms, inadequate safety monitoring during the trial and continued treatment despite documented disease progression
Special Protocol Assessment	April 2008	SPA granted with caveat that improvements in the primary endpoint of PFS must be both clinically and statistically significant
Pre-NDA meeting	January 2010	• Sponsor proposed “advanced RCC” for the indication; FDA noted that the indication will reflect the population studied • Sponsor indicated that a second ongoing Phase 3 trial in second-line advanced RCC may be amended to include treatment-naïve patients; FDA encouraged powering the trial to detect a realistic improvement in OS
NDA submission	April 2011	Standard review designated

2.6 Other Relevant Background Information

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.[1] 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%,[2,3] and high-dose IL-2 has been shown to induce durable complete responses in approximately five percent of treated patients.[4] 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.

Sorafenib was the first of these agents to receive marketing approval in December 2005. It was approved on the basis of a randomized trial in patients with advanced RCC who had received one prior systemic therapy in which a PFS advantage of 167 days versus 84 days in the placebo arm was demonstrated. Approximately 83% of patients had received a cytokine regimen as prior therapy, and the remainder of patients had received a variety of chemotherapeutic agents or hormonal agents. Although overall survival was a co-primary endpoint, the PFS results prompted submission of these results given the lack of therapy options. Regular approval was given, and overall survival results were affected as the vast majority of patients from the placebo arm crossed over to treatment with sorafenib; thus, no survival advantage ever has been demonstrated for sorafenib in advanced RCC, whether in the first-line or second-line setting.

The second targeted agent that was approved in January 2006, sunitinib, initially received accelerated approval on the basis of response rates in single-arm trials. Two single-arm trials in patients with cytokine refractory RCC demonstrated response rates of 34-37%. Full approval was given based on a randomized trial in treatment-naïve patients with advanced RCC in which sunitinib demonstrated a PFS advantage of 47 weeks compared to 22 weeks in the IFN-α arm. Again, an overall survival benefit was not demonstrated, and crossover of placebo patients to the sunitinib arm was permitted.

The third targeted agent, temsirolimus, is the only agent that has shown an overall survival advantage in this disease. Temsirolimus was compared to IFN-α in previously untreated patients with advanced RCC and poor prognostic factors; median OS in the temsirolimus group was 10.9 months versus 7.3 months in the IFN-α group.

Bevacizumab in combination with IFN-α was approved in July 2009 based on a randomized trial in previously untreated patients with advanced RCC comparing the combination to IFN-α alone. The median PFS was 9.2 months in the combination arm versus 4.2 months in the IFN- α arm. Final OS results reported in 2010 did not show a difference in OS between the two arms.

Pazopanib is the most recent addition to the armamentarium in December 2009. Full approval was granted on the basis of a randomized trial in patients who had received no prior therapy or one prior cytokine-based systemic regimen to pazopanib or placebo. Median PFS was 9.2 months in the pazopanib group and 4.2 months is the placebo group; OS data was not mature at the time of approval, and study design allowed for crossover at the time of progression for placebo-treated patients. Thus, this trial also was not designed to rigorously compare OS between the two arms.

Everolimus is the only approved agent that is specifically indicated for a second-line indication. Everolimus was compared to placebo in patients who had progressed after sunitinib or sorafenib, with a median PFS of 4.9 months compared to 1.9 months in the placebo arm; overall response rate was 2% in the everolimus arm and 0 in the placebo arm. The interim analysis of OS showed no difference between the treatment arms. The trial allowed crossover of placebo patients on progression; as 109 of 139 patients on the placebo arm crossed over to everolimus, demonstration of an OS benefit would be unlikely.

The appropriate order of targeted therapies to use in advanced RCC is not known. Several of the agents were studied in the second-line setting after cytokines, but everolimus is the only agent to be studied in a randomized trial after first-line therapy with a VEGF pathway inhibitor. Recently published trials in second-line advanced RCC after initial treatment with a VEGF pathway inhibitor are mostly single-arm trials. Sorafenib in patients with advanced RCC whose disease progressed after bevacizumab/IFN- α or sunitinib showed an unconfirmed response rate of 2% and a median PFS of 4.4 months.[5] A retrospective analysis of patients treated sequentially with either sunitinib then sorafenib or sorafenib then sunitinib demonstrated median PFS of first-line therapy with sorafenib of 8.4 months and with sunitinib of 7.8 months; second-line therapy with sunitinib was 7.9 months and with sorafenib was 4.2 months.[6] A similar retrospective study showed median PFS of the sequentially administered sunitinib-sorafenib was 17.7 months and was 18.8 months fro the sorafenib-sunitinib sequence.[7] There is some evidence that re-challenge with a VEGF pathway inhibitor may be useful. In a retrospective review in seven U.S. centers, patients who were initially treated with sunitinib and received at least one intervening treatment were re-treated with sunitinib. Median PFS with the initial sunitinib treatment was 13.7 months, and PFS with sunitinib re-treatment was 7.2 months. Patients who were re-challenged more than six months after the initial sunitinib treatment had longer median PFS (16.5 months) than patients who were re-treated within six months (6 months).[8]

The appropriate clinical trial endpoint in the second-line setting also is unclear. The full approvals for targeted agents in the first-line setting based on PFS were in a regulatory environment in which the treatment options of IL-2 and IFN-α were not recognized as automatic first-line therapy, as demonstrated by the advice given by the Oncologic Drugs Advisory Committee that randomized trials with a placebo arm were neither unethical nor would they have difficulty in accruing patients. However, in the current

setting there are multiple choices for first-line agents. Given the shorter expected duration of OS in the second-line setting, the use of OS as the primary endpoint in clinical trials sued to support a marketing application appears reasonable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 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.

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."

Reviewer 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.

3.3 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the CMC review.

4.2 Clinical Microbiology

Axitinib is administered by mouth and was not reviewed for clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

Refer to preclinical pharmacology/toxicology review

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR)-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumor growth, and metastatic progression of cancer. Axitinib has been shown to 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.

4.4.2 Pharmacodynamics

Refer to the Clinical Pharmacology review for details.

4.4.3 Pharmacokinetics

Refer to the Clinical Pharmacology review for details.

From the package insert:
Following single oral 5 mg dose administration, the median T_{max} ranged from 2.5 to 4.1 hours. Based on the plasma half-life, steady state is expected by 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady-state, axitinib exhibits approximately linear pharmacokinetics within the 1 mg to 20 mg dose range. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%.

Compared to overnight fasting, administration of INLYTA with a moderate fat meal resulted in 10% lower AUC and a high fat meal resulted in 19% higher AUC. INLYTA can be administered with or without food. *[see Dosage and Administration (2.1).]*
Axitinib is highly bound (>99%) to human plasma proteins with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. In patients with advanced RCC (N=20), at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) C_{max} and AUC_{0-24} were 27.8 (79%) ng/mL and 265 (77%) ng.h/mL, respectively. The geometric mean (CV%) apparent clearance and apparent volume of distribution were 38 (31%) L/h and 160 (140%) L, respectively.

The plasma half-life of INLYTA ranges from 2.5 to 6.1 hours. Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Following oral administration of a 5 mg radioactive dose of axitinib, approximately 41% of the radioactivity was recovered in feces and approximately 23% was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in feces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity. The sulfoxide and N-glucuronide metabolites show approximately ≥400-fold less *in vitro* potency against VEGFR-2 compared to axitinib.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Studies in Support of NDA 202324

Study #	Population	Design	Dose (mg B.I.D.)	# Any Axitinib	# Axitinib 5 mg BID
A4060010	Advanced Solid Tumors	Dose escalation	2-30	36	20
A4061012	Second-line in metastatic RCC	Single-arm, open-label	5	52	52
A4061035	Second-line in metastatic RCC	Single-arm, open-label	5	64	64
A4061023	Refractory metastatic RCC	Single-arm, open-label	5	62	62
A4061032	Second-line in metastatic RCC	Randomized, open-label versus Sorafenib 400 mg BID	5	361	361

5.2 Review Strategy

The clinical review is based on the clinical study report for the randomized trial in patients with advanced RCC after failure of treatment with one prior systemic therapy, A4061032, including the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant, study reports for other axitinib clinical trials and literature review of RCC. Efficacy is supported by three single-arm trials in previously treated RCC, A4061012, A4061023 and A4061035.

5.3 Discussion of Individual Studies/Clinical Trials

This NDA is based primarily progression-free survival from a single, randomized, open-label Phase 3 trial, A4061032.

Study Title: Axitinib (AG-013736) as Second Line Therapy for Metastatic Renal Cell Cancer: Axis Trial.

5.3.1 Study Design

A4061032 (AXIS) was a randomized, controlled, open-label, multicenter Phase 3 trial comparing axitinib to sorafenib as second-line systemic therapy in patients with metastatic renal cell carcinoma.

Tumor assessments were done at screening, every six weeks for the first 12 weeks, every eight weeks subsequently, and at the final visit. Patients were followed for AEs (with exception of SCC) up to 28 days after the last dose in all patients.

Data from this study were monitored by an external Data Monitoring Committee (DMC). The DMC consisted of one clinician who is an expert in renal cell cancer, one clinician with broader expertise in oncology clinical studies and one biostatistician. The DMC reviewed available safety data from this trial at regularly scheduled intervals specified in the DMC charter. In addition, for this trial the DMC reviewed the results of the pre-specified interim analysis of PFS and the pre-specified final analysis for PFS performed at the time of the interim analysis for OS.

5.3.2 Study Drug Administration and Schedule

A total of 680 patients were planned to be enrolled at centers in Western Europe, North America, Australia/New Zealand, and Israel. Patients were randomly assigned to treatment in a 1:1 randomization ratio to one of two treatment arms. Following the screening period (of up to 28 days), eligible patients were randomized to receive either:

- Arm A: axitinib administered 5 mg po BID
- Arm B: sorafenib administered 400 po mg BID

Randomization was stratified by prior treatment and ECOG status.

The axitinib dose could be escalated or decreased depending on the adverse events experienced by the patient. The dose could be escalated if a patient experienced no AEs related to study drug above CTCAE Grade 2 for a consecutive 2-week period by 1 dose level to a maximum of 10 mg BID (unless the patient's BP was >150/90 mm Hg or the patient was receiving antihypertensive medication). The clinical judgment of the treating physician was exercised when increasing the axitinib dose.

Table 5: Axitinib Dose Levels

Dose Level	Dose
+2	10 mg BID
+1	7 mg BID
0 (Starting Dose)	5 mg BID
-1	3 mg BID
-2	2 mg BID

5.3.3 Study Endpoints

Primary Objective

- The primary objective of this study was to compare the PFS of patients with mRCC receiving axitinib versus sorafenib following failure of one prior systemic first-line regimen containing one or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s).

Secondary Objectives

The secondary objectives were as follows:

- to compare the overall (OS) of patients in each arm;
- to compare the overall response rate (ORR) of patients in each arm;
- to evaluate the safety and tolerability of axitinib;
- to estimate the duration of response (DOR) of patients in each arm; and
- to compare the kidney-specific symptoms and health status of patients in each arm, as measured by the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) and European Quality of Life (EuroQol) EQ-5D self-report questionnaire (EQ-5D).

5.3.4 Eligibility Criteria

The target population was male or female patients ≥ 18 years of age with histologically or cytologically confirmed metastatic RCC who had received one prior systemic anti-cancer treatment.

Inclusion Criteria

- Histologically or cytologically confirmed mRCC with a component of clear cell subtype.
- Evidence of unidimensionally measurable disease (ie, ≥1 malignant tumor mass that could have been accurately measured in at least 1 dimension ≥20 mm with conventional computed tomography [CT] scan or magnetic resonance imaging [MRI] scan, or ≥10 mm with spiral CT scan using a 5 mm or smaller contiguous reconstruction algorithm). Bone lesions, ascites, peritoneal carcinomatosis or miliary

lesions, pleural or pericardial effusions, lymphangitis of the skin or lung, cystic lesions, or irradiated lesions were not considered measurable.

- Progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0) after 1 prior systemic first-line regimen for mRCC. The prior regimen had to have contained 1 or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s).
- Adequate organ function defined by the following criteria:
    - Absolute neutrophil count ≥1500 cells/mm3;
    - Platelet count ≥75,000 cells/mm3;
    - Hemoglobin ≥9.0 g/dL;
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN), unless there were liver metastases, in which case AST and ALT ≤5.0 × ULN;
    - Total bilirubin ≤1.5 × ULN;
    - Serum creatinine ≤1.5 × ULN or calculated creatinine clearance ≥60 mL/min; and
    - Urinary protein <2+ by urine dipstick. If dipstick was ≥2+, then a 24-hour urine collection could have been done and the patient could have entered only if urinary protein was <2 g per 24 hours.
- Male or female, aged ≥18 years (≥20 years in Japan).
- ECOG performance status of 0 or 1 (See Appendix 4 of Appendix A1).
- Life expectancy of ≥12 weeks.
- At least 2 weeks since the end of prior systemic treatment (4 weeks for bevacizumab + IFN-α), radiotherapy, or surgical procedure with resolution of all treatment-related toxicity to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0) Grade ≤1 or returned to baseline, except for alopecia or hypothyroidism.
- No evidence of pre-existing uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings taken at least 1 hour apart. The baseline systolic BP readings had to be ≤140 mmHg, and the baseline diastolic BP readings had to be ≤90 mmHg. Patients whose hypertension was controlled by antihypertensive therapies were eligible.
- Women of childbearing potential were required to have a negative serum or urine pregnancy test within 3 days before treatment.
- Signed and dated informed consent document indicating that the patient (or legally acceptable representative) had been informed of all pertinent aspects of the study prior to enrollment.
- Willingness and ability to comply with scheduled visits, treatment plans (including willingness to take either axitinib or sorafenib according to randomization), laboratory tests, and other study procedures, including completion of patient-reported outcome (PRO) measures (FKSI and EQ-5D questionnaires).

