Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Axitinib

Proprietary Product Name: Inlyta

Sponsor: Pfizer Australia Pty Ltd

February 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	19 July 2012
Active ingredient:	Axitinib
Product Name:	Inlyta
Sponsor's Name and Address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114 Australia
Dose form:	Tablet
Strengths:	1 mg and 5 mg
Containers:	High density polyethylene (HDPE) bottle and aluminium (Al/Al) foil blister pack
Pack sizes:	Bottle: 60 [5 mg] and 180 [1 mg] tablets; blister pack: 28 and 56 tablets
Approved Therapeutic use:	*For the treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy*
Route of administration:	Oral
Dosage:	Starting dose of 5 mg twice daily with dose titration permitted to a maximum of 10 mg twice daily
ARTG Numbers:	184856, 184857, 184858, 184859

Product background

Axitinib is claimed to be a selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3. It is proposed that inhibition of VEGFRs by axitinib will interfere with angiogenesis, which is a fundamental step in the transition of tumours from a dormant to a malignant state.

Axitinib is proposed for the treatment of renal cell carcinoma (RCC), which, in the Australian population, is the eighth and ninth most common cancer in males and females,

respectively[1]. In 2001, there were 2458 new cases (2.8% of all new cancers), with 90-95% of these arising from the kidney epithelium. Seventy five percent of all primary renal cell cancers are classified histologically as clear cell carcinomas. The prognosis for newly diagnosed patients is poor, since 25-30% will have already progressed to metastatic disease upon diagnosis.

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register axitinib (Inlyta) for the following indication:

For the treatment of patients with advanced renal cell carcinoma.

Inlyta, for the proposed indication, was designated as an Orphan Drug in April 2011.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 26 July 2012. Axitinib is approved for the treatment of advanced RCC after failure of one prior systemic therapy in the USA (January 2012), Switzerland (April 2012), Japan (June 2012), Canada (July 2012), South Korea (August 2012), the EU (September 2012) and Macao (November 2012).

Product Information

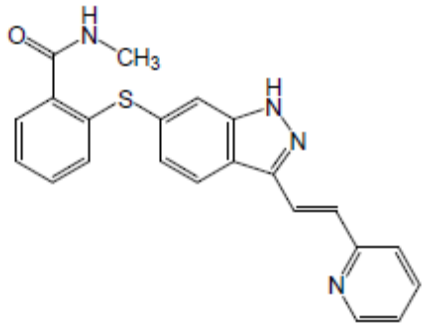
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Axitinib is an achiral, substituted indazole. The double bond has the *E* (trans) configuration:

Figure 1. Chemical structure



Axitinib has the molecular formula $C_{22}H_{18}N_4OS$ and molecular weight 386.5.

Aqueous solubility is strongly dependent on pH: it is high in acid (> 1800 µg/mL at pH 1.1; *via* pyridine protonation) but low at pH 7.0 (0.2 µg /mL). Thus the maximum single dose (10 mg twice a day; bid) would dissolve in approximately 5.5 mL acid but 50 L of pH 7.0 buffer. Bioavailability is thus potentially different in achlorhydric patients.

[1] Pavlakis, N. Drug treatment of renal cancer. *Australian Prescriber* 2006;**29:** 151-3.

Axitinib is susceptible to thiol oxidation as expected. The double bond can be photo-isomerised, although the polymorphic form used is not strongly light sensitive.

Related drugs

There are a number of TKIs already registered in Australia: imatinib (Glivec); gefitinib (Iressa); erlotinib (Tarceva); sunitinib (Sutent); dasatinib (Sprycel), lapatinib (Tykerb); nilotinib (Tasigna); pazopanib (Votrient). Axitinib does not show a close structural relationship to these.

Manufacture

Axitinib is synthetic. Particle size is controlled. The sensitivity of *in vivo* pharmacokinetics (PKs) to drug substance particle size was investigated in a clinical study. Impurity levels are low and appropriate limits now apply.

Drug product

Inlyta 1 and 5 mg immediate release tablets are proposed. These are film-coated tablets.. The two strengths are both red, but are distinguished by size, shape and markings (1 mg oval debossed "Pfizer" / "1 XNB"; 5 mg triangular debossed "Pfizer" / "5 XNB"). Tablets are not scored. Both HDPE bottle and aluminium (Al/Al) foil blister packs are proposed.

Several oral (PO) dosage forms were used in clinical development. Tablets used in early clinical trials were made by wet granulation. Later tablets were made by dry granulation. There were also changes to the drug polymorphic form. There were changes to the film coat for better light protection and change to tablet shape.

Axitinib tablets disintegrate rapidly. There is routine dissolution testing of tablet batches.

Biopharmaceutics

Axitinib is extensively metabolised, especially to an N-glucuronide metabolite and a sulfoxide metabolite. These have much lower *in vitro* potency against VEGFR-2 compared to axitinib.

Axitinib is classified according to the Biopharmaceutical Classification System (BCS) as BCS class II (low solubility and high permeability). Metabolism, and not absorption, is the major contributor (approximately 76%) toward inter-subject PK variability.

The submission includes an absolute bioavailability study (A4061007). This compared 5 mg tablet and 1 mg intravenous (IV) doses. The mean absolute bioavailability was 58%; 90% confidence interval (CI): 48-72%.

Several PK studies measured the effects of drug particle size, drug polymorphic form and different tablet manufacturing methods on bioavailability (Studies A4061033, A4061063). Tablet formulation comparisons generally showed bioequivalence of relevant, different clinical trial formulations.

Bioequivalence of 1 and 5 mg tablets was studied in A4061052. Somewhat variable effects of food were measured in different studies: A4061007 (food reduces bioavailability), A4061006 (reduces) and A4061053 (food increases bioavailability). Food effects were not dramatic.

Advisory committee considerations

This application was considered at the 142nd meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC was concerned about the lack of detailed TGA review of population PK studies in this and other applications. The subcommittee was not assured that the proposed Product Information (PI) statements regarding effects on QT interval[2] had been appropriately checked or reliably derived from the population PK analysis.

The PSC noted the high incidence of diarrhoea associated with the administration of the proposed products. The subcommittee considered that information on the impact of this on axitinib absorption in patients and on the absorption of co-administered drugs would be appropriate.

Quality summary and conclusions

Details of an acceptable tablet assay are currently being finalised.[3] The evaluator recommended that this issue should not delay consideration by the ACPM. Registration was otherwise recommended with respect to chemistry and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The nonclinical data consisted of pharmacodynamic (PD), PK and toxicity studies that were well designed and documented. The toxicity studies were compliant with Good Laboratory Practice (GLP) requirements and conformed to the relevant European Union (EU) guidelines.

Throughout the evaluation, relative exposure levels have been calculated based an estimate of the human area under the plasma concentration-time curve (AUC) of 265 ng.h/mL (geometric mean) for the proposed clinical formulation at the starting clinical dose of 5 mg bid. Although the maximum proposed clinical dose is 10 mg bid, patients who were unable to be titrated to a higher dose of axitinib (owing to poor tolerability) were found to have higher initial exposures (median AUC over 0 to 12 h; ($AUC_{0\text{-}12\,h}$) = 231 ng.h/mL) compared to those who were dose titrated to 7 mg bid (median $AUC_{0\text{-}12\,h}$ at starting dose level = 160 ng.h/mL) or those titrated to 10 mg bid (median $AUC_{0\text{-}12\,h}$ at starting dose level = 129 ng.h/mL). Median steady state $AUC_{0\text{-}12\,h}$ values for patients unable to be dose titrated above 5 mg bid, or those titrated to 7 mg bid or 10 mg bid, were 231, 228 and 258 ng.h/mL, respectively. Thus, the sponsor's argument that a human AUC of 265 ng.h/mL is an adequate approximation of the clinical exposure is accepted. Taking into account the extent of binding to human plasma proteins *in vitro* (99.5%), the unbound AUC is 1.3 ng.h/mL. The corresponding maximum plasma concentration (C_{max}) for axitinib from clinical Study A4061046 was 27.8 ng/mL (unbound C_{max} 0.14 ng/mL).

[2] The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. QTc is the QT interval adjusted for heart rate. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

[3] Sponsor comment: "Pfizer agreed to the changes to the tablet assay in the Company Response dated 17 July 2012. The revised tablet assay was submitted to the TGA on 14 August 2012."

Pharmacology

Over the past decade, much research into cancer therapies has focussed on agents that interfere with factors controlling tumour angiogenesis. Clear cell RCC (which represents 75-80% of RCC) frequently displays allelic loss on chomosome 3p, accompanied by mutational inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene. Such tumours are highly vascularised, and express high levels of VEGF. Angiogenesis, the formation and growth of new blood vessels, is a fundamental step in tumour growth and transition from dormancy to malignancy.

The angiogenic process is initiated by various factors, including VEGF, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and angiopoietins, which all act by binding to receptor TKs (RTKs) on endothelial and other stromal cells[4]. VEGF is a potent mitogen for vascular endothelial cells derived from arteries, veins and lymphatics, while having little activity on other cell types, since its receptors are selectively expressed on the vascular endothelium. Members of the VEGF family (VEGF-A, VEGF-B, VEGF-C and VEGF-D) bind to the corresponding receptor TKs, including VEGF receptor-1 (VEGFR-1, Flt-1), VEGFR-2 (Flk-1, KDR) and VEGFR-3 (Flt-4).

VEGFR-2 (flk-1/KDR) is the primary TK receptor mediating vascular permeability, endothelial cell proliferation, invasion, migration and survival[5]. Ligand binding induces dimerisation of VEGFR-2, resulting in receptor autophosphorylation and activation of downstream signalling including the Raf-MEK-Erk and the PI3K-AKT pathways, which result in the formation of mitogenic and pro-survival signals[6]. VEGFR-1(Flt-1) is a positive regulator of monocyte and macrophage migration, and has a positive and negative regulatory role on VEGFR-2 signalling. VEGFR-3 (Flt-4) is important for lymphatic and endothelial cell development and function. Compounds that inhibit the intrinsic TK activity of VEGFRs are expected to block the biological activity of the receptors, thereby disrupting angiogenesis.

Of all the pro-angiogenic cytokines, VEGF is of particular importance in normal developmental vasculogenesis and angiogenesis, as well as in pathological angiogenesis, tumour growth, and metastatic progression of cancer[4]. VEGF is essential for embryonic survival, and unlike other potent endothelial cell mitogens such as FGF-2, the major TK receptors for VEGF-A are selectively expressed on vascular endothelium.

VEGF is expressed by various tumour and host cells and is up-regulated in the tumour microenvironment[7]. VEGF-A increases vascular permeability to plasma and plasma proteins, which is a characteristic property of tumour microvasculature, and a critical early step in tumour stroma generation. The amount of VEGF-A expressed by cancer cells is a marker for prognosis in cancer treatment, including RCC. The rationale behind the treatment of RCC patients with VEGFR inhibitors is to inhibit tumour angiogenesis, thereby reducing primary and metastatic tumour growth by restricting nutrient supply. Reduction of tumour vascularity might also decrease the risk of further metastatic progression. Potential pitfalls of such an approach include the possible selection for blood

[4] Cao, Y. and Liu, Q.. Therapeutic targets of multiple angiogenic factors for the treatment of cancer and metastasis. *Advances in Cancer Research* 2007:97; 203-24.

[5] Dvorak, H.F. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumour angiogenesis and a potential target for diagnosis and therapy. *Journal of Clinical Oncology* 2002:20(21);4386-4380.

[6] Wu, L-W. *et al*. Utilization of distinct signaling pathways by receptors for vascular endothelial cell growth factor and other mitogens in the induction of endothelial cell proliferation. *The Journal of Biological Chemistry* 2000:275;5096-103.

[7] Berse, B. *et al*. Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. *Molecular Biology of the Cell* 1992:3;211-20.

vessels with reduced sensitivity to VEGF, which could see the development of resistance to such a therapy.

Primary pharmacology

Pharmacodynamic studies with axitinib were conducted to evaluate its *in vitro* potency, selectivity, functional activity, *in vivo* target modulation, and its anti-angiogenic and anti–tumour activities. Axitinib was identified using an iterative structure-based design to be an adenosine triphosphate (ATP)-competitive inhibitor that binds to the "DFG-out" conformation or "deep pocket" of the ATP site of the VEGFR-2 kinase. A total of 104 cell-free kinase assays were conducted to evaluate the inhibitory activity of axitinib against a wide range of RTKs, including VEGFR-2 as well as type III (PDGF) and type IV (FGF) TK receptors, since the ATP binding sites of these kinases are highly homologous. In these studies axitinib was shown to be a relatively selective inhibitor of the target kinases of human recombinant VEGFR-1 (Flt-1), various forms of the kinase of VEGFR-2 (FLVK), and the recombinant kinase protein of PDGF receptor-β (PDGFR-β), and exhibited much weaker activity against other Type III and IV family kinases tested (colony stimulating factor receptor 1, CSF-1R; Flt-3, and FGFR-1). Very few non-targeted kinases were inhibited.

The sulfur oxidised metabolite of axitinib (AG-028458/PF-03482595) and the N–glucuronide showed no clinically relevant activity against RTKs either in cell free (AG–028458 only) or cell based enzyme assays. The most notable activity for the metabolites was for the sulfoxide against Aurora-A and 5'-adenosine monophosphate–activated protein kinase (AMPK) at micromolar concentrations. The *in vitro* potencies against VEGFR-2 were approximately 400 fold and 8000 fold less than axitinib for the sulfoxide and N-glucuronide, respectively.

The potency and selectivity of axitinib against RTKs was examined in a range of cell based models. Axitinib inhibited the autophosphorylation of VEGFR-1, 2 and 3 with the 50% maximal inhibitory concentration (IC_{50}) values 0-06-0.3 nM, while PDGFR-β and proto-oncogene RTK (KIT) were inhibited with 10-100 fold higher IC_{50}. Activity against other TK receptors was much weaker, and hence of negligible clinical relevance. In *in vitro* studies, axitinib inhibited events downstream of VEGF RTK phosphorylation, endothelial cell adhesion and migration, vascular sprouting and tubule formation. In addition, treatment of cultured endothelial cells with axitinib induced apoptosis.

The anti-angiogenic activity of axitinib was confirmed in a number of *in vivo* studies. Inhibition of VEGFR-2 phosphorylation was inhibited in the highly vascularised retina of neonatal rats (50% maximal effective concentration (EC_{50}) = 0.49 nM), and also in human melanoma M24met tumours implanted into BALB/c mice (these tumour cells do not express VEGF or PDGF receptors, so the inhibitory effect of axitinib on VEGFR-2 phosphorylation represents an effect on angiogenic murine vascular endothelial cells). Inhibition of PDGFR-β phosphorylation in mice implanted with the highly PDGFR-β expressing C6 rat glioma tumours was observed, consistent with the IC_{50} value for PDGFR-β inhibition *in vitro*. Axitinib inhibited VEGF-induced increases in vascular permeability in skin, and also in an implanted human colon and breast carcinoma models. In the latter study, use of dynamic contrast enhanced magnetic resonance imaging (MRI) revealed that reduced tumour microvascular permeability and blood flow was associated with decreased microvessel density, cellular viability and tumour growth.

Blood vessels in tumours have multiple abnormalities, including loss of arteriole-capillary-venule hierarchy, increased tortuosity, variable diameter and leakiness of the

endothelium, and may not be characteristic of normal vasculature[8]. In spontaneous islet cell tumours of RIP-Tag2 transgenic mice[9], axitinib treatment rapidly decreased tumour vascular endothelial cell fenestration and microvessel density, and induced rapid regression of tumour blood vessels. The effects of axitinib on the tumour blood vessels were shown to be reversible upon cessation of treatment. However, the expression of VEGFR-2 was reduced in surviving endothelial cells, which may indicate that the tumour vasculature could develop resistance to axitinib treatment.

A study of the tumour growth inhibitory effect of axitinib treatment in a human xenograft model (MV522) in mice provided EC_{50} values for tumour growth inhibition (see Table 1) and a 50% maximal effective dose (ED_{50}) of 8.7 mg/kg PO, bid.

Table 1: axitinib plasma concentrations required for inhibition of VEGFR phosphorylation, angiogenesis and tumour growth based on nonclinical studies

Method	Parameters measured	Effective Concentrations (unbound)			
		IC_{50} (nM)	IC_{50} (ng/mL)	EC_{50} (nM)	EC_{50} (ng/mL)
RTK phosphorylation ELISA/ PAE cells	VEGFR2-Ⓟ	0.2	0.08		
	VEGFR1-Ⓟ	0.1	0.04		
	VEGFR3-Ⓟ	0.29	0.11		
Ocular angiogenesis model in neonatal rat	Rat VEGFR2-Ⓟ			0.49	0.19
VEGF-mediated skin permeability in mice	Evan's Blue quantification			0.46	0.18
In vivo EC_{50} derivation based on C_{min}	TGI after PO, bid dosing (8 h apart) in MV522			0.28	0.11
In vivo EC_{50} derivation based on C_{ave}				0.85	0.33
In vivo EC_{50} derivation based on C_{ss}	TGI via continuous minipump infusion in MV522			0.65	0.25

PAE: Porcine aortic endothelial (cells); Ⓟ: receptor phosphorylation; TGI: tumour growth inhibition.

The relationship between dose and response in the nonclinical studies was used to determine the concentrations of axitinib required for target modulation and anti-tumour efficacy. The plasma concentrations (unbound) required for VEGFR target modulation, based on enzyme-linked immunosorbant assay (ELISA)-determination of RTK phosphorylation in porcine aortic endothelial cells, ocular angiogenesis in neonatal rats or VEGF-mediated skin permeability increases in mice were found to be 0.10-0.49 nM, or 0.04-0.19 ng/mL (see Table 1), compared to the human Cmax of 0.014 ng/mL. The effective plasma concentrations (unbound) based on tumour growth inhibition with MV522 human colon carcinoma xenografts in athymic mice were 0.28-0.85 nM or 0.11-0.33 ng/mL.

The anti-tumour effects of axitinib were confirmed in orthotopically implanted human renal carcinoma (SN12C-GFP), human colon carcinoma (HCT-116 GFP), human melanoma (M24met), and human breast carcinoma (MDA-MB-435\HAL-Luc), as well as in subcutaneous (SC)-implanted xenograft models of human colon carcinoma (MV522 and

[8] Inai, T. e*t al.* Inhibition of vascular endothelial growth factor (VEGF) signalling in cancer causes loss of fenestrations, regression of tumour vessels, and appearance of basement membrane ghosts. *Am J Pathology* 2004:165;35-52.

[9] A mouse strain in which the rat insulin promoter (RIP) directs expression of the SV40 Large T antigen transgene (TAg) to beta cells of the pancreatic islets.

HT29), human small cell lung cancer (NCI-H526), human breast carcinoma (MDA-MB-435), human melanoma (M24met, A2058 and A375), human pancreas (MiaPaCa-2), human and rat glioma (U87MG and C6), human primary hepatocellular carcinoma (LIMSH050), human lymphoma (Namalwa), and murine Lewis lung carcinoma (LLC). Tumour growth inhibition was independent of RTK expression status, suggesting that the anti-tumour activity of axitinib in RTK-negative tumour models was mediated by inhibition of angiogenesis *in vivo*. These studies were relatively short term (generally 2-4 weeks), and do not provide any information on the possible development of resistance to axitinib treatment, for example, by favouring survival of endothelial cells lacking VEGFRs. Inhibition of tumour growth was associated with reduced tumour microvessel density, reduced expression of the cell proliferation marker Ki-67, and enhancement of tumour apoptosis.

In these anti-tumour studies, efficacy was not notably reduced by short dosing "holidays" (for example, weekends), but more prolonged cessation of treatment led to a rapid and aggressive tumour regrowth. Although this was susceptible to a second course of treatment with axitinib, the efficacy after repeated breaks in treatment was not examined.

Axitinib in combination with docetaxel, carboplatin, gemcitabine or fractionated radiotherapy had enhanced-synergistic anti-tumour effects. Combination with other agents targeting the VEGF pathway (the tyrosine/theonine kinase (MEK) inhibitor PD–0325901or bevacizumab) also produced additive effects, with the latter combination showing improved anti-metastatic activity and survival compared with monotherapy. In a further study, a tumour that had developed resistance to bevacizumab was found to possess sensitivity to axitinib.