Exclusion Criteria

- Prior treatment of mRCC with more than 1 systemic first-line regimen.
- Patients treated with any neoadjuvant or adjuvant systemic therapy.
- Major surgery <4 weeks or radiation therapy <2 weeks before starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) was permitted, provided there was at least 1 measurable lesion that had not been irradiated.
- Gastrointestinal abnormalities including:
    - Inability to take oral medication;
    - Requirement for intravenous alimentation;
    - Prior surgical procedures affecting absorption (including total gastric resection);
    - Treatment for active peptic ulcer disease in the past 6 months;
    - Active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia, or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy; or
    - Malabsorption syndromes.
- Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (e.g., grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, delavirdine).
- Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (e.g., carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, St. John's Wort).
- Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access device or prevention of deep venous thrombosis were allowed. Therapeutic use of low molecular weight heparin was allowed.
- Active seizure disorder or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis.
- A serious uncontrolled medical disorder or active infection that would have impaired the ability to receive study treatment.
- Any of the following within the 12 months before study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.
- Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness.
- History of a malignancy (other than RCC), except those treated with curative intent for skin cancer (other than melanoma), in situ breast, or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 2 years.

- Dementia or significantly altered mental status that would have prohibited the understanding or rendering of informed consent and compliance with the requirements of the protocol.
- Female patients who were pregnant or lactating, or men and women of reproductive potential not willing or not able to employ an effective method of birth control/contraception to prevent pregnancy during treatment and for 6 months after discontinuing study treatment. The definition of effective contraception was in agreement with local regulation and based on the judgment of the principal investigator or a designated associate.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that could have increased the risk associated with study participation or study drug administration, or could have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

5.3.5 Duration of Treatment

Patients were treated until the development of progressive disease, unacceptable toxicity, protocol deviation, and/or consent withdrawal. Patients who withdrew from the study for any reason could start other anti-cancer treatments.

Dosing beyond progression of the underlying malignancy with either axitinib or sorafenib was permitted if the patient was experiencing clinical benefit, provided that the treating physician assessed the risk/benefit of taking such an approach and provided that the sum of longest diameters (SLD) of measurable lesions was remaining less than or equal to the baseline SLD per investigator and no alternative treatment was available.

5.3.6 Primary Endpoint Evaluation

The primary endpoint for the trial was PFS as assessed by an Independent Review Committee (IRC). Radiographic images were evaluated by a blinded IRC to assess tumor status and to confirm response and progression of disease. The radiographic images documenting efficacy endpoints were made available to allow the independent review. Two independent reviewers read scans. Differences between the two independent reviewers were to be resolved by a third reviewer (adjudicator) for final determination.

PFS was defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. A stratified (ie, ECOG PS and prior therapy) log-rank test (1-sided, α=0.025) was used to compare PFS between the 2 treatment arms. The median event time for each treatment arm and corresponding 2-sided 95% CI for the median were provided for PFS. The HR and its 95% CI were estimated.

5.3.7 Secondary Endpoint Evaluation

Progression-Free Survival, Investigator Assessment
A secondary evaluation was PFS, as assessed by the investigator. The same procedure used for the primary endpoint was used for this analysis.

Overall Survival
OS was defined as the time from the date of randomization to the date of death due to any cause. OS (in months) was calculated as (date of death − randomization date +1)/30.4 For patients still alive at the time of the analysis, the OS time was censored on the last date they were known to be alive. Patients lacking data beyond randomization had their OS times censored at the date of randomization.

Overall Response Rate (ORR)
ORR was defined as the percent of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST criteria, relative to all randomized patients. Confirmed responses were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. Third-party blinded review and qualification were performed retrospectively by the IRC. Patients who did not have on-study radiographic tumor re-evaluation or who died, progressed, or dropped out for any reason before reaching a CR or PR were counted as nonresponders in the assessment of ORR. A patient who initially met the criteria for a PR and then subsequently became a confirmed CR was assigned a best response of CR.

Duration of Response (DoR)
DoR was defined as the time from the first documentation of objective tumor response (CR or PR), that was subsequently confirmed, to the first documentation of progressive disease (PD) or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. DoR (in months) was calculated as (the end date for DoR − date of first CR or PR that was subsequently confirmed +1)/30.4

Patients who achieved a PR and then a CR had times calculated using the date of the PR as the first day. DoR was only calculated for the subgroup of patients with a confirmed objective tumor response. DoR data were censored on the date of the last tumor assessment documenting absence of progressive disease for patients:

- Who were alive, on-study, and progression free at the time of the analysis;
- Who discontinued treatment without documented disease progression and without death on-study;
- For whom documentation of PD or death occurred after ≥2 consecutive missed tumor assessments (ie, >12 weeks for the first 2 assessments and then subsequently >16 weeks after last tumor assessment); or
- Who were given antitumor treatment, other than the study treatment, prior to documented disease progression.

5.3.8 Major Protocol Amendments

As of the cutoff date for this CSR, the original protocol, dated February 28, 2008, was amended four times. The first amendment occurred before the first patient was enrolled, and the subsequent three amendments were implemented after the first patient was randomized. As this protocol had an SPA agreement, any changes to the protocol required agreement by the FDA; otherwise, the SPA would be null and void. Changes that had a major impact on the *conduct* of the study are summarized below.

Amendment 3, February 10, 2009

- Change the stratification by prior systemic first line regimen to sunitinib-containing regimen vs. bevacizumab-containing regimen vs. temsirolimus-containing regimen vs. cytokine-containing regimen in this order of hierarchy, respectively.
- Revise eligibility criteria #3 to read as follows “Patient must have progressive disease by RECIST after one prior systemic first-line regimen for metastatic renal cell cancer.”
- A stratification variable for prior disease progression would not be necessary, but the method of the documentation of prior disease progression should be captured in the case report form (CRF).
- Collection of scans to document prior disease progression not necessary.

Reviewer comment: This amendment was agreed upon with the FDA.

Amendment 4, November 16, 2009

- Increase planned enrollment from 540 to 650 patients. Due to an underestimation of the dropout rate in the original protocol, the planned enrollment has been increased from the initial target enrollment of 540 patients. The sample estimate was modeled without unblinding of the clinical data and in consultation with the Data Monitoring Committee (DMC).
- Revise population PK sample collection for patients randomized to the axitinib arm to allow drawing of PK samples from patients who have already completed Cycle 3 without PK sampling. These patients may have PK samples taken at any one cycle beyond the Cycle 3.
- Allow collection of UGT1A1 and other pharmacogenomic samples at anytime during the study if they were not collected at Cycle 1 Day 1.
- Revise, and allow flexibility for, the pre-dose thyroid function tests to be performed within 7 days of Cycle 1 Day 1.
- Revise Section 9.2.1 (Analysis for Primary Endpoint) of the protocol in line with protocol Amendment 3 dated 10 February 2009 (which was previously agreed by FDA; see FDA’s meeting minutes dated 3 February 2009), wherein pre-study scans confirming progression were no longer protocol requirements. The guidelines for analysis of primary end point will not include sensitivity analysis for patients with confirmed prior progression compared to those who did not have confirmed prior progression based on pre-study scan data.

- Update the Patient Reported Outcome Analysis to include time to deterioration analysis.

Reviewer comment: This protocol amendment was submitted 12/11/2009 with the admission by the sponsor that the amendment would be implemented prior to FDA approval, as the applicant believed enrollment was occurring too rapidly to wait for FDA review of the amendment. The first change involving increasing the planned enrollment from 540 to 650 patients should have been discussed with FDA before implementation; however, the number of events required for analysis of either the primary endpoint of PFS or the key secondary endpoint of OS was not changed. Therefore, this amendment would not change the analysis or interpretation of results from this trial.

6 Review of Efficacy

Efficacy Summary

This application is based mainly on the primary endpoint of PFS in a single, randomized trial comparing axitinib with sorafenib in 723 patients with advanced RCC after failure of one prior systemic regimen.

- The applicant reports an improvement in median PFS of two months in patients treated with axitinib compared to the active comparator sorafenib with a hazard ratio of 0.67 (95% CI: 0.54, 0.81).
- The final overall survival analysis shows no difference between the two arms with a hazard ratio of 0.97.
- The efficacy data is supported by three Phase 2, single-arm trials in patients with advanced RCC who have had failure of either sorafenib or cytokines with response rates ranging from 22% to 50%.

6.1 Indication

The proposed indication is for the treatment of patients with advanced renal cell carcinoma

6.1.1 Methods

Clinical review is based primarily on the CSR for the A4061032 trial, the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant and literature review of advanced RCC.

6.1.2 Demographics

The demographics of the pivotal study (b) (4) are presented in Table 6. The median age was 61 years on both arms. The majority of patients on both arms where White (77% on axitinib, 74.3% on sorafenib). Three hundred fifty-four patients (98.1%) on the

axitinib arm entered with an ECOG performance status of 0 or 1 compared to 360 patients (99.4%) on the sorafenib arm. Over half the patients on both arms had MSKCC risk group status of intermediate or poor (56.2% on axitinib, 59.1% on sorafenib).

Table 6: Patient Baseline Characteristics

	Axitinib N=361	**Sorafenib N=362**
Median Age, Years (Min, Max)	61 (20, 82)	61 (22, 80)
Sex (%)		
Male	265 (73.4)	258 (71.3)
Female	96 (26.6)	104 (28.7)
ECOG PS (%)		
0	192 (54)	200 (55.2)
1	162 (44.9)	160 (44.2)
>1	1 (<1)	0
Geographic Region		
North America	88 (24.4)	98 (27.1)
Europe	187 (51.8)	170 (47)
Asia	73 (20.2)	79 (21.8)
Other	13 (3.6)	15 (4.1)
Race		
White	278 (77)	269 (74.3)
Black	1 (<1)	4 (1.1)
Asian	77 (21.3)	81 (22.4)
Other	5 (1.4)	13 (3.6)
MSKCC Risk Group		
Favorable	158 (43.8)	148 (40.9)
Intermediate	199 (55.1)	210 (58)
Poor	4 (1.1)	4 (1.1)

Sunitinib and cytokines were the two most frequent prior treatments patients received for mRCC prior to enrolling in this trial. However, in North America and Europe, patients were almost twice as likely to receive sunitinib as prior treatment than cytokines (see Table 8).

Table 7: Prior Treatment

Prior Treatment	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Sunitinib	194 (53.7)	195 (53.9)
Bevacizumab	29 (8)	30 (8.3)
Temsirolimus	12 (3.3)	12 (3.3)
Cytokine	126 (34.9)	125 (34.5)

Table 8: Prior treatment in North America and Europe

Treatment	North America N=186	Europe N=357	Total N=543
Sunitinib	126 (67.7)	180 (50.4)	306 (56.4)
Cytokine	37 (19.9)	125 (34.5)	162 (29.8)

6.1.3 Subject Disposition

Table 9: Patient Disposition

	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Disease Progression	160 (44.3)	180 (49.7)
Adverse Event	22 (6.1)	33 (9.1)
Death	12 (3.3)	13 (3.6)
Lost To Follow-Up	1 (0.3)	3 (0.8)
Protocol Violation	4 (1.1)	2 (0.6)
Other	7 (1.9)	10 (2.6)
Patient Refused Further Treatment	10 (2.8)	7 (1.9)
Global deterioration of health status	9 (2.5)	9 (2.5)

Applicant's Analysis

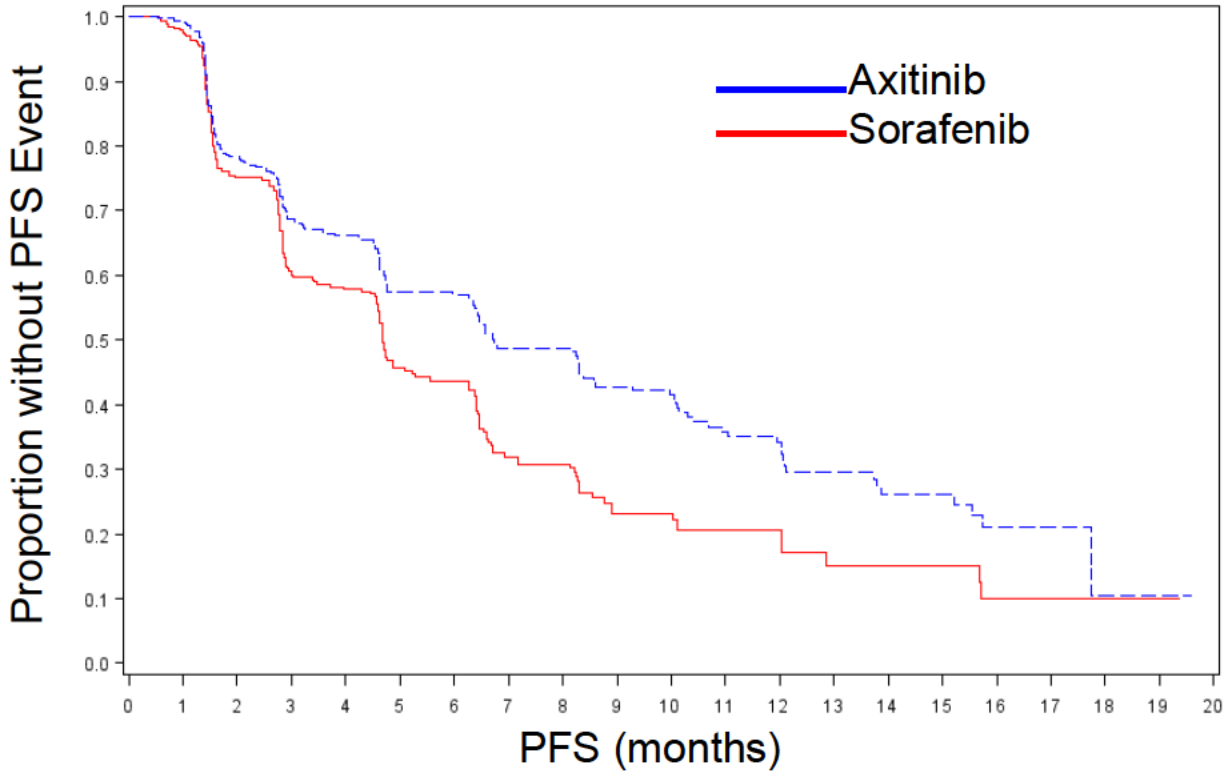
6.1.4 Analysis of Primary Endpoint(s)

PFS as assessed by the IRC was the primary efficacy endpoint. At the time of the final analysis, 402 patients had experienced a PFS event. The results for PFS are shown in Table 10 and Figure 2 below.

Table 10: Progression-free Survival by IRC

	Axitinib N=361	Sorafenib N=362
Number of patients with progression (%)	180 (49.9)	200 (55.2)
Number of patients with deaths (%)	12 (3.3)	10 (2.8)
PFS event (%)	192 (53.2)	210 (58)
Median PFS in months (95% CI)	6.7 (6.3-8.6)	4.7 (4.6-5.6)
Hazard ratio (95% CI)	0.67 (0.54-0.81)	
P-value	<0.0001	

Figure 2: Kaplan-Meier Plot of Progression-free Survival



The median PFS as assessed by investigator was 8.3 months (95% CI 6.6-9) for axitinib and 5.6 months (95% CI 4.7-6.5)) for sorafenib, with a hazard ratio of 0.66.

Table 11: Discordance between IRC and Investigators

Discordance Type	**Axitinib N=361**	**Sorafenib N=362**
Event discordance* (%)	83 (23)	89 (24.6)
Time discordance		
Early discordance§ (%)	61 (37.7)	72 (39.6)
Late discordance† (%)	101 (62.4)	110 (60.4)
Overall discordance rate (%)	162 (44.9)	182 (50.3)

* IRC or investigator assesses PFS, other does not
§ Investigator date earlier than IRC date, includes event discordance
† IRC date earlier than investigator date, includes event discordance

There was discordance between the IRC and investigators in nearly a quarter of the patient population over whether a PFS event occurred. In combination with time discordance, the IRC and investigators overall discordance rate approached 50%.

Table 12: IRC versus Investigator Assessment of PFS

	Axitinib N=361		**Sorafenib N=362**	
	IRC	Investigator	IRC	Investigator
Number of patients with progression (%)	180 (49.9)	187 (51.8)	200 (55.2)	214 (59.1)
Number of patients with deaths (%)	12 (3.3)	14 (3.9)	10 (2.8)	13 (3.6)
PFS event (%)	192 (53.2)	201 (55.7)	210 (58)	227 (62.7)
Median PFS in months (95% CI)	6.7 (6.3-8.6)	8.3 (6.6-9)	4.7 (4.6-5.6)	5.6 (4.7-6.5)
Hazard ratio (95% CI)	IRC 0.67 (0.54-0.81)		INV 0.66 (0.54-0.8)	
P-value	IRC <0.0001		INV <0.0001	

There was little difference between the IRC and investigator assessment of the number of patients with a PFS event, with the investigators assessing slightly more patients with a PFS event. Although the investigators assessed PFS later than the IRC, the hazard ratio was nearly identical for both analyses.

Table 13: Rates of Discordance between IRC Reviewers per Applicant

	Axitinib N=360	Sorafenib N=361	Total N=721
Total event discordance rate* (%)	76 (21.1)	86 (23.8)	162 (22.5)
Total timing discordance rate† (%)	59 (16.4)	67 (18.6)	126 (17.5)
Early discordance rate§ (%)	29 (49.2)	37 (55.2)	66 (52.4)
Late discordance rate# (%)	30 (50.9)	30 (44.8)	60 (47.6)
Overall discordance rate¤ (%)	135 (37.5)	153 (42.2)	288 (39.9)

*Total event discordance: IRC Radiologist 1 and Radiologist 2 disagree whether or not there was an occurrence of a PD event
†Total timing discordance: IRC Radiologist 1 and Radiologist 2 agree on the occurrence of a PD event but differ on their assessment of the timing
§Early discordance rate: For cases where timing of PD is assessed differently, adjudicator agrees with earlier timepoint of IRC Radiologist 1 or Radiologist 2
#Late discordance rate: For cases where timing of PD is assessed differently, adjudicator agrees with later timepoint of IRC Radiologist 1 or Radiologist 2
¤Overall discordance rate: IRC Radiologist 1 and Radiologist 2 disagree on either occurrence of a PD event or timing of PD event

The event discordance rate between IRC radiologists was 22.5% for the entire study. Approximately 18% of patients were assessed differently for timing of a PFS event, with slightly more assessments of early discordance versus late discordance. Overall, the discordance rate between IRC radiologists was 40% for the trial.

Reviewer comment: The discordance rate between IRC radiologists is more alarming than the discordance rate between the IRC and the investigators. In the case of discordance between investigators and IRC, different lesions may have been chosen as target lesions, and investigators may have more clinical information at hand to assess PFS. However, the discordance rate between IRC radiologists is more troubling. If two independent radiologists disagree on nearly a quarter of the patient population as to whether a progression event occurred, this indicates to this reviewer that PFS may not be a reliable measurement of disease in this particular clinical setting.

Table 14: Patients Censored for PFS

	Axitinib N=361	**Sorafenib N=362**
Total number patients censored	169	152
Alive, on study and progression free	148	115
No baseline or on-study assessments	14	28
At least 1 on-study assessment and discontinued treatment prior to documented PD	4	4
PD or death occurred after ≥2 consecutive missed assessments	1	3
PR occurred after given new anti-cancer therapy	2	0
Withdrew consent	0	0
Lost to follow-up	0	2

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary efficacy endpoints included OS, ORR as assessed by the IRC and duration of response.

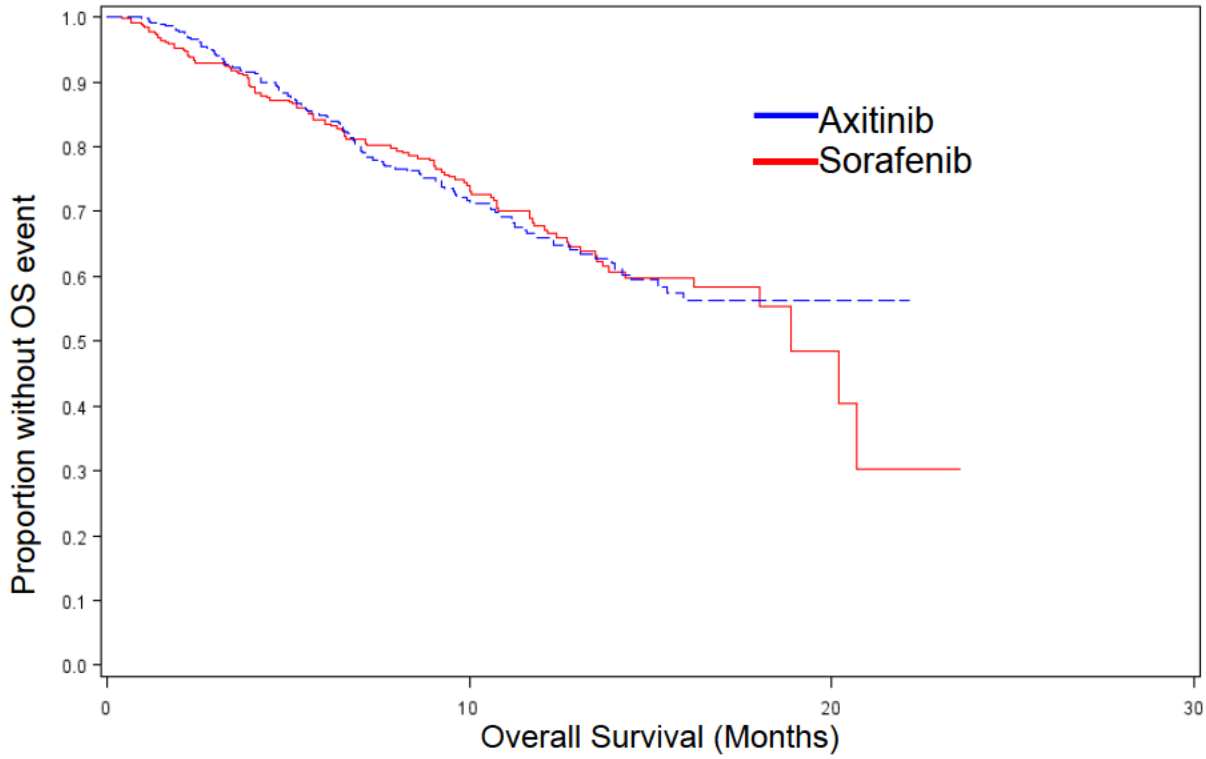
At the time of the NDA submission, the interim analysis for overall survival occurred at 223 events, which is approximately 53% of the events needed for the final OS analysis. As seen in Table 15 and Figure 3 below, there was no difference in OS at the interim analysis. As per protocol the primary overall survival analysis was the stratified Log Rank, using the pre-randomization stratification factors.

Table 15: Interim Overall Survival

	Axitinib N=361	**Sorafenib N=362**
Deaths (%)	113 (31.2)	110 (30.4)
Median OS in months (95% CI)	NR (15.9, NR)	18.9 (18, NR)
Hazard Ratio (95% CI)	1.009 (0.77-1.31)	
P-value	0.53	

*Not reached

Figure 3: Kaplan-Meier Plot of Interim Overall Survival

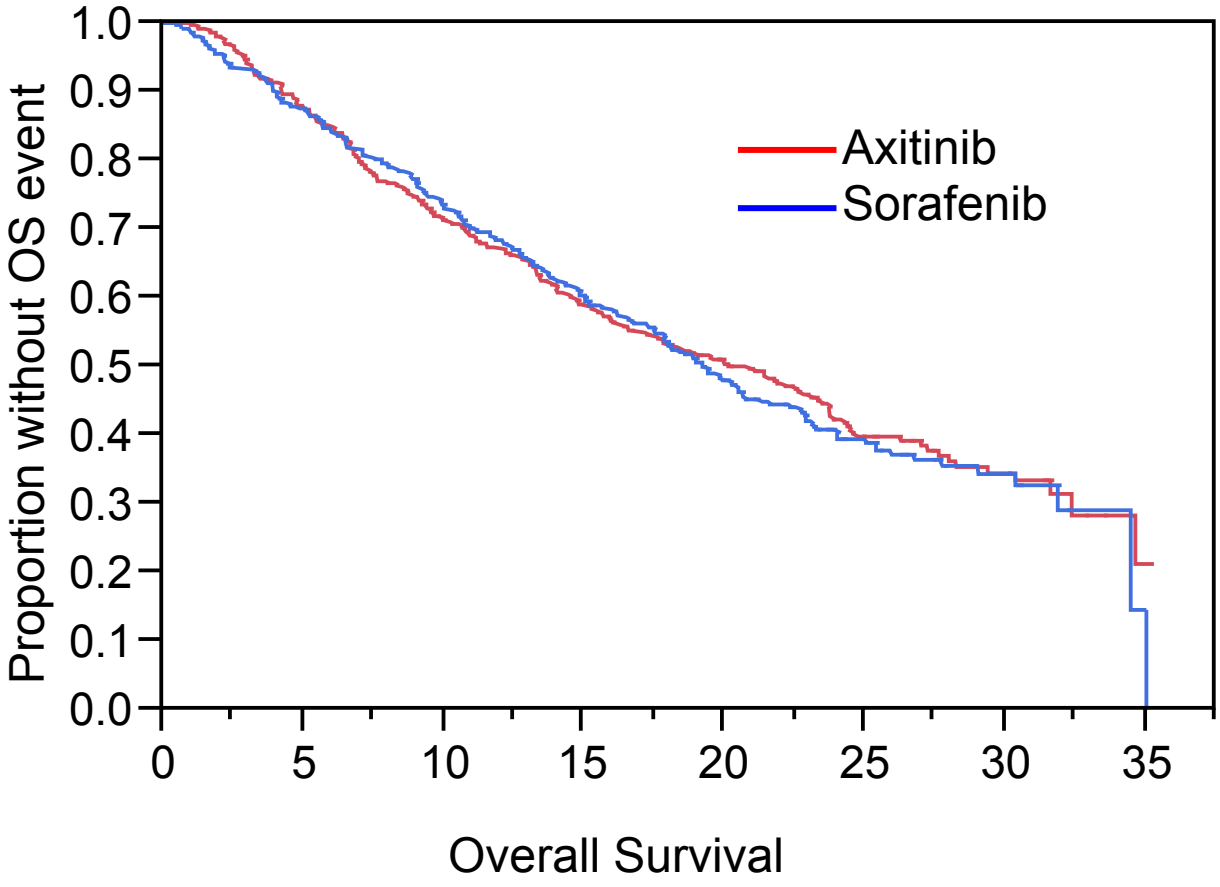


The data for the final analysis of OS was submitted to the Agency on 12/14/2011. The final analysis included 423 deaths overall, with 210 deaths on the axitinib arm and 213 deaths on the sorafenib. As seen in the table and figure below, there were no differences between the two arms in terms of overall survival.