In summary, axitinib was shown to be a selective VEGFR TKI, with no clinically relevant inhibition of non-VEGFR kinases in all the kinase panels tested. The principal mechanism of action of axitinib is anti-angiogenesis though the inhibition of VEGFR-1, 2 and 3 in tumour vasculature, rather than though a direct action on tumour cells. Inhibition of VEGFRs results in the blocking of intracellular signalling mediated by all VEGF ligands secreted from tumour cells, endothelial cells, stromal perivascular cells, inflammatory cells and bone marrow derived myeloid cells.

Secondary pharmacodynamics and safety pharmacology

Axitinib was tested against 37 receptors and ion channels, with weak binding activity observed at adenosine $A_{2A,}$ muscarinic M_2 and neuropeptide Y_2 receptors, but there was no functional antagonism associated with this binding activity. Hence, axitinib is not expected to exhibit any notable secondary pharmacological activity.

Specialised safety pharmacology studies, conducted under GLP conditions, covered the central nervous system (Irwin test), and cardiovascular, respiratory (whole body plethysmography) and gastrointestinal systems (intestinal transit and gastric emptying). Axitinib treatment (doses ≥ 5 mg/kg/day PO) increased gastric emptying in male Wistar rats. Although there were no toxicokinetic data accompanying this study, based on the toxicokinetic data obtained in conscious telemetered rats (see Table 2), this effect may be of clinical relevance.

Axitinib (and its glucuronide conjugate and sulfoxide metabolite) showed only weak inhibition of the human Ether-à-go-go Related Gene (hERG) channels at micromolar concentrations or above, and there were no effects on electrocardiogram (ECG) waveforms in conscious telemetered dogs, which is supportive of a lack of potential for prolongation of the QT interval.

Treatment with VEGFR inhibitors has been associated with increases in arterial blood pressure, and so axitinib effects on heart rate and arterial blood pressure were studied in conscious, telemetered mice, rats and beagle dogs. In general, the class effect on blood

pressure was confirmed (associated with reduced heart rate), although there was a high degree of inter-individual variability which meant that effects were not consistently significant in statistical terms.

Table 2 summarises the plasma C_{max} levels in studies in conscious telemetered mice, rats and dogs in which axitinib treatment was associated with increased blood pressure and reduced heart rate. Table 2 displays the lowest observed effect level (LOEL), the measured plasma C_{max} and the exposure ratio compared with both total and free plasma C_{max} at the recommended starting clinical dose. This is discussed more fully below (see *Major toxicities*).

Table 2 Relative exposure in cardiovascular safety pharmacology studies

Species	Study	LOEL (mg/kg/day)	C_{max} (ng/mL)	Exposure ratio#	Exposure ratio†
Mouse (CD-1)	SP-4009-2	30	144	5.2	31
Rat (Wistar)	SP0304	≥ 100	102	3.7	13
Dog (Beagle)	SPT04-029	≥ 50	172	6.2	25
Human (healthy volunteers)	steady state	0.2*	27.8**	-	-

#animal:human total plasma Cmax; †animal:human unbound plasma Cmax , based on fraction unbound of 0.03 in mice, 0.018 in rats, 0.02 in dogs, and 0.005 in humans; *based on a 50 kg individual at a daily dose of 5 mg bid (10 mg/day); **human Cmax (total) with the proposed clinical formulation at the starting dose of 5 mg bid.

Pharmacokinetics

The results of studies using the Caco-2 (a human intestinal cell line used as a model of the intestinal barrier) cell culture model indicated moderate to high permeability in the absorptive direction. Axitinib is a substrate for P-glycoprotein (P-gp; see discussion below under *Pharmacokinetic interactions*). Pharmacokinetic studies with axitinib were carried out in mice, rats, dogs and monkeys. Maximum plasma concentrations of axitinib were observed from 0.2 to 4.7 h, although absorption was delayed at higher doses ≥ 1000 mg/kg in the rat, and 1000 mg/kg in the dog, which is suggestive of saturation of absorption. The PO bioavailability was 16% in mice and 59% in dogs, with moderate values for clearance (1.5 and 0.72 L/h/kg) and volume of distribution (1.67 and 1.17 L/kg) in mice and dogs, respectively. In rats, the clearance and volume of distribution were both high (23.8 L/h/kg and 32.3 L/kg, respectively), with very low PO bioavailability (3% in one study, although in another study a value of 31% was reported with a different vehicle). The plasma half life following IV administration was 5.3 h in mice, 4.3 h in the rat, and 0.8 h in the dog. The PO bioavailability was only 3% in monkeys, while the plasma half life was 11.1 h. In this species, clearance was moderate at 0.67 L/h/kg, while the volume of distribution was low at 0.8 L/kg. Based on the comparative PK properties of axitinib in these species, the mouse and dog were selected as being the most suitable for repeat-dose toxicity studies.

The extent of binding to plasma proteins was high in all species, with mean values of 97%, 98%, 98% and 99% in mouse, rat, dog and human plasma, respectively (human plasma protein binding at clinically relevant concentrations was approximately 99.5%). For highly protein bound drugs, a small interspecies difference in protein binding can make a considerable interspecies difference to the unbound fraction for the same total drug

concentration. Thus, at face value these data suggest that the free axitinib concentration in mice and dogs are six and four times higher, respectively, than in humans.

It is sometimes argued that when the extent of protein binding is high then it may be more appropriate to cite unbound rather than total concentrations of drug[10]. However, at such high levels of protein binding, the resulting interspecies differences in estimated free drug concentrations are extremely sensitive to variations of plasma protein binding. A careful examination of the mean human plasma protein binding data indicates that the percentage bound to proteins in human plasma ranged from 97.89 to 99.50% at different assay concentrations, which corresponds to unbound fractions ranging from 0.005 to 0.021. Thus, the estimated unbound axitinib concentrations in mice and dogs could range from approximately equal to up to six times higher than the unbound concentration in humans. Possible sources of variability or uncertainty in estimating the extent of interspecies differences in unbound axitinib concentrations include the intrinsic variability of the protein binding assay, the extrapolation of *in vitro* data to the situation *in vivo*, physiological state, disease status and co-medication status. There are also large individual variations of clinical plasma axitinib concentrations. In view of the considerable degree of variability of relative unbound fraction between species, it is not appropriate to estimate relative levels of systemic exposure based on unbound axitinib concentrations. Thus, total plasma axitinib concentrations are used in the assessment of potential adverse effects in humans based on animal studies. Nonetheless, Tables 2 (above), 3 and 4 (below) show relative exposure estimates based on both total and unbound axitinib to indicate possibly higher animal to human exposure ratios based on unbound plasma axitinib concentration than based on total plasma drug concentrations.

The blood to plasma concentration ratios and red cell distribution fractions in mice, dogs and human indicated that axitinib was relatively equally distributed between plasma and blood cells. Thus, analysis of plasma axitinib concentrations is expected to reflect the concentration of axitinib in whole blood adequately. The extent of binding to proteins in human plasma is sufficiently high to warrant consideration of potential interactions with other highly protein bound drugs in clinical use.

The results of a quantitative whole body autoradiographic study of the distribution of carbon-14 radiolabelled (^{14}C)–axitinib following PO administration to pigmented male mice found that the highest levels of radioactivity were in the gall bladder, kidney, liver, uveal tract and stomach mucosa. Tissue to blood concentration ratios in the kidney (the proposed therapeutic target organ) were 1.3 to 3.1. The passage of axitinib or its metabolites across the blood brain barrier appeared to be limited in this species. Slow elimination of radioactivity from the uveal tract is suggestive of melanin binding.

Axitinib metabolism was studied *in vitro* using hepatic microsomes from mouse, rat, dog and human, and with recombinant cytochrome P450 (CYP) and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes. The results of these studies indicate that axitinib is extensively metabolised, predominantly in the liver by isozymes 3A4 and 3A5, with lesser contributions from CYP1A2, and CYP2C19, to yield the major oxidative metabolite, a sulfoxide (referred to as M12, PF-03482595, or AG–028458). Additional minor Phase I metabolic pathways included depyrinidylation, methyl hydroxylation, mixed sulfoxidation and *N*-oxidation and sulfonation. Phase II reactions were mediated by UGT1A1 and UGT1A4. Formation of the major human metabolite (the N-glucuronide) was due solely to the activity of UGT1A1, and hence this isoform is quantitatively more important for axitinib metabolism.

[10] ICH Topic S 3 A. Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies; CPMP/ICH/384/95

The N-glucuronide metabolite, M7, was the predominant metabolite circulating in human plasma, accounting for approximately 50% of an administered radioactive dose of axitinib, and was the main route of axitinib metabolism in the rat and monkey *in vitro.* M7 was also formed in mice, accounting for approximately 8-13% and 14% of radioactivity in plasma and excreta, respectively. In the dog, however, it was only detected in trace amounts. The sulfoxide accounted for approximately 20-29%, 20% and 16% of radioactivity in plasma from mice, dogs and humans, respectively. Excretion was predominantly in the faeces for mice and dogs (> 70% of dose), with negligible urinary excretion (< 10% of dose) in 48–72 h. In healthy humans, urinary elimination accounted for 23% of the administered dose in eight days, with 16-78% eliminated in the faeces.

Overall, the results of the metabolism and excretion studies in animals confirm their suitability for use in repeat-dose toxicity studies, in terms of the metabolic reactions involved, CYP isozymes responsible, the numbers and types of metabolites formed, the dominant circulating species and the elimination pathways. The major discrepancy was the relative lack of N-glucuronidation in dogs. However, this is not considered to limit the usefulness of the dog for the repeat-dose toxicity studies, since glucuronides are unlikely to exhibit pharmacological or toxicological effects in addition to those seen with the parent compound.

Pharmacokinetic drug interactions

In studies with Caco-2 cell cultures and Madin Darby Canine Kidney cells (MDCK) transfected with human transporter proteins, axitinib was a weak substrate for the P–gp efflux transporter and the human breast cancer resistance protein (BCRP). In addition, axitinib was a substrate for the human organic anion transporting (OAT) polypeptides OAT-1B1 and OAT-1B3 expressed in human embryonic kidney cells (HEK293). However, the moderate to high passive membrane permeability to axitinib would be likely to dominate any active uptake.