Table 16: Final Overall Survival

	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	

Figure 4: Kaplan-Meier Plot of Final Overall Survival



The response rate (CR + PR) by blinded IRC assessment was 70 (19.4%) patients in the axitinib arm and 34 (9.4%) patients in the sorafenib arm. There were no CRs in either arm. Among patients previously treated with sunitinib, 22 patients on the axitinib arm had a PR compared to 15 on the sorafenib arm. Among patients previously treated with a cytokine regimen, 41 patients on the axitinib arm had a PR compared to 17 on the sorafenib arm. The median duration of response was 11 months (7.4, NE) in the axitinib arm and 10.6 months (8.8, 11.5) in the sorafenib arm.

Reviewer Comment: Despite a two-month difference in PFS and a doubling of response rate, axitinib has not shown an overall survival advantage compared to sorafenib. Sorafenib itself has never demonstrated a survival benefit in the advanced RCC population. The pivotal trial for sorafenib compared to placebo was terminated early based on interim PFS results, and patients on the placebo arm were allowed to cross over to the sorafenib arm. Thus the evidence for the efficacy of axitinib is a modest PFS difference of two months compared to sorafenib and no survival advantage compared to this active control.

6.1.6 Other Endpoints

The sponsor has several exploratory endpoints associated with study A4061032. Due to the exploratory nature of the endpoints, the lack of data quality associated with these endpoints, the lack of labeling claims associated with these endpoints, and the lack of statistical power to support the findings from these endpoints, a thorough review was not performed.

6.1.7 Subpopulations

The applicant performed multiple subpopulation analyses, including PFS results according to the stratification factor of prior systemic therapy. For prior sunitinib or cytokine therapy, results are summarized in Table 17 below. For prior bevacizumab or temsirolimus, the number of patients was too small in these two groups to permit an analysis with any reliability. The difference between arms for median PFS in patients previously treated with cytokines is 5.6 months, whereas the difference for patients previously treated with sunitinib is 1.4 months.

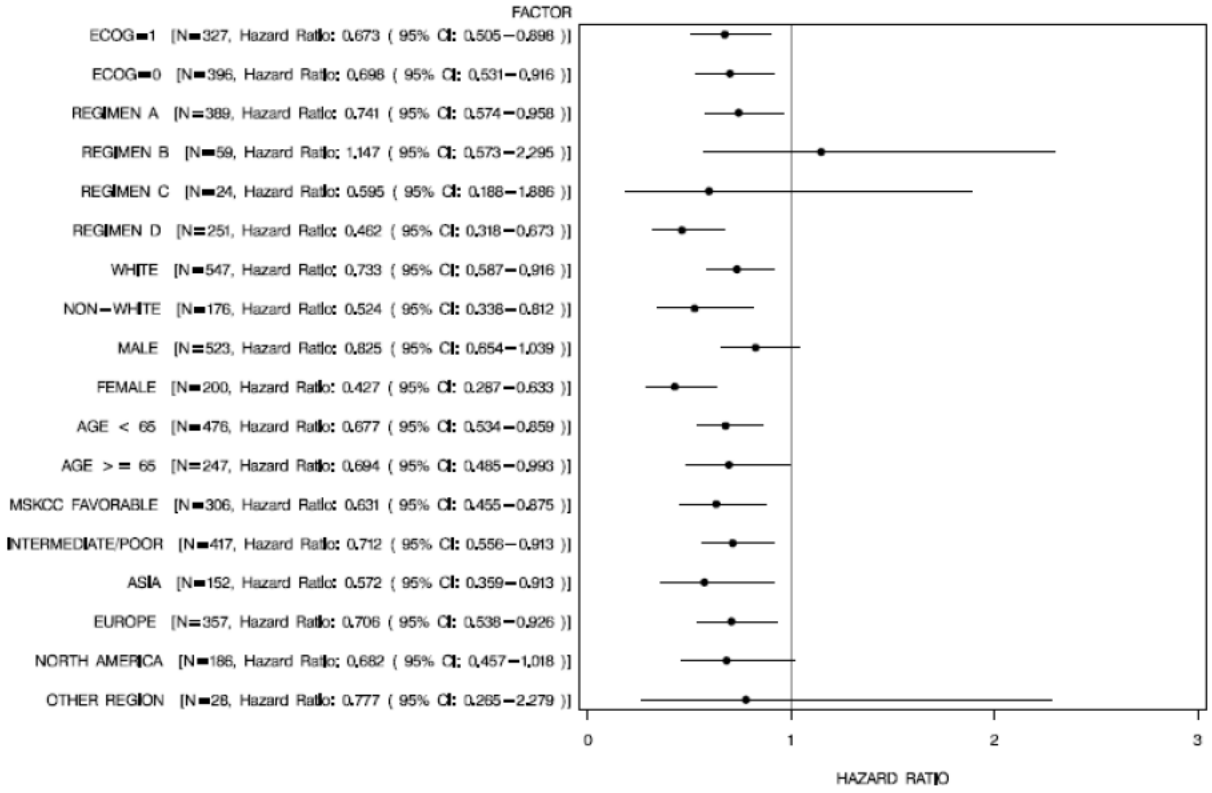
Table 17: Progression-free Survival Stratified by Prior Treatment

	Axitinib (N=361)	**Sorafenib (N=362)**
PFS events (%)		
Sunitinib	117 (32.4)	120 (33.1)
Cytokine	50 (13.9)	69 (19.1)
Median PFS in months (95% CI)		
Sunitinib	4.8 (4.5-6.4)	3.4 (2.8-4.7)
Cytokine	12.1 (10.1-13.9)	6.5 (6.3-8.3)
Hazard ratio (95% CI)		
Sunitinib	0.74 (0.57-0.96)	
Cytokine	0.46 (0.32-0.68)	
P-value		
Sunitinib	0.01	
Cytokine	<0.0001	

Reviewer Comment: This analysis of PFS by prior first-line treatment demonstrates that most of the benefit seen with axitinib is after first-line treatment with a cytokine. In the U.S., cytokines are rarely used as first-line therapy before sunitinib as sunitinib showed an advantage over IFN-α in treatment-naïve patients. Therefore, for the vast majority of patients in the U.S., the benefit of axitinib after sunitinib is paltry at best.

The applicant also provided information regarding other subgroup analyses in terms of treatment effect for axitinib versus sorafenib. These analyses are presented in the figure below.

Figure 5: Forest Plot PFS Hazard Ratios in Subgroups (from applicant's CSR)



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The randomized, Phase 3 trial allowed dose escalation of axitinib from 5 mg BID up to a maximum of 10 mg BID. The applicant performed an analysis comparing the PFS for patients who received a total of ≤10 mg to patients who received a total of >10 mg daily. The median PFS was 8.3 months for patients who received ≤10 mg daily and 6.6 months for patients who received >10 mg daily compared with 4.7 months in the sorafenib arm.

Reviewer comment: This was a post-hoc analysis of a subset that was not pre-specified, thus this data must be interpreted with caution and viewed as hypothesis-generating.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Supportive Studies

The applicant submitted results from three single-arm, open-label, Phase 2 trials in patients with advanced RCC who had failed one prior systemic therapy.

Study A10461012 enrolled 52 patients with advanced RCC who were refractory to prior cytokine therapy. Patients received axitinib 5 mg po BID and were allowed to dose escalate up to 10 mg BID under the same guidelines as were in place in the Phase 3 AXIS trial. The primary endpoint was objective response (ORR) rate as assessed by investigator. The ORR was 44.2%, with two patients who achieved a complete response and 21 patients who achieved a partial response.

Study A4061035 enrolled 64 patients with advanced RCC who were refractory to prior cytokine therapy. Patients received axitinib 5 mg po BID and were allowed to dose escalate up to 10 mg BID under the same guidelines as were in place in the Phase 3 AXIS trial. The primary endpoint was objective response (ORR) rate as assessed by an independent review committee. The ORR was 50%, with all 32 patients achieving a partial response.

Study A4061023 enrolled 62 patients with advanced RCC who were refractory to prior sorafenib therapy. Patients received axitinib 5 mg po BID and were allowed to dose escalate up to 10 mg BID under the same guidelines as were in place in the Phase 3 AXIS trial. The primary endpoint was objective response (ORR) rate as assessed by investigator. The ORR was 22.6%, with all 14 achieving a partial response.

Reviewer comment: These single-arm, Phase 2 trials in patients who had received prior therapy with either sorafenib or a cytokine demonstrate that axitinib has activity in this disease. The response rates are among the highest reported in advanced RCC; in particular, Study A4061035 had an ORR of 50% as assessed by an IRC and Study A10461012 had two patients who achieved a CR. This demonstrates that axitinib not only prolongs PFS as established in the Phase 3 AXIS trial but actually decreases tumor burden.

6.1.10.2. Data Integrity

There were a total of 27 major protocol violations in the Phase 3 trial. The highest number (8, 30%) of major protocol deviations were for patients who were randomized despite presence of brain metastasis at baseline. The major protocol violations are noted in the table below.

Table 18: Protocol Deviations

Protocol Deviation	Number of Patients
Previously received sorafenib as first-line therapy	1
Stratified incorrectly as prior bevacizumab-containing group; should have been stratified as prior temsirolimus-containing group	4
CT scan of the brain during screening not performed	2
Baseline scans missing.	2
Received two prior lines of therapy prior to enrollment.	4
Randomized despite lack of histologically confirmed component of clear cell subtype of renal cell carcinoma.	1
Randomized despite violation of exclusion criterion number 10 (negative pregnancy test)	3
Presence of brain metastasis.	8
Patient took axitinib 20 mg BID for 4 days rather than protocol-specified 10 mg BID	1
Enrolled despite elevated urine protein	1

Reviewer's Comment: It is believed that these protocol violations do not impact the overall integrity of site-generated data as related to primary safety and efficacy analyses. See also section 3.2: Compliance of Good Clinical Practice.

7 Review of Safety

Safety Summary

The safety profile of axitinib is comparable to that of other drugs in the same class of small molecule inhibitors of the VEGF pathway in terms of the types of adverse events observed. Common adverse events include diarrhea, nausea, fatigue, asthenia, hypertension, dysphonia and dermatologic adverse events. Less common serious adverse events include arterial and venous thrombotic events, gastrointestinal perforation, bleeding events, hypothyroidism, proteinuria and reversible posterior leukoencephalopathy syndrome. These serious adverse events previously have been identified for this class of drugs, thus none are unique to axitinib.

7.1 Methods

The Phase 3 trial A4061032 included safety assessments at baseline, every two weeks in the first cycle, on day 1 ± four days of every subsequent 28-day cycle, at the end of treatment and at a follow-up visit (28 days after the last dose). Serious adverse events that had not recovered completely by the end of treatment were to be followed until resolution.

At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, blood pressure, physical examination, laboratories (hematology, chemistries, liver enzymes and function, thyroid function, urine evaluation, pregnancy test), assessment of ECOG PS and ECG. Safety assessments performed at the start of each cycle were the same as at baseline, except thyroid function tests were required every other cycle starting at cycle 4. Post-treatment follow-up for survival was to occur every 3 months until at least three tears after randomization of the last patient.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The ten completed trials in patients with cancer for which the applicant submitted safety data are summarized in Table 19. These ten trials were included in the integrated summary of safety (ISS), while data from A4061032 also were presented separately.

Table 19: Summary of Axitinib Trials in Safety Analysis

Study #	Population	Design	Dose (mg B.I.D.)	# Any Axitinib	# Axitinib 5 mg B.I.D.
A4060010	Advanced Solid Tumors	Dose Escalation/Food Effects	2-30 QD to BID	36	20
A4061011	Advanced NSCLC	Activity	5	32	32
A4061012	2nd-line Advanced RCC after Cytokine	Activity	5	52	52
A4061014	Advanced Thyroid Cancer	Activity	5	60	60
A4061015	Metastatic Melanoma	Activity	5	32	32
A4061022	Advanced Solid Tumors	Activity	5	12	12
A4061023	2nd-line Advanced RCC after Sorafenib	Activity	5	62	62
A4061032	2nd-line Advanced RCC	Phase 3 Axitinib vs. Sorafenib	5	359	359
A4061035	2nd-line Advanced RCC after Cytokine	Activity	5	64	64
A4061044	Advanced Solid Tumors	PK	5	6	6
Total Exposed				**715**	**715**
ISS Total					**715**
ISS RCC					**545**

The Integrated Summary of Safety (ISS) included a total of 715 patients treated with axitinib. Among these 715 patients, 699 (97.8%) received the same dose and schedule as used in the Phase 3 trial A4061032.