Axitinib was also able to inhibit the activity of P-gp, with an IC_{50} estimated to be 3.0 μM, which is approximately 40 fold higher than the clinical C_{max} (72 nM or 27.8 ng/mL) for total axitinib, and much higher than the free fraction drug concentration. It has been argued that the luminal concentration is of greater relevance than plasma concentration with respect to inhibition of intestinally expressed transporters, since the P-gp transporter is located on the luminal membrane[11]. The sponsor used a modelling software (Gastroplus) to provide an estimate for the maximum concentration of dissolved axitinib in the intestinal lumen of 33.9 μM (based on the highest proposed therapeutic dose of 10 mg under conditions of fasting). This value is 11.3 times the IC_{50} (3.0 μM). According to the draft FDA guidance document on drug interaction studies[12], drugs with luminal concentrations less than 10 times the P-gp inhibition IC_{50} are not expected to affect the absorption of other P-gp substrate drugs. Thus, the weak P-gp inhibitory activity of axitinib is unlikely to be of major clinical relevance.

Axitinib was found to inhibit human liver microsomal CYP2C8 and CYP1A2 *in vitro* with inhibitory constant (K_i) values 3-5 times C_{ss}, while inhibition of CYP3A4, CYP2C9 and CYP2A6 was relatively weak ($K_i \geq 50 \times C_{ss}$). There was no inhibition for CYP2E1, CYP2C19, CYP2D6 or UGT1A1. These findings indicate that axitinib has the potential to inhibit the metabolism of drugs metabolised by CYP2C8 or CYP1A2. However, according to the draft

[11] Zhang, L. *et al*. A regulatory viewpoint on transporter-based drug interactions. *Xenobiotica* 2008:38:709-24.

[12] Guidance for Industry – *Drug Interaction Studies – Study design, data analysis, implications for dosing and labelling recommendations*, Updated February 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

PI, a clinical study with paclitaxel, a CYP2C8 substrate, indicated no clinical inhibition of CYP2C8.

The plasma axitinib concentration is expected to be affected by CYP3A inhibitors or inducers, since axitinib is extensively metabolised by CYP3A4/5. Increased axitinib exposure following co-administration with the CYP3A inhibitor ketoconazole and decreased exposure with the CYP3A inducer rifampin was observed clinically.

The N-glucuronide was found to be the predominant circulating metabolite in human plasma, and *in vitro* studies with recombinant human UGTs (UDP-GTs) found that the glucuronide was formed exclusively by the action of UDP-GT1A1 (UGT1A1). This is a polymorphic isoform involved in glucuronidation of bilirubin. Modelling based on a comparative study of recombinant CYP isozyme and UGT1A1 enzyme kinetics suggested that metabolism of axitinib by UGT1A1 was a minor pathway. The sponsor argues that the high level of the N-glucuronide circulating in plasma is due to the highly polar nature of this metabolite, which would have a low volume of distribution. However, it is possible that the *in vitro* study of axitinib metabolism might not fully reflect the situation *in vivo*, and this needs to be determined from the clinical data. If UGT1A1 is a major metabolic pathway, then drugs which interfere with the activity of UGT1A1 (for example, atazanavir) could potentially affect axitinib metabolism. In addition, axitinib metabolism may be affected if it is co-administered with another UGT1A1 substrate. Patients with compromised bilirubin metabolism such as in Gilbert and Crigler-Najjar syndromes (where bilirubin cannot be broken down) might be expected to exhibit increased plasma concentrations of axitinib, since these disorders result from impaired UGT1A1 function[13].

Toxicology

Acute toxicity

The acute toxicity of axitinib was examined in GLP-compliant studies in mice and dogs after administration of PO doses of up to 2000 mg/kg, but a second route of administration was not examined. Toxicity was low, with no mortalities, and abnormal faeces in dogs being the only clinical sign observed. Toxicokinetic data in this species provided evidence of systemic exposure, which was approximately 11 and 25 times the human C_{max} at the recommended starting dose in males and females, respectively.

Repeat-dose toxicity

GLP-compliant repeat-dose studies were carried out in mice and dogs for up to 26 weeks and 9 months, respectively, using bid dosing by the PO route, as is proposed for clinical use. The duration of the pivotal studies, the species used (PK suitability and the similarity of axitinib metabolism to humans), group sizes and the use of both sexes were consistent with ICH guidelines.

In the pivotal mouse study the maximum tolerated dose was exceeded at the maximum dose (250 mg/kg/day), resulting in early sacrifice at 22 weeks associated with dental abnormalities, reduced body weight and poor condition. However, three additional dose levels were studied, enabling the dose-dependence of target organ toxicities to be explored. In the dog studies, severe gastrointestinal toxicity associated with reduced body weight gain or loss of body weight in the non-pivotal studies resulted in lower doses being selected for the pivotal studies, and as a result, relative exposure levels based on unbound axitinib were comparable to or lower than the proposed clinical levels. However, the 14

[13] Burchell, B. *et al*. Drug-mediated toxicity caused by genetic deficiency of UDP-glucuronosyltransferases. *Toxicology Letters* 2000:112-113: 333-340.

and 28 day studies provide information on potential toxicity at higher exposure levels. Toxicokinetic data were provided for all of the repeat dose toxicity studies. In mice, exposure levels tended to be higher in females than in males, although this was not apparent at the higher dose levels. Exposure levels increased more than dose-proportionally in this species, which may be indicative of saturation of elimination pathways.

Relative exposure

As discussed above, in view of the considerable degree of uncertainty surrounding the precise extent of the interspecies difference in binding of axitinib to plasma proteins and thus potential variability of unbound fraction, total plasma axitinib concentrations are used in the assessment of potential adverse effects in humans based on animal studies. However, for comparative purposes, Table 3 shows relative exposure estimates based on both total and unbound axitinib, to indicate the relative exposure based on the free fraction would be higher than that estimated by the total axitinib concentration, although the relative exposure based on the free fraction could vary considerably due to the variability of *in vitro* protein binding assays and other factors.

Table 3: Relative exposures in repeat dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL)	Exposure ratio#	Exposure Ratio† (free fraction)
Mouse (CD-1)	26 weeks	10	400	1.5	9
		30	2265	8.5	51
		100	13249	50	300
		250	16834	64	380
	Micronucleus (3 days)	250 (♀)	18350	69	414
		500 (♂)	58550	221	1326
Dog (Beagle)	26 weeks	1	8.6	0.03	0.12
		3	31	0.12	0.48
		6	137	0.52	2.1
		10	494	1.9	7.6
	9 months	1	6.91	0.03	0.12
		3	25.5	0.10	0.4
		6	114	0.43	1.7
	28 day	10	1680‡	6.3	25
		30	4150	15.7	63
		100	4400	16.6	66
Human (healthy volunteers)	steady state	0.2*	265**	-	-

#animal:human plasma $AUC_{0-24\ h}$; †animal:human unbound plasma $AUC_{0-24\ h}$, based on fraction unbound of 0.03 in mice, 0.02 in dogs, and 0.005 in humans; ‡day 1 value. *based on a 50 kg individual at a daily dose of 5 mg bid (10 mg/day); ** human AUC with the proposed clinical formulation at the starting dose of 5 mg bid.

Although the relative exposure to axitinib was well in excess of the proposed clinical exposure in the mouse toxicity studies (> 50 times, and approximately 70-220 times in the mouse micronucleus assay), the doses of axitinib used in the pivotal repeat-dose toxicity studies in dogs failed to produce exposure levels exceeding the anticipated clinical systemic exposure level (maximum relative exposure 0.4 times the human AUC over time 0 to 24 h ($AUC_{0-24\ h}$) in the 9 month study). Relative exposures for the 28 day repeat dose study in this species have therefore been included in Table 3, indicating that exposure levels were approximately 17 times the human $AUC_{0-24\ h}$ at doses ≥ 30 mg/kg/day.

Major toxicities

The major targets for axitinib toxicity were the gastrointestinal tract, haematopoietic, musculoskeletal and reproductive systems, with some effects also observed on the cardiovascular system, liver and exocrine pancreas. Many of the effects observed in the repeat-dose toxicity program for axitinib are consistent with the drug's primary

pharmacological actions, and similar to other drugs in this class (for example, sorafenib, pazopanib and sunitinib). In the following discussion, relative exposure comparisons are given with respect to the anticipated clinical $AUC_{0\text{-}24\,h}$ at the recommended starting dose, based on total axitinib concentrations as discussed above.

Gastrointestinal toxicity in dogs was dose-limiting, with widespread effects in the alimentary tract. Abnormal faecal excretions (including discoloured, mucoid, liquid or non-formed faeces) were observed at doses ≥ 1 mg/kg/day, but were not associated with any adverse effect on body weight or weight gain, food consumption or clinical signs. Evidence of gastrointestinal toxicity was more severe and widespread at doses ≥ 10 mg/kg/day including reddening of the gums, inflammation of the tongue and oral mucosa (associated with oral mucosal ulcers), and mucosal haemorrhage associated with ulceration, necrosis and chronic inflammation or fibroid necrosis of vessels in the stomach, small and large intestine. Fibroid necrosis of blood vessels associated with mucosal haemorrhage may be the result of local increases in blood pressure, as the haemodynamic effects of hypertensive or vasoconstricting agents are known to be associated with vascular toxicity[14]. The adverse gastrointestinal effects observed at doses ≥ 10 mg/kg/day (corresponding to axitinib exposure levels approximately 2 times the anticipated clinical $AUC_{0\text{-}24\,h}$ at the recommended starting dose) were probably responsible for the poor clinical condition seen at this dose level or higher in the 28 day and 26 week studies. It is not known if the microscopic changes in the gastrointestinal tract were reversible since they were not observed in the studies having recovery groups. The no observed effect level (NOEL) of 6 mg/kg/day for adverse gastrointestinal effects in dogs corresponds to axitinib exposure levels approximately 0.4 times the anticipated clinical $AUC_{0\text{-}24\,h}$ at the recommended starting dose. Consistent with the observations in dogs, diarrhoea has been observed clinically with axitinib treatment.

In mice, adverse gastrointestinal effects were confined to the intestinal tract in the 26 week study, and consisted of epithelial hyperplasia and inflammation predominantly in the caecum at doses ≥ 30 mg/kg/day, and to a lesser extent in the colon and rectum at doses ≥ 100 mg/kg/day. This effect which was not observed in the 28 day study did not increase in severity or incidence between the 13 and 26 week assessments and showed a tendency to reverse in the 4 week recovery period. The NOEL for large intestinal hyperplasia in the mouse 26 week study was 10 mg/kg/day, which corresponds to exposure levels 1.5 times the anticipated clinical $AUC_{0\text{-}24\,h}$ at the recommended starting dose.

Hematopoietic effects observed in both mice and dogs included either decreased reticulocyte numbers, or a regenerative reticulocytosis, associated in mice with variable and mild reductions in red cell parameters. In dogs, this was accompanied by bone marrow hypocellularity, which was observed at 10 mg/kg/day in the 26 week repeat-dose study as well as in the 28 day study at doses of 100 mg/kg/day. Bone marrow effects were not observed in mice, but there was an increase in iron-containing pigment deposition in the liver and spleen at doses ≥ 30 mg/kg/day. These effects may be considered to be a class effect, and may at least in part be accounted for by the pharmacological properties of axitinib, since VEGF signalling is known to play a role in haematopoiesis[15]. The haematological effects were found to be reversible in the 4 week recovery period in both species. The NOEL for these haematopoietic effects was 10 mg/kg/day in the mouse and 6 mg/kg/day in the dog (1.5 and 0.4 times the anticipated clinical $AUC_{0\text{-}24\,h}$ at the recommended starting dose, respectively). Additional haematological effects observed in

[14] Greaves, P. Patterns of cardiovascular pathology induced by diverse cardioactive drugs. *Toxicology Letters* 2000:112-113:547-552.

[15] Gerber HP and Ferrara, N. The role of VEGF in normal and neoplastic hematopoiesis. *J Mol Med* 2003:81;20-31.

the 14 and 28 day studies in dogs included decreased prothombin time or increased activated partial thromboplastin time at 100 mg/kg/day (approximately 17 times the anticipated clinical $AUC_{0\text{-}24\,h}$ at the recommended starting dose). Coagulation parameters were unaffected in the mouse toxicity studies at exposure levels up to approximately 50 times the anticipated clinical $AUC_{0\text{–}24\,h}$ at the recommended starting dose, and in the 28 day, 26 week and 9 month toxicity studies in dogs at exposure levels approximately 16, 2 and 0.4 times the anticipated clinical $AUC_{0\text{–}24\,h}$ at the recommended starting dose, respectively.

Reductions in splenic and thymic weight, associated with lymphoid depletion, were observed in the mouse at doses ≥ 100 mg/kg/day and in dogs at doses ≥ 10 mg/kg/day (NOELs 30 and 6 mg/kg/day, respectively; relative exposure approximately 9 and 0. 5, respectively). Similar findings have been reported for other tyrosine kinase inhibitors (for example, sunitinib and sorafenib).

Musculoskeletal changes consisted of incisor tooth odontopathies in mice and thickening of the growth plate in the femur and tibia of both species, which are both related to the role of angiogenesis in the development of teeth and bone. The dental effect in mice was manifested as broken, missing or maloccluded teeth, and was a dose-limiting toxicity. Histologically, the dental effects consisted of odontoblast degeneration and necrosis, dentin degeneration or malformation, ameloblast degeneration and periodontal and pulp cavity inflammation. The dental effects were confined to mice, since incisors are continuously growing in rodents and are thus susceptible to inhibition of angiogenesis. Although a NOEL was not established, this effect is of limited clinical significance for the proposed adult patient population.

Thickening of the physeal cartilage in both mice and dogs was associated with an expanded zone of hypertrophic chondrocytes in the growth plate of the femur and/or tibia. This effect was shown to be reversible in mice 4 weeks after cessation of treatment, and is consistent with the pharmacological action of a VEGFR inhibitor, since the ossification process is dependent on angiogenesis. The growth plate effect was observed in the 28 day study in mice at doses ≥ 30 mg/kg/day (NOEL 10 mg/kg/day, approximately equal to the clinical $AUC_{0\text{-}24h}$), and the 28 day dog study at doses ≥ 30 mg/kg/day (NOEL 10 mg/kg/day, approximately 6 times the clinical $AUC_{0\text{-}24\,h}$). In the latter study, the dogs were approximately 9 months old at the start of treatment, and therefore would be expected to be susceptible to the effects of axitinib, since growth plate closure occurs at around 12 months of age. However, the observed effects on the growth plate and teeth in mice and dogs are of limited clinical relevance to adult humans, who are not actively growing.

Effects on the reproductive organs were observed in mice and dogs of both sexes. The effects in males included reduced testicular weight corresponding to testicular atrophy in both species. In mice, histological findings included hypospermia in the testes and abnormal sperm morphology in the epididymis, while in dogs, degeneration or atrophy of germinal epithelial cells, increased incidences of syncytial cells or multinucleated giant cells and hypospermatogenesis were reported. These effects were shown to be reversible or tending to reverse or reduce in severity 4 weeks after cessation of treatment. The NOEL in the repeat dose study was 30 mg/kg in mice. The results from the mouse study provide an exposure margin of 9 times the clinical $AUC_{0\text{-}24\,h}$. In the mouse fertility study (see below), however, adverse effects on sperm density were observed at all doses (10–100 mg/kg/day) tested. Based on the results in dogs, adverse testicular effects might occur in clinical use, since testicular toxicity was evident at doses ≥ 3 mg/kg/day in the 9 month study, when exposure levels were 0.1 times those anticipated with clinical use.

Female reproductive toxicity consisted of reduced numbers of corpora lutea and uterine atrophy in mice, while the absence of corpora lutea, small follicles, inactive uterus and mammary gland were evidence of delayed sexual maturity in female dogs at all doses

(≥ 10 mg/kg/day) in the 28 day study, although no female reproductive toxicity was evident at this dose in the 26 week study, nor at 6 mg/kg/day in the 9 month study. Reversibility of the female reproductive toxicity was evident after the 4 week treatment-free recovery period in mice. In the 26 week mouse study, a NOEL could not be defined, and the LOEL was 10 mg/kg/day, corresponding to 1.5 times the clinical exposure level. Based on the LOEL of 10 mg/kg/day in the 28 day study in dogs, adverse effects on female reproductive function might be anticipated in women during clinical exposure to axitinib. The female reproductive effects are expected for a VEGFR inhibitor since follicular development and corpus luteum formation are dependent on angiogenesis, and similar effects have been reported with similar agents. Further consideration of the potential reproductive toxicity of axitinib is presented below.

As discussed above (see *Secondary pharmacodynamics and safety pharmacology*) haemodynamic changes were observed in conscious telemetered mice, rats and dogs in cardiovascular safety pharmacology studies. In mice, reversible reductions in arterial blood pressure and bradycardia were observed at a dose of 30 mg/kg/day for 4 days, while a LOEL of 300 mg/kg/day was established in the rat (NOEL 100 mg/kg/day). Similar effects on heart rate were observed in female dogs in the 9 month repeat-dose toxicity study at doses ≥ 3 mg/kg/day, and on blood pressure and heart rate in the safety pharmacology study at ≥ 50 mg/kg/day (NOEL 10 mg/kg/day), although there was a high degree of inter-individual variability. As indicated above in Table 2, the LOEL for haemodynamic effects in mice, rats and dogs corresponded to relative exposures approximately 5, 4 and 6 times the anticipated clinical C_{max} respectively. Hypertensive effects of VEGF inhibitors have been observed clinically, and the mechanism underlying this effect is probably related to the role of VEGF in stimulating mediators of vasodilation such as endothelial nitric oxide synthase (eNOS) activity is recognised as a plausible mechanism[16]. In the primary pharmacology data submitted with the current application, axitinib was shown to inhibit VEGF-mediated signalling though eNOS and the serine/theonine protein kinase, Akt in endothelial cells *in vitro*. Consistent with the animal data, axitinib was found to have a hypertensive effect in clinical studies.

Adverse hepatic effects observed in mice included significantly increased aspartate aminotransferase (AST) in females in the 28 day repeat dose study at doses ≥ 30 mg/kg/day, which was not associated with any histological changes. This effect could not be confirmed in the 26 week study due to insufficient serum. In dogs, a reversible increase in mean serum cholesterol concentration was observed in females dosed at 6 mg/kg/day towards the end of the 9 month study, and both cholesterol and triglyceride levels were elevated in the 14 and 28 day studies at doses ≥ 30 mg/kg/day. A single female dosed at 100 mg/kg/day for 28 days exhibited elevated serum alanine aminotransferase (ALT). The NOEL for hepatic toxicity was 10 mg/kg/day in the mouse and 10 mg/kg/day in the 28 day dog study (discounting the mild effect on cholesterol seen at the end of the 9 month study at 6 mg/kg/day), corresponding to relative exposures of 1.5 times and approximately 6 times the clinical $AUC_{0\text{-}24\,h}$, respectively.

The potential for exocrine pancreas toxicity was evident in the dog, but not in the mouse. In the 26 week study, evidence of pancreatic zymogen depletion was reported in three dogs dosed at 10 mg/kg/day and terminated early owing to severe weight loss. Acinar cell proliferation, zymogen depletion and increased acinar cell apoptosis was observed in the 28 day repeat dose study at doses ≥ 30 mg/kg/day. The NOEL of 6 mg/kg/day in the 9 month study corresponds to a relative exposure of 0.4 times the clinical $AUC_{0\text{-}24\,h}$.

[16] Granger JP. Vascular endothelial growth factor inhibitors and hypertension: a central role for the kidney and endothelial factors? *Hypertension* 2009:54; 465-467.