Reviewer Comment: *The majority of patients with advanced RCC who received axitinib on the 5 mg twice daily dosing schedule were treated on the Phase 3 trial A4061032. For this reason, the safety analyses, other than those provided in section 7.1.3 below, will focus primarily on data from this trial.*

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 13.1) was used to characterize all adverse events in the Phase 3 trial A4061032. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data from ten trials were included in the integrated safety database (see Section 7.1.1, Table 19 above). The rates of the most common (>15% of patients) treatment-emergent adverse events in the entire ISS database were compared to event rates in axitinib-treated patients on A4061032. This analysis is presented in the table below.

Table 20: Incidence of Most Common Treatment-Emergent Adverse Events (≥15%) in the ISS Database

	A4061032 N=359		ISS N=715	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Fatigue	146 (40.7)	41 (11.4)	416 (58.2)	90 (12.6)
Diarrhea	197 (54.9)	38 (10.6)	407 (56.9)	65 (9.1)
Hypertension	146 (40.7)	56 (15.6)	378 (52.9)	168 (23.5)
Decreased appetite	123 (34.3)	17 (4.7)	311 (43.5)	28 (3.9)
Nausea	117 (32.6)	9 (2.5)	287 (40.1)	15 (2.1)
Dysphonia	114 (31.8)	0	269 (37.6)	0
Constipation	74 (20.6)	4 (1.1)	210 (29.4)	6 (<1)
Weight decreased	89 (24.8)	8 (2.2)	209 (29.2)	22 (3.1)
Palmar-plantar erythrodysaesthesia syndrome	98 (27.3)	18 (5)	205 (28.7)	46 (6.4)
Cough	59 (16.4)	3 (<1)	192 (26.9)	9 (1.3)
Dyspnea	57 (15.9)	11 (3.1)	180 (25.2)	37 (5.2)
Vomiting	86 (24)	12 (3.3)	178 (24.9)	17 (2.4)
Headache	53 (14.8)	2 (<1)	169 (23.6)	12 (1.7)
Arthralgia	56 (15.6)	7 (1.9)	166 (23.2)	18 (2.5)
Hypothyroidism	69 (19.2)	1 (<1)	159 (22.2)	1 (<1)
Back pain	51 (14.2)	9 (2.5)	140 (19.6)	19 (2.7)
Stomatitis	55 (15.3)	5 (1.4)	133 (18.6)	14 (2.0)
Pain in extremity	46 (12.8)	2 (<1)	126 (17.6)	9 (1.3)
Proteinuria	41 (11.4)	11 (3.1)	124 (17.3)	25 (3.5)
Abdominal pain	54 (15)	10 (2.8)	121 (16.9)	24 (3.4)
Insomnia	30 (8.4)	0	117 (16.4)	1 (<1)
Dyspepsia	36 (10)	0	114 (15.9)	1 (<1)
Rash	45 (12.5)	1 (<1)	111 (15.5)	2 (<1)
Mucosal inflammation	55 (15.3)	5 (1.4)	109 (15.2)	6 (<1)

The above information was verified using the ADVERS (Adverse Event) dataset from the A4061032 trial and the ADVERS dataset from the Complete Single Agent Analysis dataset.

The incidences of the most common treatment-emergent adverse events occurring in axitinib-treated patients in the Phase 3 trial were similar to the incidences in the integrated safety database.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to axitinib and comparator therapy in the phase 3 trial A4061032 is summarized in Table 21 below.

Table 21: 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%)

The above information was verified using the DISCON (Subject Summary Analysis) and DRGSUM (Treatment Summary) datasets.

Axitinib arm patients had a longer duration of treatment than did comparator arm patients. The relative dose intensity approached 100% on both arms. The number of dose reductions on the dose reductions was higher on the sorafenib arm; however, the number of patients with dose interruptions was similar between arms.

Reviewer comment: Although it would appear from the data in Table X above that patients treated with axitinib tolerated treatment better both by dose-per-day measures and relative dose intensity, this does not take into account the dose escalation that was permitted for axitinib. Approximately 36.8% of patients on axitinib arm had dose

escalations. In fact, the mean dose intensity for axitinib was 102% and ranged from 32.4% to 194.4%, thus artificially inflating other parameters in this chart. Furthermore, it would appear that more patients had dose reductions on the sorafenib arm. However, if the dose reductions for patients who had initial dose escalations and subsequent dose reductions are taken into account, the rate of dose reductions appears similar between arms. The only firm conclusion that can be drawn from this table is that patients treated with axitinib had a longer duration of treatment than those treated with sorafenib.

Patients on the axitinib arm were started on 5 mg twice daily dosing (10 mg total daily). They were permitted to dose escalate under certain circumstances up to a maximum of 10 mg twice daily (20 mg total daily). Table 22 below summarizes the number of patients who had dose escalations and reductions and to which levels during the trial.

Table 22: Summary of Axitinib Dose Escalations and Reductions

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

The above information was verified using the DISCON (Subject Summary Analysis) dataset.

Adverse events leading to dose modification in ≥3 patients on either arm are summarized in Table 23 below. In addition, discontinuations due to adverse events occurred in 9.7% of axitinib arm patients and 13% of sorafenib arm patients (see section 7.3.3).

Table 23: Events Leading to Dose Modification (≥3 Patients on Either Arm)

	Axitinib N=359		Sorafenib N=355	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Diarrhea	69 (19.2)	33 (9.2)	42 (11.8)	19 (5.4)
Hypertension	59 (16.4)	31 (8.6)	31 (8.7)	15 (4.2)
Fatigue	32 (8.9)	26 (7.2)	22 (6.2)	10 (2.8)
Asthenia	29 (8.1)	12 (3.3)	8 (2.3)	3 (<1)
Decreased appetite	25 (7)	8 (2.2)	8 (2.3)	5 (1.4)
Palmar-plantar erythrodysasthesia syndrome	24 (6.7)	16 (4.5)	75 (21.1)	53 (14.9)

Vomiting	24 (6.7)	6 (1.7)	12 (3.4)	1 (<1)
Proteinuria	24 (6.7)	10 (2.8)	6 (1.7)	4 (1.1)
Nausea	19 (5.3)	5 (1.4)	9 (2.5)	1 (<1)
Mucosal inflammation	12 (3.3)	5 (1.4)	7 (2)	2 (<1)
Stomatitis	12 (3.3)	5 (1.4)	5 (1.4)	1 (<1)
Weight decreased	11 (3.1)	3 (<1)	2 (<1)	0
Dehydration	10 (2.8)	9 (2.5)	2 (<1)	2 (<1)
Abdominal pain	8 (2.2)	3 (<1)	4 (1.1)	0
General physical health deterioration	6 (1.7)	3 (<1)	4 (1.1)	2 (<1)
Rash	5 (1.4)	1 (<1)	31 (8.7)	14 (3.9)
Back pain	5 (1.4)	2 (<1)	3 (<1)	2 (<1)
Constipation	5 (1.4)	1 (<1)	2 (<1)	0
Dyspnea	5 (1.4)	3 (<1)	2 (<1)	1 (<1)
Dizziness	5 (1.4)	2 (<1)	1 (<1)	0
Pyrexia	4 (1.1)	0	10 (2.8)	1 (<1)
Pain in extremity	4 (1.1)	2 (<1)	6 (1.7)	2 (<1)
Cough	4 (1.1)	2 (<1)	3 (<1)	1 (<1)
Pulmonary embolism	4 (1.1)	4 1.1	1 (<1)	1 (<1)
Hypothyroidism	4 (1.1)	1 (<1)	0	0
Abdominal pain upper	4 (1.1)	1 (<1)	0	0
Dysphonia	4 (1.1)	0	0	0
Arthralgia	3 (<1)	2 (<1)	5 (1.4)	3 (<1)
Pneumonia	3 (<1)	3 (<1)	4 (1.1)	4 (1.1)
Chest pain	3 (<1)	1 (<1)	3 (<1)	1 (<1)
Headache	3 (<1)	1 (<1)	3 (<1)	0
Hypotension	3 (<1)	2 (<1)	3 (<1)	2 (<1)
Dysphagia	3 (<1)	0	1 (<1)	0
Renal failure acute	3 (<1)	3 (<1)	1 (<1)	1 (<1)
Pneumothorax	3 (<1)	1 (<1)	1 (<1)	0
Pharyngitis	3 (<1)	0	0	0
Anemia	1 (<1)	0	6 (1.7)	6 (1.7)
ALT increased	2 (<1)	1 (<1)	4 (1.1)	3 (<1)
AST increased	1 (<1)	1 (<1)	4 (1.1)	3 (<1)
Hyponatraemia	1 (<1)	1 (<1)	4 (1.1)	4 (1.1)
Rectal hemorrhage	2 (<1)	0	3 (<1)	0
Pain	1 (<1)	0	3 (<1)	3 (<1)
Nasopharyngitis	1 (<1)	0	3 (<1)	0
Hemoptysis	1 (<1)	0	3 (<1)	1 (<1)
Pleural effusion	1 (<1)	1 (<1)	3 (<1)	3 (<1)

The above information was verified using the ADVERS (Adverse Event) dataset.

Diarrhea and hypertension accounted for the majority of dose modifications on the axitinib arm, while sorafenib patients more often had dose modifications for palmar-plantar erythrodysasthesia syndrome and diarrhea. Hypothyroidism, upper abdominal pain, dysphonia and pharyngitis each accounted for dose modification in at least 3 patients on the axitinib arm but none on the comparator arm.

7.2.2 Explorations for Dose Response

There is evidence of an exposure-response relationship for several AEs, including hypertension, diarrhea and fatigue. See Section 7.5.1 of this review and the Clinical Pharmacology Review.

7.2.3 Special Animal and/or In Vitro Testing

See the summary of the pharmacology/toxicology review in section 4.3.

7.2.4 Routine Clinical Testing

See sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the clinical pharmacology review in section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Axitinib is an inhibitor of the vascular endothelial growth factor receptors (VEGF-R1, VEGFR-2 and VEGFR-3). Other drugs in this class include sunitinib, sorafenib and pazopanib. The labels for these drugs include warnings and precautions for hepatotoxicity (sunitinib and pazopanib), left ventricular dysfunction (sunitinib), hypertension, hemorrhagic events, arterial thrombotic events (pazopanib), gastrointestinal perforation (pazopanib and sorafenib), wound healing, thyroid dysfunction (sunitinib), QT interval prolongation, adrenal function (sunitinib) and proteinuria (pazopanib). Hypertension, hemorrhagic events, arterial thrombotic events, gastrointestinal perforation, thyroid dysfunction, hepatotoxicity and proteinuria are discussed in Section 7.3.4. QT interval prolongation is discussed in Section 7.4.4.

7.3 Major Safety Results

7.3.1 Deaths

More total deaths occurred on the axitinib arm than on the sorafenib arm, and more deaths on the axitinib arm were associated with treatment-emergent adverse events

than on the sorafenib arm (2.5% versus 1.1%). Deaths within 28 days of last drug dose were 9.7% on the axitinib arm and 6.5% on the sorafenib arm. All deaths occurring in the safety population are included in the table below.

Table 24: All Safety Population Deaths on A4061032

	Axitinib N = 359	Sorafenib N = 355
Total Deaths	113 (31.5%)	109 (30.7%)
Deaths within 28 Days of Last Dose	35 (9.7%)	23 (6.5%)
TEAEs	8 (2.2%)	5 (1.4%)
Progression	26 (7.2%)	14 (3.9%)
Other	1 (<1%)	4 (1.1%)
Unknown	1	2
Other Events	0	2
Deaths in follow-up*	78 (21.7%)	86 (24.2%)
TEAEs	0	0
Progression	65 (18.1%)	72 (20.3%)
Other	13 (3.6%)	14 (3.9%)
Unknown	3	7
Other Events†	10	7

*More than 28 days after last dose of study drug to clinical data cutoff of August 31, 2010.
† Other events on the axitinib arm included acute renal failure, acute myocardial infarction, cardiopulmonary failure, interstitial lung disease, intrapulmonary and intrabronchial bleeding, and respiratory hemorrhage.

Eight axitinib-treated patients experienced a grade 5 TEAE other than disease progression within 28 days of the last dose of study drug. Details for these eight patients are provided in the table below. Two deaths were considered related to study drug: patients 11571002 and 11561004.

Table 25: All Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 28 Days of Last Dose on the Axitinib Arm

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Onset AE (Day)	Death (Day)	Days from Last Dose to Death
10721001	Cerebrovascular Accident	459	459	459	0
10771006	General Weakness	196	195	198	2
10971003	Cardiorespiratory Failure	252	252	256	4
12571002	Cardiorespiratory Failure	59	59	61	2
10991007	Dyspnea	212	211	211	1
11551002	Pulmonary Embolism	195	215	215	20
11571002	Sepsis	144	141	144	2
11561004	GI hemorrhage	204	206	206	2

Patient 10721001 was a 79 yo female with hypertension who previously had presented with transient symptoms of aphasia; she died suddenly of a CVA following acute onset of neurologic symptoms.

Patient 10771006 was a 72 yo male who began to have symptoms of weakness and difficulty in getting out of bed for three days prior to his sudden death at home; no autopsy was performed, and the last efficacy assessment a month prior had shown stable disease.