Genotoxicity

Axitinib was tested in a standard battery of GLP-compliant genotoxicity studies in accordance with ICH guidelines[17]. Formation of the sulfoxide metabolite, PF-03482595, was confirmed in S9 fractions[18] from rat liver, so the potential genotoxicity of this metabolite was not investigated in dedicated studies. In the *in vitro* studies, the concentrations or doses of axitinib tested were appropriate, being limited by compound insolubility and/or cytotoxicity. The maximum dose administered in the *in vivo* study was associated with a marked and significant reduction in body weight gain and marked cytotoxicity and was supported by toxicokinetic data. Axitinib was not mutagenic in the bacterial reverse mutation assay and was not clastogenic in the chomosomal aberration assay, but a dose-dependent increase in polyploidy was observed in axitinib treated cultures both in the absence and presence of a metabolic activation system. Consistent with the findings *in vitro,* an increase in micronucleated polychomatic erythocytes was observed in the bone marrow of treated mice, with a NOEL of 500 and 250 mg/kg/day in male and female mice, respectively (relative exposures >200 and approximately 70 times the clinical $AUC_{0\text{-}24\ h}$, respectively). Further examination of bone marrow slides from treated mice found that approximately 75% of micronuclei stained positive for kinetochore, suggesting that axitinib may interfere with the mitotic separation of chomosomes. This is consistent with an aneuploidic mechanism for micronuclei formation. Thus, the nonclinical data do not support the sponsor's assertion that axitinib is non-genotoxic.

Aneuploidy is a potential mechanism for reproductive toxicity (including birth defects and pregnancy loss) as well as carcinogenicity although the extent of contribution of chemically induced aneugenesis to human disease is at present unknown[19]. The forthcoming International Conference on Harmonization (ICH) genotoxicity guidelines (*Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceutical Intended for Human Use, S2(R1)*), which is currently recommended for adoption to the regulatory bodies of the EU, Japan and the USA, suggest follow-up studies in the event of a positive *in vivo* micronucleus assay. In the event that these follow-up studies are supportive of an aneugenic mechanism for micronuclei formation, the guidelines suggest that it might be possible to determine whether an appropriate safety margin exists compared with clinical exposure, since there is evidence that there is a non-linear dose-response relationship for chemically induced aneugenesis[20,21,22]. The micronucleus assay data provided in the current application are supportive of a relatively high margin of safety for exposure, suggesting that the aneugenicity of axitinib is not relevant at the proposed clinical dose.

Carcinogenicity

Carcinogenicity studies were not conducted with axitinib, in accordance with ICH guidelines[23], which state that carcinogenicity studies are not warranted to support marketing of therapeutics intended to treat patients with advanced cancer. Furthermore,

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[17] ICH S2A: *Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.* [CPMP/ICH/141/95]**;** ICH S2B: *Note for guidance on Genotoxicity: A standard battery for Genotoxicity testing of Pharmaceuticals.* [CPMP/ICH/174/95]

[18] Subcellular fractions of the liver that contain drug-metabolizing enzymes including the CYP450s, flavin monooxygenases, and UDP-GTs.

[19] Aardema, M. *et al.* Aneuploidy: a report of an ECETOC task force IV. *Mutation Research* 1998:410(1);3-79.

[20] Bentley K.S., *et al.* Evaluation of thesholds for benomyl- and carbendazim-induced aneuploidy in cultured human lymphocytes using fluorescence in situ hybridization. *Mutation Research*; 2000:464(1);41-51.

[21] Elhajouji A., *et al.* Indications for a theshold of chemically-induced aneuploidy *in vitro* in human lymphocytes. *Environmental and Molecular Mutagenesis* 1995:26(4):292-304.

[22] Parry, J.M. *et al.* Thresholds for aneuploidy-inducing chemicals. *Mutagenesis* 1994:9(6);503-4.

[23] ICH Topic S9, *Note for guidance on nonclinical evaluation for anticancer pharmaceuticals* [EMEA/CHMP/ICH/646107/2008]

the *in vitro* and *in vivo* genotoxicity tests carried out with axitinib did not provide evidence of mutagenicity and while axitinib was aneugenic, this is not considered to be clinically relevant since the NOEL corresponded to exposure levels 70 times the maximum anticipated clinical $AUC_{0\text{-}24\,h}$ level.

Reproductive toxicity

Studies to investigate the potential reproductive toxicity of axitinib included a fertility study in male and female mice, and GLP compliant embryofetal development studies in mice and rabbits. Although the rabbit study was only a pilot study, maternal and fetal toxicity was clearly evident at very low relative exposure levels, and developmental toxicity was clearly demonstrated in the mouse. The experimental design, doses administered and timing of dosing were all consistent with TGA adopted EU guidelines[24].

Exposure ratios for the developmental toxicity studies (shown below, Table 4) in both species were below one, indicating that adverse reproductive effects observed in the nonclinical studies are considered to be clinically relevant. Higher levels of exposure were examined in the mouse fertility study. Exposure to both axitinib and its sulfoxide metabolite, PF-03482595, were confirmed in both species, confirming their suitability for developmental toxicity studies.

Table 4: Relative exposures in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0\text{-}24\,h}$ (ng·h/mL)	Exposure ratio#	Exposure ratio† (free fraction)
Mouse (CD-1)	Fertility (♂)	10	947	3.6	21
		30	3180	12	72
		100	15200	57	344
	Fertility (♀)	30	2850	11	65
		100	15200	57	344
		250	47900	181	1085
	Embryofetal development	0.3	11.1	0.04	0.25
		1	39.5	0.15	0.9
		3	142	0.54	3.2
Rabbit (NZW)	Embryofetal development	10	54.4	0.21	N/A***
Human (healthy volunteers)	steady state	0.2*	265**	-	-

#animal:human plasma $AUC_{0\text{-}24\,h}$; †animal:human unbound plasma $AUC_{0\text{-}24\,h}$, based on fraction unbound of 0.03 in mice and 0.005 in humans; *based on a 50 kg individual at a daily dose of 5 mg bid (10 mg/day); **human AUC with the proposed clinical formulation at the starting dose of 5 mg bid; ***data on the extent of axitinib binding to proteins in rabbit plasma are unavailable.

[24] 3BS4a: *Detection of Toxicity to Reproduction for Medicinal Products Including Toxicity to Male Fertility. Guideline on Risk Assessment of Medicinal products on Human Reproduction and Lactation: From data to labelling* (effective June 2009) [EMEA/CHMP/203927/2005]

Consistent with the effects seen in the repeat dose studies, adverse effects on male fertility in the mouse study included reduced testicular weight, and reductions in sperm density, although there were no apparent consequences for reproductive performance in this species. The LOEL in males was 10 mg/kg/day, corresponding to a level of systemic exposure 4 times the clinical $AUC_{0\text{-}24\,h}$. Treatment of female mice with axitinib at doses ≥ 30 mg/kg/day in the combined fertility and general reproductive toxicity study had adverse effects on fertility and embryonic viability at all dose levels, including an increase in cohabitation period and post-implantation loss, and reductions in fertility index and embryonic viability (systemic exposure 11 times the clinical $AUC_{0\text{-}24\,h}$).

Lower doses of axitinib were explored in the dedicated embryofetal development studies. The NOEL for maternal toxicity (reduced body weight gain) was 3 mg/kg/day (systemic exposure approximately half the clinical $AUC_{0\text{-}24\,h}$). Most dams dosed at ≥ 30 mg/kg/day in the fertility study exhibited total litter loss as a result of fetal resorption. Postimplantation toxicities included an increased incidence of interfrontal ossification sites, incomplete ossification of the supraoccipitals and reduced ossification of the caudal vertebrae and hindlimb tarsals at doses ≥ 1 mg/kg/day, with cleft palate evident at doses ≥ 3 mg/kg/day. A single fetus which survived maternal dosing at 30 mg/kg/day had cleft palate, depressed eye bulges, absent digits on both forepaws, whole body oedema and gastroschisis. The developmental NOEL in the mouse was 1 mg/kg/day, approximately 0.15 times the clinical $AUC_{0\text{-}24\,h}$.

Axitinib was not well tolerated by pregnant rabbits, since maternal mortality at doses ≥ 100 mg/kg/day, and a dose of 30 mg/kg/day was associated with total post-implantation loss. As a result, developmental toxicity data are only available at a dose of 10 mg/kg/day, which corresponds to systemic exposure 0.2 times the clinical $AUC_{0\text{-}24\,h}$. At this dose, axitinib was maternally toxic (reduced body weight gain or body weight loss, associated with reduced food consumption), and post-implantation loss was increased. Developmental abnormalities seen in the offspring of the only dam to have live fetuses included a shortened tail and bilateral local oedema in the hindlimbs.

In accordance with Guideline ICH S92, a prenatal and postnatal development study has not been conducted with axitinib given the intended treatment of patients with advanced cancer. The adverse reproductive and developmental effects of axitinib are not unexpected given its pharmacological action. The results obtained in the developmental toxicity studies are consistent with the finding that deletion of genes encoding VEGFRs is incompatible with embryonic survival in knockout mice[25]. In addition, axitinib was aneugenic in the *in vivo* micronucleus assay, which could have adverse consequences for reproductive performance in both sexes. However, as discussed above under the heading *"Genotoxicity"*, micronuclei formation *via* an aneugenic mechanism was observed at relative exposures approximately 70 and 220 times the clinical $AUC_{0\text{-}24\,h}$ in male and female mice respectively. These levels are considerably higher than the exposure levels associated with adverse reproductive effects in mice, and therefore inhibition of VEGFRs is a more plausible underlying mechanism.

Axitinib is not intended for administration in pregnant women or women planning to get pregnant (see below, *Pregnancy classification*). In addition, the draft PI states breastfeeding is not advised while taking axitinib.

[25] Dvorak, H.F. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumour angiogenesis and a potential target for diagnosis and therapy. *J Clin Oncol* 2002:20 (21):4386-4380.

Pregnancy classification

The sponsor has proposed that axitinib should have a Pregnancy classification of D[26]. This is appropriate since both the pharmacological characteristics and the results of the developmental toxicity studies are consistent with the view that axitinib may be expected to cause an increased incidence of human fetal malformations or irreversible damage.

Local tolerance

A parenteral formulation of axitinib was tested for its potential to cause local vascular irritation following IV or perivascular administration to rabbits for 3 consecutive days. Minimal to moderate signs of vascular irritation, including mild erythema and oedema, were observed following perivascular but not IV administration of both axitinib and its vehicle, comparable to the effects of vehicle alone. In a study using human blood, the parenteral formulation of axitinib did not produce clinically relevant haemolysis at formulation: blood ratios of 1:10 or 1:6. The results of these studies support the lack of vascular irritancy and compatibility of the parenteral formulation with human blood.

Phototoxicity

There was no evidence of phototoxic potential for axitinib in an *in vitro* fibroblast neutral red uptake assay or following oral administration of single doses of up to 100 mg/kg to hairless albino mice.

Antigenicity, Immunotoxicity

Antigenicity studies with axitinib were not conducted based on its lack of antigenic properties. In accordance with the ICH S92 guideline, immunotoxicity studies with axitinib were not conducted. It is considered that the repeat dose toxicity studies were adequate to evaluate the immunotoxic potential.

Metabolites

The major circulating metabolites in humans are the N-glucuronide (PF-04621675) and the sulfoxide (PF-03482595). Neither metabolite was found to show any clinically relevant interaction with the hERG channel, which is supportive of a lack of potential for prolongation of the cardiac QT interval.

Dedicated repeat-dose toxicity studies were not carried out with PF-03482595, since it is a major metabolite in the mouse and dog, the two species used in the repeat-dose studies. In addition, the demonstration of the formation of the sulfoxide by rat S9 fractions confirmed the suitability of the S9 metabolic activation system for the genotoxicity studies. Specific studies were not carried out with the major glucuronide metabolite. The sponsor argued that glucuronide conjugation generally detoxifies xenobiotics and endobiotics, so glucuronide compounds are typically not reactive or associated with adverse effects. This argument is accepted.

Paediatric use

Axitinib is not proposed for paediatric use and no specific studies in juvenile animals were submitted. The nonclinical safety findings of particular interest to a paediatric population include the potential for axitinib to cause effects on the musculoskeletal system (growth of teeth and long bones) and reproductive organs. These effects and their reversibility have been characterised from repeat-dose toxicity studies performed in the mouse and dog.

[26] The definition of Australian use in pregnancy category D is: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.* Accompanying texts should be consulted for further details.

Nonclinical summary and conclusions

- Axitinib is proposed for the treatment of advanced RCC at a recommended starting oral dose of 5 mg bid, which may be increased up to a maximum daily dose of 10 mg bid, or decreased to a minimum daily dose 2 mg bid, according to individual safety and tolerability.
- Nonclinical data consisted of well designed and documented studies that were conducted in compliance with GLP requirements when required and conformed to the relevant ICH guidelines. The sponsor considered the role of axitinib metabolites in pharmacological and toxicological studies.
- Axitinib was shown to inhibit the RTK activities of VEGFR-1, VEGFR-2, and VEGFR-3 with nanomolar potency. *In vitro* studies demonstrated inhibition of events downstream of RTK activation, including phosphorylation of the Akt, eNOS and other kinase (for example, MAPK44/42 (ERK1/2)) signal transduction pathways, as well as endothelial migration and adhesion, and vascular sprouting and tube formation. Oral administration of axitinib inhibited growth in a broad range of SC or orthotopically implanted human xenograft and rodent tumour models, including SN-12C-GFP (human RCC). *In vivo* evidence was provided for an anti-angiogenic mechanism of action for tumour inhibition. The effective concentrations (unbound) for in vivo anti-angiogenic or anti-tumour activity in animal models were 0.04-0.19 and 0.11-0.33 ng/mL, respectively, compared to the clinical C_{max} (unbound) of 0.14 ng/mL.
- A screening assay for binding to a variety of receptors and ion channels indicated that axitinib is not expected to exhibit any notable secondary PD activity. Safety pharmacology studies showed no probable effects on central nervous, respiratory or gastrointestinal systems, other than an increased gastric emptying in rats. Cardiovascular safety studies showed no clinically relevant effects in the hERG assay or on ECG waveforms. Consistent with findings for other VEGFR inhibitors, increases in arterial blood pressure were observed, associated with reduced heart rate, and this is likely to be clinically relevant.
- Pharmacokinetic studies showed a moderate to high clearance and moderate to large volume of distribution in the mouse, rat, dog and monkey, with plasma half lives ranging from 0.8 to 9.5 h. Intestinal permeability determined in Caco-2 cells *in vitro* was moderate to high, with evidence of active efflux. The PO bioavailabilities in mice and dogs, the two species selected for the repeat-dose toxicity studies, were 16% and 59%, respectively.
- The extent of protein binding by axitinib in human plasma *in vitro* was very high (97.9–99.5%), and consideration should be given to the potential for interactions with other highly protein bound agents with a narrow therapeutic window. Allowing for an apparent interspecies difference in the extent of protein binding (approximately 97% in mice and 98% in rats and dogs), the same total plasma axitinib concentration may correspond to unbound concentrations ranging from approximately equal to up to six times higher in mice and dogs compared with humans. Due to considerable variability in the extent of relative unbound fraction between species, total plasma drug concentrations are used in comparing exposures obtained in animal studies with the estimated clinical exposure.
- Quantitative whole body autoradiography in pigmented mice showed widespread distribution following oral administration, with peak tissue concentrations generally coinciding with the plasma T_{max}. Exposure of the kidney (the site of the tumours to be treated) to radioactivity was 1.5-3 times higher than for blood. Transfer across the blood-brain barrier was limited. There was some evidence of melanin binding, but no ocular toxicity was observed in the toxicity studies.

- Axitinib is extensively metabolised in the liver. The N-glucuronide is the major circulating human metabolite (formed by UGT1A1), with the sulfoxide (formed mainly by the action of CYP3A4/5) being the predominant Phase I metabolite. Comparative metabolic studies confirmed the suitability of the mouse and dog as models for toxicity in humans. Excretion was predominantly *via* the faeces for mice and dogs, with negligible urinary excretion. In humans, urinary elimination was slightly higher, but faecal elimination was still predominant.
- Based on *in vitro* data, axitinib showed the potential to increase plasma concentrations of substrates for CYP2C8, CYP1A2, and CYP3A4/5. The efficacy and/or toxicity of axitinib could potentially be affected by agents that affect the activity of CYP3A4/5. In addition, patients suffering from impaired UGT1A1 metabolism (for example, Gilbert's syndrome) may exhibit reduced axitinib clearance based on the nonclinical data, and plasma axitinib concentrations may be affected by UGT1A1 inhibitors and/or inducers.
- Axitinib displayed a low level of toxicity in acute studies, with maximum non-lethal single oral doses >2000 mg/kg in mice and dogs. Acute toxicity following IV administration was not investigated.
- Pivotal repeat-dose toxicity studies were appropriate in terms of animal species, numbers and study duration (26 weeks in mice and 9 months in dogs). Relative exposures in the mouse studies, based on total or unbound axitinib, were high in comparison with the anticipated human exposure. In the 9 month dog study, exposure was lower than that anticipated clinically, as the maximum doses were limited by severe gastrointestinal toxicity. However, higher exposure levels were achieved in the 28 day repeat dose study in dogs.
- Major toxic effects were evident in the gastrointestinal tract (abnormal faecal excretions, chronic inflammation, ulceration, necrosis or fibroid necrosis of blood vessels in the oral or gastrointestinal mucosa in dogs, and epithelial hyperplasia and inflammation in the intestinal tract of mice), haematopoietic (decreased reticulocyte numbers or regenerative reticulocytosis, associated with variable and mild reductions in red cell parameters, and lymphoid depletion in the spleen and thymus), musculoskeletal (incisor tooth odontopathies in mice, and thickening of the growth plate in the femur and tibia of both species), reproductive tract (testicular atrophy, hypospermia and abnormal sperm morphology in males, and reduced numbers of corpora lutea, uterine atrophy and evidence of delayed sexual maturity in females), liver (elevated AST in female mice, and mild increases in serum cholesterol and triglycerides in dogs) and the exocrine pancreas in dogs (pancreatic zymogen depletion, acinar cell proliferation or apoptosis). Most of these effects can be attributed to the pharmacological effects of axitinib. Exposure comparisons indicate that many of these effects are of potential clinical relevance, although the musculoskeletal toxicity is of limited significance to an adult target population.
- The potential genotoxicity of axitinib was examined in an adequate battery of tests. Axitinib was not mutagenic in the bacterial reverse mutation assay, and was not clastogenic in an *in vitro* mammalian chomosomal aberration assay, although an increased incidence of polyploidy was observed. Increased numbers of micronuclei were shown to be formed in the mouse bone marrow *in vivo*, but these were strongly associated with kinetochore, indicating their relationship with the spindle apparatus during mitosis. The results indicate that axitinib is aneugenic, albeit at very high levels of systemic exposure (no effect levels corresponding to systemic exposure levels approximately 70 and 220 the anticipated clinical exposure in female and male mice, respectively). The carcinogenic potential of axitinib was not investigated, which is acceptable given the lack of clinically relevant genotoxicity, and is in accordance with

TGA adopted EU guidelines on nonclinical testing of pharmaceuticals for the treatment of advanced cancer[27].

- In the combined fertility and developmental toxicity in mice, adverse effects on the male reproductive tract were confirmed. Male fertility was not reduced, but females exhibited increased post-implantation loss and reductions in fertility index and embryonic viability at exposure levels 11 times those anticipated clinically. Lower dose levels were investigated in the dedicated embryofetal development study, in which exposures below those anticipated clinically were associated with increased incidences of variations in skeletal ossification, while cleft palate was observed at exposures approximately half of the anticipated clinical exposure level. Rabbits were considerably more sensitive to the adverse reproductive effects of axitinib, as doses producing exposure levels many times lower than the anticipated clinical exposure level were incompatible with fetal survival. The reproductive effects observed were consistent with the primary pharmacological activity of axitinib. No postnatal development studies were conducted and no studies investigated transfer of axitinib or its metabolites across the placenta or into the milk of lactating animals.
- A parenteral formulation of axitinib was found to be compatible with human blood, and showed no potential for vascular irritancy compared with the vehicle. Axitinib did not exhibit a potential for phototoxicity either in vitro or *in vivo*.