Patient 10971003 was a 78 yo male with a PMH significant for chronic renal failure, hypertension and diabetes mellitus presented with a four-day history of abdominal pain, nausea, vomiting, diarrhea and positive peritoneal signs; he died shortly after hospitalization. An autopsy revealed diffuse metastases in the lungs, splenic capsule, and the wall of the large intestine, which caused partial obstruction and development of extensive ascites; the cause of death was noted as cardiopulmonary failure secondary to progressive disease.

Patient 12571002 was a 63 yo male with a PMH significant for hypertension, type 2 diabetes mellitus and hypercholesterolemia who was admitted to an outside hospital with severe pain and generalized worsening of condition; he died of cardiopulmonary failure two days later, and no autopsy was performed.

Patient 10991007 was a 62 yo female who began to complain of dyspnea a day prior to her death; her family reported to the investigator that she died at home the next day, and no autopsy was performed.

Patient 11551002 was a 59 yo male who discontinued treatment with axitinib on day 195 for disease progression; he began treatment with everolimus three days prior to his death. On the morning of his death, he complained of chest symptoms including pain and "bubbling;" he collapsed and died shortly afterwards of a presumed pulmonary embolus.

Patient 11571002 was a 79 yo male who died of sepsis at home; the patient had been diagnosed with a urinary tract infection three days prior and placed on antibiotics.

Patient 11561004 was a 69 yo male who had a PMH significant for deep venous thrombosis and was receiving low-molecular weight heparin at the time of randomization. The patient discontinued axitinib secondary to disease progression. Two days later, he was admitted to the hospital with severe abdominal pain and found to have a large intra-abdominal hematoma; he died later the same day with cause of death noted as gastrointestinal hemorrhage.

Reviewer comment: For the patients described above, it is highly unlikely that the deaths of patients 10971003 and 11551002 are related to axitinib. For patient 10971003, disease progression clearly was the cause of death. For patient 11551002, he had been off study drug for over three weeks and had started a new systemic treatment. Additionally, patient 11571002, who died secondary to sepsis presumably originating in the urinary tract, the infection is not likely related to axitinib, and the patient had normal neutrophil counts prior to the onset of infection. However, the remaining five deaths may be related to axitinib. Axitinib is associated with arterial thrombotic and venous thrombotic events and bleeding, and three of these patients had events that could be ascribed to these. For the remaining events, insufficient information is available to rule in or out any relatedness to axitinib.

Five sorafenib-treated patients experienced Grade 5 TEAEs other than disease progression within 28 days of the last dose of study drug. Details for these patients are provided in the table below. Three deaths were considered related to study drug: patients 10991010, 11491007 and 12251001.

Table 26: All Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 28 Days of Last Dose on the Sorafenib Arm

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Onset AE (Day)	Death (Day)	Days from Last Dose to Death
10621005	Cerebrovascular Accident	248	248	254	6
10991010	General Deterioration	172	172	172	0
11091007	Duodenal ulcer hemorrhage	33	32	35	2
11491007	Gastrointestinal bleed	12	12	19	7
12251001	Retroperitoneal hemorrhage	17	17	20	3

Patient 10621005 was a 70 yo male with no significant PMH who was suffered a CVA during a hypertensive crisis and subsequently died.

Patient 10991010 was a 72 yo male with a PMH significant for hypertension and previous myocardial infarction who briefly interrupted treatment for asthenia and loss of appetite approximately two months before his death. The patient's family informed the investigator of the patient's death secondary to general deterioration; no autopsy was performed, and no additional information was provided.

Patient 11091107 was a 71 yo male with a history of diabetes mellitus and arthritis secondary to gout who had been started on prednisolone five days prior to the duodenal ulcer hemorrhage secondary to worsening arthritis; the patient died secondary to duodenal ulcer hemorrhage.

Patient 11491007 was a 71 yo female who was admitted to the hospital after a fall at home and developed urinary sepsis while hospitalized; subsequently, the patient developed hyponatremia, hypokalemia, atrial fibrillation, hypotension and ischemia of distal extremities. The day before her death, the patient had a cardiac arrest and was arrhythmic for a short period of time; after resuscitation and a transfer to the intensive care unit, gastrointestinal bleeding concomitant with hypotension and decreased hemoglobin were noted, and the patient died the following day.

Patient 12251001 was a 63 yo female with a PMH significant for bilateral pulmonary embolism who was receiving anticoagulation at the time of randomization; she collapsed at home and upon admission to the hospital was found to have a large retroperitoneal hemorrhage that was continuing to bleed and a hemoglobin level of 4.8 g/dL. An embolization procedure was performed, but the patient's condition deteriorated, and she died two days later.

Reviewer comment: The death secondary to a CVA is potentially related to sorafenib. However, the other four deaths either did not have enough information to rule in or out relatedness or had extenuating circumstances or concomitant medications that likely contributed to death.

Deaths not attributed to disease progression or a TEAE are summarized in the table below.

Table 27: Deaths not Attributed to Disease Progression or TEAE

Patient ID	Treatment arm	Cause of Death	Last Dose (Day)	Death (Day)	Days from Last Dose to Death
10971004	Sorafenib	Unknown	32	52	20
10981004	Sorafenib	Unknown	403	421	18
10981014	Sorafenib	Unknown	193	218	25
11791005	Sorafenib	Unknown	410	419	9
10981015	Axitinib	Unknown	478	484	6

Patient 10981004 was a 61 yo male who was hospitalized at a local hospital 20 days prior to his death for a respiratory tract hemorrhage; further details were not provided by the investigator. The patient's family informed the investigator that the patient died during this hospitalization; cause of death is unknown, and an autopsy was not performed.

Patient 10981014 was a 67 yo male who permanently discontinued sorafenib for the adverse event of left hemiparesis 25 days before his death; the investigator noted his death as due to unknown cause, and an autopsy was not performed.

Patient 11791005 was a 40 yo male with no significant PMH who discontinued treatment on day 410 for a serious adverse event (SAE), according to the case report form (CRF). The SAE is not documented in the CRF, but the investigator notes that disease progression was not present. The patient died of an unknown cause nine days later; no autopsy was performed.

Patient 10981015 was a 63 yo male with PMH significant for asthma. The patient experienced Grade 3 dehydration on Day 478 and temporarily interrupted axitinib treatment. However, the family informed the investigator that the patient died suddenly on Day 484; cause is unknown, and an autopsy was not performed. However, the last recorded efficacy assessment in the patient's CRF reveals progressive disease per the investigator with no explanation as to why axitinib was continued despite disease progression.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events occurred in 34.8% of patients on the axitinib arm and 32.7% on the sorafenib arm. SAEs that occurred in ≥1% of patient on either arm are summarized in the table below.

Table 28: Nonfatal Serious Adverse Events (≥1% on Either Arm)

	Axitinib N=359	**Sorafenib N=355**
Any SAE (%)	125 (34.8)	116 (32.7)
Disease progression	27 (7.5)	16 (4.5)
Dehydration	9 (2.5)	1 (<1)
Diarrhea	8 (2.2)	5 (1.4)
Pyrexia	7 (1.9)	3 (<1)
Dyspnea	5 (1.4)	3 (<1)
Pulmonary Embolism	5 (1.4)	1 (<1)
Pneumonia	4 (1.1)	4 (1.1)
Pneumothorax	4 (1.1)	1 (<1)
Fatigue	4 (1.1)	0
Pleural Effusion	3 (<1)	5 (1.4)
Pain	2 (<1)	5 (1.4)
General Physical Health Deterioration	2 (<1)	4 (1.1)
Myocardial Infarction	1 (<1)	4 (1.1)
Hypotension	1 (<1)	4 (1.1)
Anemia	0	4 (1.1)

Other than disease progression, dehydration and diarrhea were the most common serious adverse events on the axitinib arm.

7.3.3 Dropouts and/or Discontinuations

Reasons for treatment discontinuation are summarized in the table below. Disease progression was the most common reason for treatment discontinuation on both arms. More patients discontinued treatment due to adverse events on the sorafenib arm than on the axitinib arm.

Table 29: Reasons for Treatment Discontinuation per Applicant

	Axitinib N = 359	Sorafenib N = 355
Disease Progression	160 (44.6%)	180 (50.7%)
Adverse Event	22 (6.1%)	33 (9.3%)
Other Reason	3 (<1%)	9 (2.5%)
Global Deterioration of Health Status	9 (2.5%)	9 (2.5%)
Refuse Treatment	10 (2.8%)	7 (2%)
Protocol Violation	4 (1.1%)	2 (<1%)
Death	12 (3.3%)	13 (3.7%)

Specific adverse events leading to treatment discontinuation are summarized in the table below.

Table 30: 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

The above information was verified using the ADVERS (Adverse Event) dataset.

The rate of discontinuation due to adverse event was low on both arms. There was little overlap in the adverse events that led to discontinuation both between the two treatment arms and within each treatment arm. The reasons for discontinuation mirror the most common Grade 3-4 adverse events overall for the Phase 3 trial.

7.3.4 Significant Adverse Events

Bleeding

There were 58 events of bleeding on the axitinib arm compared to 64 on the sorafenib arm. The overwhelming majority were less than or equal to Grade 2 events. However, episodes of clinically relevant bleeding occurred on both arms. There was one Grade 4 event of cerebral hemorrhage on the axitinib arm, as well as one Grade 3 event of hematuria and one Grade 3 event of hemoptysis. There were Grade 5 bleeding events on both arms: one gastric hemorrhage on the axitinib arm, and one event each of duodenal ulcer hemorrhage, gastrointestinal hemorrhage and retroperitoneal hemorrhage on the sorafenib arm. This is a known class effect for VEGF pathway inhibitors. There were no additional deaths from hemorrhage in patients treated with axitinib in the ISS.

Table 31: 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

Reviewer comment: This known class effect for VEGF pathway inhibitors was not unexpected. In this trial, there were more Grade 3-5 events on the sorafenib arm (11) versus the axitinib arm (5); thus axitinib did not show any more propensity to be associated with bleeding events that an approved agent.

Hypothyroidism

Hypothyroidism was reported in 69 (19.2%) patients treated with axitinib and 30 (8.5%) patients treated with sorafenib. There was one Grade 3 event of hypothyroidism on the axitinib arm. No patients discontinued treatment secondary to hypothyroidism.

Reviewer comment: The rate of hypothyroidism on the axitinib arm was more than double that on the sorafenib. However, nearly all of the events were Grade 2 or lower and managed with thyroid hormone replacement when required. It appears that the

unique side effect profile of axitinib results in a higher rate of hypothyroidism, which is a known effect in this class of agents.

Arterial thrombotic events

Arterial thrombotic events are another known side effect of VEGF pathway inhibitors. There were no myocardial infarctions on the axitinib arm and two on the sorafenib arm. There was one Grade 3 event of retinal artery occlusion on the axitinib. There were three transient ischemic attacks on the axitinib arm and none on the sorafenib arm; however, there was no cerebral ischemia or stroke reported on the axitinib arm and two events on the sorafenib arm. See Table 32 below for details. In the ISS population, there was one Grade 5 event secondary to cardiac arrest and two Grade 5 events secondary to cerebrovascular accident. In the ISS, there were 19 (2.7%) arterial thrombotic events, including myocardial infarction (2), myocardial ischemia (3), retinal artery occlusion (1) cerebral infarction (1), lacunar infarction (1), transient ischemic attack (7) and cerebrovascular accident (4).

Table 32: 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

Venous thrombotic events

Venous thrombotic events are a known side effect of the VEGF pathway inhibitors. There was one Grade 5 event of pulmonary embolism on the axitinib arm and no Grade 5 events on the sorafenib arm. Overall, there were 15 (4.2%) venous thrombotic events on the axitinib arm and two (<1%) on the sorafenib arm (see Table 33 below for details). In the ISS database for axitinib, there were two Grade 5 events of pulmonary embolism. In 715 patients in the ISS, there were 32 (4.5%) venous thrombotic events, including retinal vein occlusion (2), retinal vein thrombosis (1), mesenteric vein thrombosis (1), pulmonary embolism (13), deep vein thrombosis (4), jugular vein thrombosis (2), subclavian vein thrombosis (1), thrombosis(4), vena cava thrombosis(1), venous thrombosis (1), and venous thrombosis limb (1).

Table 33: 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

Gastrointestinal perforation and fistulas

There was one event of intestinal perforation on the axitinib arm and none on the sorafenib arm. Additionally, there was one event of intestinal fistula on the axitinib arm and none on the sorafenib arm. In the ISS database, there were 5 (1%) events of intestinal perforation and four events of fistulas.

Reviewer comment: It appears that intestinal perforation, although rare, is a more prominent event for patients treated with axitinib than other VEGF receptor small molecule inhibitors. However, the rate of gastrointestinal perforation for axitinib is lower than that observed for bevacizumab in clinical trials.

Hypertension

Hypertension was a frequent adverse event in this randomized trial and is a common side effect within the VEGF-R inhibitor class. There were 152 (42.3%) events on the axitinib arm and 109 (30.7%) events on the sorafenib arm, with more Grade 3/4 events on the axitinib arm at 60 (16.7%) versus 41 (11.5%) on the sorafenib arm. There were two events of hypertensive crisis; one was a Grade 4 event and one was a Grade 3 event. Additionally, one patient discontinued axitinib secondary to hypertension, and 59 (16.4%) patients had dose modifications secondary to hypertension. In the ISS population, there were 381(53.3%) episodes of hypertension, including 171 (23.9%) Grade 3/4.

Table 34: Hypertensive Adverse Events

	Axitinib N=359		Sorafenib N=355	
	All Gr (%)	Gr 3-5 (%)	All Gr (%)	Gr 3-5 (%)
Blood pressure increased	3 (1)	1 (<1)	3 (1)	2 (1)
Accelerated hypertension	1 (<1)	1 (<1)	0	0
Diastolic hypertension	0	0	1 (<1)	0
Hypertension	146 (40.7)	56 (15.6)	104 (29.3)	39 (11)
Hypertensive crisis	2 (1)	2 (1)	0	0
Systolic hypertension	0	0	1 (<1)	0

Reverse Posterior Leukoencephalopathy Syndrome (RPLS)
There was one Grade 3 event of RPLS on the axitinib arm and none on the sorafenib arm. This patient had axitinib held temporarily; upon resolution of the RPLS, axitinib was restarted. There were a total of two cases of RPLS reported in the ISS database.

Proteinuria and Renal Failure
There were 41 (11.4%) events of proteinuria on the axitinib arm and 26 (7.3%) events on the sorafenib arm, with 11 (3.1%) and 6 (1.7%) Grade 3/4 events, respectively. There were seven (1.9%) events of renal failure in axitinib-treated patients, with 5 (1.4%) Grade 3/4 events. Two events of renal failure occurred in the context of sepsis. One patient had multiple episodes of proteinuria and renal insufficiency, though temporally they were not related. Another two events of renal failure were related to prerenal azotemia that progressed to renal failure. One patient had proteinuria documented on Day 1 of the first cycle of axitinib treatment; proteinuria continued intermittently throughout treatment, and renal failure occurred in the setting of diarrhea and vomiting. In another patient, the renal failure occurred in the context of a urinary tract infection and hypovolemia without proteinuria. In the ISS database, there were 124 (17.3%) proteinuria events, with 25 (3.5%) Grade 3/4 events. There were a total of 13 (1.8%) events of renal failure.

Reviewer Comment: Although there were some events of renal failure in axitinib-treated patients, the majority of cases had concomitant events that likely contributed to the failure. There were only two patients in whom both proteinuria and renal failure occurred.

Hepatic adverse events
There were a number of abnormalities with liver enzyme levels observed; please see Section 7.4.2. below for details. There were two events of hepatic function impaired and no events of hepatic failure on the axitinib arm. One Grade 3 event occurred after the patient had discontinued treatment for progressive disease, and the investigator attributed the impaired hepatic function to disease progression with new metastatic liver lesions. The other event of Grade 3 impaired hepatic function was demonstrated by

elevated liver enzymes that resolved with temporary interruption of axitinib; the patient restarted axitinib without recurrence of the impaired hepatic function. In the ISS database, there were 13 (1.8%) events of impaired hepatic function and no events of hepatic failure.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common grade 1-4 adverse events in axitinib-treated patients on A4061032 were: diarrhea (55%), hypertension (41%), fatigue (41%), decreased appetite (35%), nausea (33%), dysphonia 32%), palmar-plantar erythrodysesthesia (hand-foot) syndrome (27%), weight decreased (25%), vomiting (24%), asthenia (21%), and constipation (21%).

Table 35: Grade 1-4 TEAEs (≥5% of Patients on Either Treatment Arm)

	Axitinib N=359		**Sorafenib N=355**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Blood and lymphatic system disorders				
Anemia	17 (4.7)	4 (1.1)	44 (12.4)	14 (3.9)
Endocrine disorders				
Hypothyroidism	69 (19.2)	1 (0.3)	30 (8.5)	0
Gastrointestinal disorders				
Abdominal pain	54 (15)	10 (2.8)	38 (10.7)	3 (0.8)
Abdominal pain upper	31 (8.6)	3 (0.8)	14 (3.9)	1 (0.3)
Constipation	74 (20.6)	4 (1.1)	76 (21.4)	3 (0.8)
Diarrhea	197 (54.9)	38 (10.6)	192 (54.1)	26 (7.3)
Dyspepsia	36 (10)	0	9 (2.5)	0
Flatulence	19 (5.3)	0	8 (2.3)	0
Nausea	117 (32.6)	9 (2.5)	80 (22.5)	4 (1.1)
Stomatitis	55 (15.3)	5 (1.4)	44 (12.4)	1 (0.3)
Vomiting	86 (24)	12 (3.3)	63 (17.7)	3 (0.8)

General disorders and administration site conditions				
Asthenia	75 (20.9)	19 (5.3)	51 (14.4)	9 (2.5)
Chest pain	22 (6.1)	2 (0.6)	16 (4.5)	4 (1.1)
Fatigue	146 (40.7)	41 (11.4)	114 (32.1)	18 (5.1)
Mucosal inflammation	55 (15.3)	5 (1.4)	44 (12.4)	2 (0.6)
Edema peripheral	17 (4.7)	1 (0.3)	22 (6.2)	3 (0.8)
Pain	22 (6.1)	2 (0.6)	17 (4.8)	6 (1.7)
Pyrexia	27 (7.5)	3 (0.8)	38 (10.7)	1 (0.3)
Investigations				
Lipase increased	9 (2.5)	2 (0.6)	19 (5.4)	12 (3.4)
Weight decreased	89 (24.8)	8 (2.2)	74 (20.8)	5 (1.4)
Metabolism and nutrition disorders				
Decreased appetite	123 (34.6)	17 (4.7)	103 (29)	13 (3.7)
Dehydration	23 (6.4)	13 (3.6)	9 (2.5)	4 (1.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	56 (15.6)	7 (1.9)	39 (11)	5 (1.4)
Back pain	51 (14.2)	9 (2.5)	51 (14.4)	6 (1.7)
Muscle spasms	11 (3.1)	1 (0.3)	18 (5.1)	1 (0.3)
Musculoskeletal pain	19 (5.3)	2 (0.6)	23 (6.5)	1 (0.3)
Myalgia	25 (7)	3 (0.8)	10 (2.8)	0
Pain in extremity	46 (12.8)	2 (0.6)	50 (14.1)	2 (0.6)
Nervous system disorders				
Dizziness	33 (9.2)	2 (0.6)	16 (4.5)	0
Dysgeusia	39 (10.9)	0	29 (8.2)	0
Headache	53 (14.8)	2 (0.6)	40 (11.3)	0
Psychiatric disorders				
Insomnia	30 (8.4)	0	18 (5.1)	0
Renal and urinary disorders				
Proteinuria	41 (11.4)	11 (3.1)	26 (7.3)	6 (1.7)
Respiratory, thoracic and mediastinal disorders				
Cough	59 (16.4)	3 (0.8)	63 (17.7)	2 (0.6)
Dysphonia	114 (31.8)	0	50 (14.1)	0
Dyspnea	57 (15.9)	11 (3.1)	46 (13)	11 (3.1)
Epistaxis	22 (6.1)	0	15 (4.2)	0
Oropharyngeal pain	20 (5.6)	0	19 (5.4)	0

Skin and subcutaneous tissue disorders				
Alopecia	14 (3.9)	0	117 (33)	0
Dry skin	36 (10)	0	38 (10.7)	0
Erythema	9 (2.5)	0	36 (10.1)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	98 (27.3)	18 (5)	181 (51)	57(16.1)
Pruritus	24 (6.7)	0	44 (12.4)	0
Rash	45 (12.5)	1 (0.3)	112 (31.5)	14 (3.9)
Vascular disorders				
Hypertension	146 (40.7)	56(15.6)	104 (29.3)	39 (11)
Hypotension	19 (5.3)	3 (0.8)	10 (2.8)	4 (1.1)

The above information was verified using the ADVERS (Adverse Event) dataset. Minor discrepancies (<1%) exist between this table and applicant's analysis.

Tinnitus, dry mouth, gingival pain, hemorrhoids, nasopharyngitis, rhinitis, blood creatinine increased, blood TSH increased each occurred more frequently in the axitinib-treated patients (≥2% difference between arms) but are not included in the table above because they occurred in <5% of patients on either arm.

The most common grade 3-4 adverse events are included in the table below. The most common grade 3-4 adverse events in axitinib-treated patients on A4061032 were: hypertension (16%), fatigue (11%), diarrhea (11%), asthenia (5%), palmar-plantar erythrodysaesthesia syndrome (5%) and decreased appetite (5%).

Table 36: Grade 3-4 TEAEs (≥1% of Patients on Either Arm)

	Axitinib N=359	**Sorafenib N=355**
	Grade 3-4 (%)	Grade 3-4 (%)
Hypertension	56 (15.6)	39 (11)
Fatigue	41 (11.4)	18 (5.1)
Diarrhea	38 (10.6)	26 (7.3)
Asthenia	19 (5.3)	9 (2.5)
Palmar-plantar erythrodysaesthesia syndrome	18 (5)	57 (16.1)
Decreased appetite	17 (4.7)	13 (3.7)
Dehydration	13 (3.6)	4 (1.1)
Vomiting	12 (3.3)	3 (<1)
Proteinuria	11 (3.1)	6 (1.7)
Dyspnea	11 (3.1)	11 (3.1)
Abdominal pain	10 (2.8)	3 (<1)
Nausea	9 (2.5)	4 (1.1)
Back pain	9 (2.5)	6 (1.7)

Weight decreased	8 (2.2)	5 (1.4)
Arthralgia	7 (1.9)	5 (1.4)
Pulmonary embolism	7 (1.9)	2 (<1)
Stomatitis	5 (1.4)	1 (<1)
Mucosal inflammation	5 (1.4)	2 (<1)
Hyperkalaemia	5 (1.4)	3 (<1)
Anaemia	4 (1.1)	14 (3.9)
Constipation	4 (1.1)	3 (<1)
Pneumonia	4 (1.1)	6 (1.7)
General physical health deterioration	3 (<1)	4 (1.1)
Hemoglobin decreased	3 (<1)	4 (1.1)
Pleural effusion	3 (<1)	7 (2)
Hypotension	3 (<1)	4 (1.1)
Chest pain	2 (<1)	4 (1.1)
Pain	2 (<1)	6 (1.7)
Lipase increased	2 (<1)	12 (3.4)
Hyponatraemia	2 (<1)	7 (2)
Neutropenia	1 (<1)	4 (1.1)
Alanine aminotransferase increased	1 (<1)	6 (1.7)
Aspartate aminotransferase increased	1 (<1)	4 (1.1)
Hypercalcaemia	1 (<1)	4 (1.1)
Rash	1 (<1)	14 (3.9)
Hypophosphataemia	0	7 (2)

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in the table below.

Table 37: Laboratory Grade 1-4 Adverse Events in >10% in Either Arm

	Axitinib N=359*		**Sorafenib N=355***	
	Gr 1-4 %	Gr 3-4 %	Gr 1-4 %	Gr 3-4 %
ALT Increased	21.8	<1	21.7	2.2
ALP Increased	29.8	1.1	33.5	1.1
AST Increased	20.2	<1	24.8	1.1
Bicarbonate decreased	43.7	<1	43	0
Creatinine Increased	54.8	0	40.9	<1
Hyperglycemia	27.6	2.1	22.6	1.6
Hyperkalemia	15.3	3.1	9.8	3.1
Hypernatremia	17.1	<1	12.9	<1
Hypoalbuminemia	14.8	<1	17.6	<1
Lipase increased	26.6	4.7	45.7	14.7
Amylase Increased	24.9	1.8	32.6	1.6
Hypoglycemia	10.8	<1	8.2	<1
Hyponatremia	13.3	4.4	11.4	2.2
Hypophosphatemia	13.3	2.2	46.8	15.5
Hypocalcemia	39	1.4	58.8	2.2
Hemoglobin Decreased	34.7	<1	51.6	3.8
Lymphocytes Decreased	33.1	3.3	35.8	4.2
Platelets Decreased	15	<1	14.9	0
White blood cells Decreased	10.6	0	15.5	<1

*Denominator varies depending on data available

7.4.3 Vital Signs

Vital signs recorded during the active treatment period were examined for extreme abnormalities. Among 359 axitinib-treated patients in the safety population, none had a recorded temperature >39°C. Twenty-four (6.7%) axitinib-treated patients had a heart rate recorded at less than 50 beats per minute (bpm), and 11 (3.1%) patients had a heart rate recorded at > 120 bpm. Elevated systolic blood pressure (BP) was commonly reported, with systolic BP $\geq$ 150 mm HG and systolic BP $\geq$ 170 mm HG in 130 (36.2%) patients and 36 (10%) patients, respectively. Elevated diastolic blood pressures also commonly were reported, with diastolic BP ≥90 mm Hg and diastolic BP ≥100 mm Hg reported for 241 (67.1%) and 91 (25.3%) patients, respectively.

7.4.4 Electrocardiograms (ECGs)

The applicant conducted a dedicated QT study titled "Population Pharmacokinetic/Pharmacodynamic Evaluation of the Effect of AG-013736 Alone, and in Combination with Ketoconazole, on QT Intervals in Healthy Volunteers." The following is excerpted from the review conducted by the QT-IRT team.

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 Tmax of axitinib) following a single dose of 5 mg axitinib in the absence and presence of 400 mg ketoconazole.

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

7.4.5 Special Safety Studies/Clinical Trials

In a dedicated hepatic impairment trial compared to patients with normal hepatic function, systemic exposure following a single dose of axitinib was similar in patients with baseline mild hepatic impairment (Child-Pugh class A) and higher in patients with baseline moderate hepatic impairment (Child-Pugh class B). The final labeling for axitinib will recommend no starting dose adjustment for patients with mild hepatic impairment (Child-Pugh class A) but will recommend a starting dose decrease of 50% for patients with moderate hepatic impairment (Child-Pugh class B). Axitinib was not studied in patients with severe hepatic impairment (Child-Pugh class C), and no recommendations can be made for this patient population.

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, mild, moderate or severe renal impairment did not have a significant effect on the clearance of axitinib (see Pharmacometrics review for details). The baseline renal function data included in the analysis was collected from 381 patients 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. The final labeling for axitinib will recommend no starting dose adjustment for patients with pre-existing mild to severe renal impairment and that caution should be used in patients with end-stage renal disease (CLcr < 15 mL/min).

7.4.6 Immunogenicity

The following adverse event preferred terms were considered possibly related to immunogenicity: chills, drug hypersensitivity, hypersensitivity, hypotension, pruritis, rash, rash erythematous, respiratory failure, swelling face, wheezing and Stevens-Johnson syndrome. For each of these preferred terms, events that occurred within three days of axitinib administration were reviewed. Six patients experienced events within three days of starting axitinib, four patients with pruritus and two patients with chills. All were Grade 1, with the exception of one episode of Grade 2 chills. No action was taken with regard to axitinib for any of these patients, and all AEs resolved. Upon review of the case report forms for each of these patients, none of these AEs appear to be drug hypersensitivity reactions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

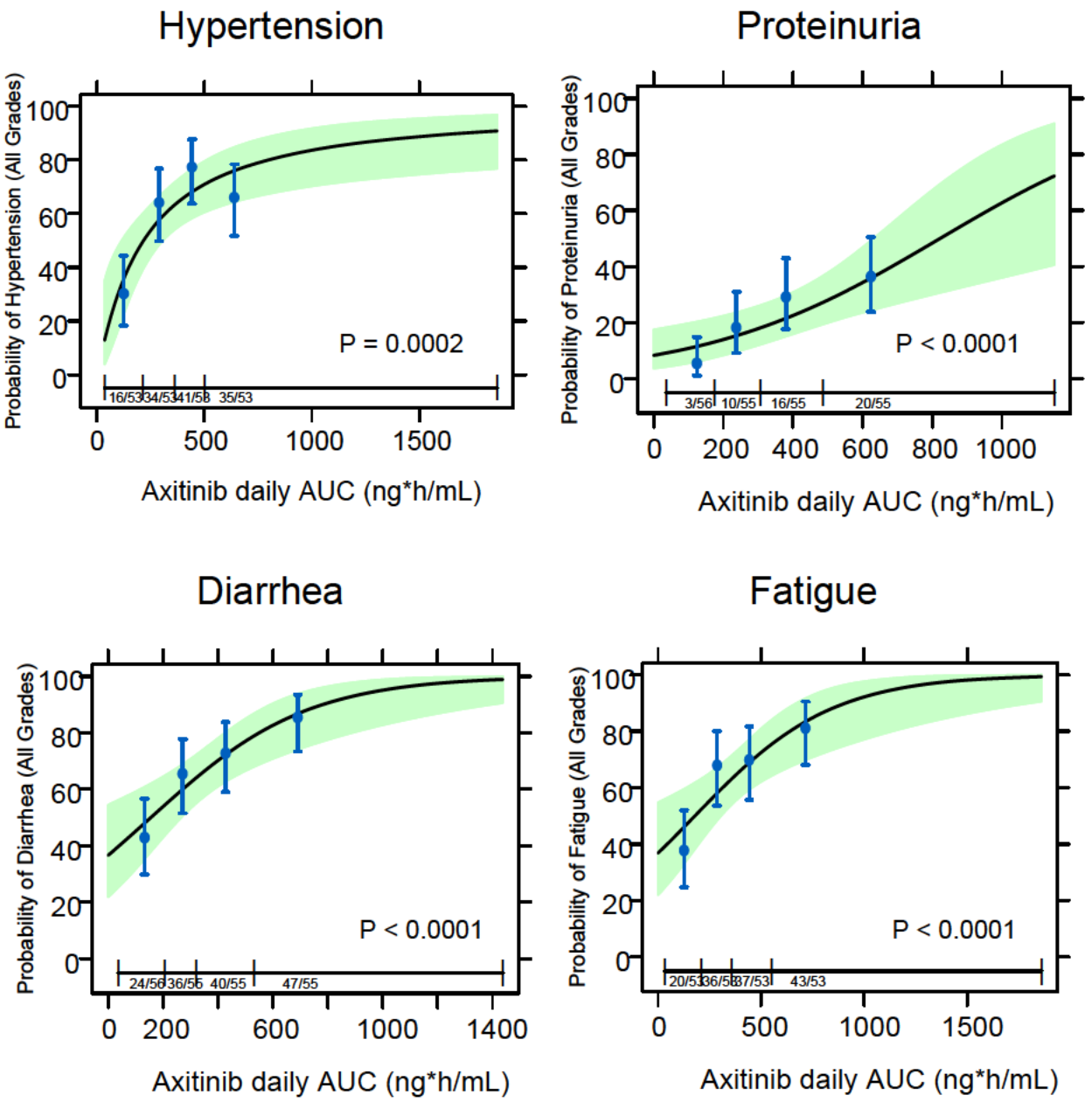
The following is excerpted from the Pharmacometics review:

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 (see figure below). The exposure-response relationship was significant after adjusting for other

confounding baseline factors such as age, baseline ECOG, patient type and baseline blood pressure.

The applicant 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 6: Exposure-Adverse Event Relationship



7.5.2 Drug-Demographic Interactions

Rates of grade 1-4 adverse events were examined by age (<65 years of age versus ≥65 years of age) and are presented in Table X below. Overall, grade 1-4 adverse event rates were similar in patients <65 years old and ≥65 years old. However, several grade 1-4 adverse events occurred more frequently (≥5% difference) in older patients, while others occurred more frequently in the younger patients. The grade 1-4 events that

occurred more frequently in patients ≥65 years old were anemia, palmar-plantar erythrodsyaesthesia syndrome, decreased weight, dysphonia, fatigue, decreased appetite and diarrhea.. The adverse events that occurred more frequently in patients <65 years old were hypertension, dry skin, myalgia and pyrexia.

Table 38: Grade 1-4 Adverse Events by Age

	Age	
	< 65 years N=238	**≥ 65 years N=123**
Hypertension	106 (44.5)	40 (32.5)
Dry skin	29 (12.2)	7 (5.7)
Myalgia	21 (8.8)	4 (3.3)
Pyrexia	22 (9.2)	5 (4.1)
Anemia	7 (2.9)	10 (8.1)
Palmar-plantar erythrodysaesthesia syndrome	59 (24.8)	39 (31.7)
Weight decreased	52 (21.8)	37 (30.1)
Dysphonia	68 (28.6)	46 (37.4)
Fatigue	86 (36.1)	60 (48.8)
Decreased appetite	70 (29.4)	53 (43.1)
Diarrhea	118 (49.6)	79 (64.2)

Overall, grade 3-4 adverse event rates were similar in patients <65 years old and ≥65 years old. Among the grade 3-4 adverse events, several occurred more frequently (≥2% difference) in older patients, including fatigue, decreased appetite, back pain, asthenia, abdominal pain, pneumonia, cough and transient ischemic attack. No events occurred more frequently in patients <65 years old.

Table 39: Grade 3-4 Adverse Events by Age

	Age	
	< 65 years N=238	< 65 years N=238
Fatigue	25 (10.5)	16 (13)
Decreased appetite	10 (4.2)	8 (6.5)
Back pain	8 (3.4)	1 (0.8)
Asthenia	7 (2.9)	11 (8.9)
Abdominal pain	4 (1.7)	5 (4.1)
Pneumonia	1 (0.4)	3 (2.4)
Cough	0	3 (2.4)
Transient ischemic attack	0	3 (2.4)

Overall, Grade 1-4 adverse event rates were similar in male and female patients.

Several Grade 1-4 adverse events occurred more frequently (≥5% difference) in male patients, including: hypertension, dysphonia, nausea, decreased weight, vomiting and cough. Events of arthralgia, mucosal inflammation, abdominal pain, headache, exertional dyspnea, oropharyngeal pain, urinary tract infection, flank pain and alopecia were more common in females.

Table 40: Grade 1-4 Adverse Events by Sex

	Sex	
	Male N=265	Female N=96
Hypertension	97 (36.6)	49 (51)
Dysphonia	88 (33.2)	26 (27.1)
Nausea	78 (29.4)	39 (40.6)
Weight decreased	61 (23)	28 (29.2)
Vomiting	57 (21.5)	29 (30.2)
Cough	49 (18.5)	10 (10.4)
Arthralgia	37 (14)	19 (19.8)
Mucosal inflammation	36 (13.6)	19 (19.8)
Abdominal pain	34 (12.8)	20 (20.8)
Headache	32 (12.1)	21 (21.9)
Dyspnea exertional	14 (5.3)	0
Oropharyngeal pain	10 (3.8)	10 (10.4)
Urinary tract infection	6 (2.3)	8 (8.3)
Flank pain	5 (1.9)	7 (7.3)
Alopecia	4 (1.5)	10 (10.4)

Overall, grade 3-4 adverse event rates were similar in male and female patients. Among the grade 3-4 adverse events that occurred more frequently in males (≥2% difference) were hypertension, fatigue, diarrhea, dehydration and vomiting. Grade 3-4 adverse events that occurred more frequently in females were decreased appetite, decreased weight, hypokalemia, malaise, pain, hyponatremia, dizziness, headache and depression.

Table 41: Grade 3-4 Adverse Events by Sex

	Sex	
	Male N=265	Female N=96
Hypertension	38 (14.3)	18 (18.8)
Fatigue	28 (10.6)	13 (13.5)
Diarrhoea	26 (9.8)	12 (12.5)
Dehydration	12 (4.5)	1 (1)
Vomiting	11 (4.2)	1 (1)
Decreased appetite	10 (3.8)	7 (7.3)
Weight decreased	4 (1.5)	4 (4.2)
Hypokalemia	0	3 (3.1)
Malaise	0	2 (2.1)
Pain	0	2 (2.1)
Hyponatraemia	0	2 (2.1)
Dizziness	0	2 (2.1)
Headache	0	2 (2.1)
Depression	0	2 (2.1)

7.5.3 Drug-Disease Interactions

See Clinical Pharmacology review.

7.5.4 Drug-Drug Interactions

See Clinical Pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No axitinib-treated patients developed other neoplasms while enrolled on clinical trials and receiving axitinib.

7.6.2 Human Reproduction and Pregnancy Data

There are no data in humans at this time. See Pharmacology-Toxicology review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Axitinib has not been studied in a pediatric population. The applicant has received a waiver for studies in the pediatric population as renal cell carcinoma does not occur in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse potential, withdrawal, and rebound are not relevant to this application.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

As this application is for a new molecular entity with no prior approval history, there is no postmarket experience.

9 Appendices

9.1 Labeling Recommendations

Please refer to the package insert for Inlyta which was revised by the FDA review team.

9.2 Advisory Committee Meeting

The Oncologic Drugs Advisory Committee discussed this application on December 7, 2011. The committee voted unanimously 13-0 that axitinib has a favorable risk: benefit profile in the second-line setting for patients with advanced RCC.

9.3 Literature Review/References

[1] Jemal, A., R. Siegel, et al. (2010). "Cancer statistics, 2010." CA Cancer J Clin **60**(5): 277-300.
[2] Interferon-alpha and survival in metastatic renal carcinoma: Early results of a randomised controlled trial—Medical Research Council Renal Cancer Collaborators. *Lancet* 353:14-17, 1999.
[3] Coppin C, Porzsolt F, Awa A, et al.: Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev (1): CD001425, 2005.
[4] Rosenberg SA, Lotze MT, Muul LM, et al.: A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Engl J Med 316 (15): 889-97, 1987.
[5] Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. Cancer. 2010;116(23):5383-90.
[6] Porta C, Procopio G, Cartenì G et al. Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (**RCC**): an Italian multicentre retrospective analysis of 189 patient cases. BJU Int. 2011; 108(8b):E250-E257.
[7] Buchler T, Klapka R, Melichar B et al. Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma--data from the Czech registry. Ann Oncol. 2011 May 2. [Epub ahead of print]
[8] Zama IN, Hutson TE, Elson P et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer. 2010;116(23):5400-6.

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

/s/

AMY E MCKEE
01/10/2012

JOHN R JOHNSON
01/10/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202324 **Applicant: Pfizer Inc** **Stamp Date: 04/14/2011**

Drug Name: Axitinib **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: A4060010 Study Title: Phase 1, Open-Label, Multicenter, Dose Escalation Study of the Tyrosine Kinase Inhibitor of VEGFR-2, AG013736, in Patients With Advanced Solid Tumors Sample Size: 36 Arms: 1 Location in submission: 5.3.3.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: A4061032	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Second-Line Therapy for Metastatic Renal Cell Cancer Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes._____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Reviewing Medical Officer	Date
Clinical 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/

AMY E MCKEE
05/13/2011

JOHN R JOHNSON
05/13/2011