Conclusions

- The pharmacology, PK and toxicology of axitinib were adequately investigated, using appropriate *in vitro* studies and animal models.
- *In vitro* and *in vivo* primary PDs support its potential for anti-tumour activity, and were consistent with a mechanism involving TK inhibition at VEGFRs involved in angiogenesis at clinically relevant concentrations and doses.
- Axitinib is predominantly metabolised by CYP3A4/5. The *N*-glucuronide, formed by the activity of UGT1A1, is the main metabolite circulating in human plasma, and thus UGT1A1would appear to be an important metabolising enzyme *in vivo*, although it is cited as playing a relatively minor role in the proposed Product Information. There may be implications for efficacy and/or tolerability if axitinib is co-administered with other agents which interfere with CYP3A4/5 or UGT1A1 activity, or in patients with impaired UGT1A1 metabolism such as Gilbert's syndrome. In addition, the high level of binding to proteins in human plasma may warrant consideration of potential interactions with other highly bound drugs with a narrow therapeutic window.
- Dose-limiting toxicity occurred in the repeat-dose studies in dogs in particular, resulting in low exposures to axitinib in this species, and adverse gastrointestinal toxicity in particular may be observed clinically. The main toxicologically significant findings in mice and dogs were consistent with exaggerated pharmacological effects arising from the inhibition of the relevant receptor kinases, and with the findings noted previously with other multi-kinase inhibitors. Haemodynamic effects (increased arterial blood pressure, associated with reduced heart rate), observed in the safety pharmacology studies and reduced heart rate in the 9 month dog study may also be of clinical relevance. Axitinib showed aneugenic potential in a standard genotoxicity test battery, although this is unlikely to be clinically relevant since it was associated with systemic exposure levels approximately 150 times those anticipated clinically. The lack of carcinogenicity data is acceptable for the proposed indication.

[27] ICH Topic S9, *Note for guidance on nonclinical evaluation for anticancer pharmaceuticals* [EMEA/CHMP/ICH/646107/2008]

- Axitinib had adverse effects on the male and female reproductive system in mice and dogs, and adversely affected fertility in female mice. As noted in the proposed Product Information, axitinib may impair fertility in human males and females. A full battery of reproductive toxicity studies was not conducted. However, the studies were adequate to determine that axitinib was embryotoxic, fetotoxic, abortifacient and teratogenic. The sponsor's proposed Pregnancy Category D is appropriate. Axitinib should not be used during pregnancy or lactation or in children.
- In conclusion, there are no nonclinical objections to the registration of axitinib for the proposed indication provided the above identified risks are appropriately addressed in the risk management plan. The evaluator also recommended revisions to the PI; details of these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

Clinical rationale

Until recent years advanced stage RCC has proved very resistant to standard forms of chemotherapy. It has been recognised that most RCCs are highly vascularised tumours overexpressing a number of growth factors including VEGF, PDGF and FGF. Several compounds have been developed demonstrating evidence of significant activity in advanced stage RCC, including a group of TKIs such as sorafenib, sunitinib, pazopanib; inhibitors of the mammalian Target of Rapamycin (mTOR) such as temsirolimus and everolimus; and monoclonal antibodies including bevacizumab. All these agents have demonstrated significant activity in the treatment of advanced stage RCC and have been registered for treatment of this condition.

Axitinib has been developed as a further TKI on the basis of potential improved efficacy and a more favourable side effect profile than the currently available TKIs. Targeted therapies, despite sharing some aspects of their safety profiles, have important differences based on their action, that is, whether they target VEGF signalling or mTOR. For the VEGF targeted signalling inhibitors, potency and selectivity for the VEGF/VEGFR target are also considered to play a role. One of the goals for the development of axitinib was to provide a selective targeting of the VEGFR, which could potentially reduce the off-target effects of the multi-target VEGFR TKIs such as sorafenib, sunitinib and pazopanib. Such reduction in the off-target effects could potentially result in reduced myelosuppression associated with sunitinib or pazopanib as well as reduced skin toxicities associated with sorafenib.

Formulation

The proposed commercial formulation of axitinib is a Form XLI red, film coated immediate release (FCIR) tablet supplied in 1 mg and 5 mg strengths. During clinical development, in addition to the Form XLI tablet, Form-IV FCIR tablets manufactured using two processes were studied. The Form-IV FCIR tablets manufactured by these processes were shown to be bioequivalent. The Form XLI FCIR tablets were used in the pivotal Phase III study presented in this submission. The 5 mg tablet used in the study is identical to the proposed commercial formulation.

Axitinib is supplied as a red film-coated tablet containing either 1 mg or 5 mg axitinib together with cellulose-microcrystalline, lactose, croscarmellose sodium, magnesium stearate and Opadry II red as inactive ingredients.

Contents of the clinical dossier

A total of thirty two studies are provided in this submission. In relation to clinical pharmacology studies there are three bioavailability trials, one on absolute bioavailability and two on food effects. There are seven relative bioavailability or bioequivalence trials comparing bioavailability of various formulations of the drug. There are nine other initial tolerability PK/PD trials. There are two drug interaction trials. There are two principal population PK analyses and several population PK/PD analyses combining data from several trials.

There is one pivotal Phase III efficacy and safety study in advanced stage RCC and three supportive Phase II studies. There are also seven studies conducted in other malignancies, which contain variable amounts of safety data.

All aspects of good clinical practice (GCP) were undertaken within these studies.

Biopharmaceutics

This submission comprises ten Phase I single dose axitinib studies examining the bioavailability, bioequivalence and food effect of various axitinib formulations. The bioanalytical methods used to measure axitinib concentrations in human plasma and urine PK samples involved high pressure liquid chromatography (HPLC) coupled with tandem mass spectrometric (MS-MS) detection.

The Inlyta product proposed for commercial use contains axitinib Form XLI. Initial studies utilised Form-IV FCIR tablets, which were manufactured using two processes. The switch was based on findings from Study A4061021 establishing the bioequivalence of the tablets produced by the two processes. Accordingly subsequent clinical studies were conducted using Form-IV tablets produced by the second process. Subsequently, Form XLI tablets of axitinib were manufactured.

Study A4061033 is a relative bioavailability study comparing Form XLI to Form-IV tablets. The results demonstrated that the Form XLI had typical bioequivalence parameters compared to the reference Form-IV when administered in a fed state.

A further bioequivalence study, A4061047, was conducted to compare the proposed commercial Form XLI formulation to Form-IV 5 mg tablets in the fasted state. Axitinib tablet Form XLI and Form-IV were not found to be bioequivalent when administered in a fasted state. This is presumably because Form-IV is more influenced by changes in pH than Form XLI, which is generally less soluble.

Study A4061063 was conducted to assess bioequivalence between Form-IV and Form XLI in the fed state. This demonstrated the 5 mg Form XLI tablets, which became a commercial formulation, are bioequivalent to the 5 mg Form-IV tablets under fed conditions.

Conclusion: These data demonstrated that the proposed commercial formulation, that is, Form XLI FCIR tablets, and the Form-IV FCIR tablets used in the supportive Phase II studies are bioequivalent in the fed state.

A review of the by-study estimates for intra-subject and inter-subject variability in C_{max} and AUC over time zero to infinity ($AUC_{0-\infty}$) parameters following administration of axitinib tablets revealed that the inter-subject variability in axitinib exposure (AUC) generally ranges from 39-57% for the proposed commercial formulation (axitinib Form XLI); the intra-subject variability in axitinib exposure generally ranges from 20-33% for the proposed commercial Form XLI formulation. The results of Study A4061007 combined with the findings from Study A4061018 revealed that there was no reduction in axitinib PK variability with two additional formulations intended to improve absorption, which led to the conclusion that metabolism rather than absorption is the major contributor

(approximately 76%) toward inter-subject PK variability following axitinib administration.

Bioavailability and food effect studies

An absolute bioavailability study (A4061007) was conducted to compare the variability in plasma PK of axitinib following 5 mg PO and 1 mg IV axitinib administered in the fasted state. The absolute bioavailability of a single 5 mg PO dose (geometric mean value) was 58% (CI: 48-72%). Therefore approximately 58% of the administered dose of axitinib reaches the systemic circulation after PO administration.

With regards to relative bioavailability and food effect, this was assessed in four biopharmaceutic studies: A4061006, A4061007, A4061018 and A4061053. The results from these studies, most particularly the definitive food effects study with Form XLI in Study A4061053, are not considered to show a clinically meaningful effect on axitinib exposure in the presence of food. It is therefore recommended that the commercial Form XLI FCIR axitinib tablets be taken with or without food.

Pharmacokinetics

Pharmacokinetic data included in this evaluation were obtained from a total of 24 Phase I, II and III studies with axitinib. They included five studies in patients with advanced RCC, four studies in patients with various solid tumours, fourteen studies in healthy subjects and one study in subjects with hepatic impairment, which included a control, healthy volunteer group. Multiple plasma samples to determine a full PK profile were collected in selected studies. As previously indicated, PK samples were analysed according to HPLC coupled with MS-MS detection. Axitinib PK parameter values were derived from axitinib concentration-time data and estimated by non-compartmental methods using a validated software programme.

Single dose studies

Review of results across the various studies: In relation to single dose PK, these were evaluated in a total of eighteen clinical studies, fourteen in healthy volunteers, one in patients with hepatic impairment and three in patients with advanced solid tumours.

Following single dosing with 5 mg axitinib Form-IV tablets in healthy volunteers, the time to C_{max} (T_{max}) was achieved by approximately 1.5-3 h post-dose in the fasted state and 2.5–3.5 h in the fed state. Axitinib exposure (C_{max} and $AUC_{0-\infty}$) appeared comparable between studies. Mean C_{max} ranged from 21.8-62.5 ng/mL in the fasted state and from 23–49 ng/mL in the fed. Mean $AUC_{0-\infty}$ ranged from 126-240 ng.h/mL fasted and from 136–246 ng.h/mL fed. The mean estimates of half-life in these studies ranged from 3.41–9.44 h fasted and from 3.02-6.1 h fed.

Following single dosing of 5 mg axitinib Form XLI in healthy volunteers, maximum axitinib concentrations were achieved by approximately 1.75-2.0 h post-dose fasted and 2.5-3.25 h fed. Axitinib exposure appeared comparable between studies. Mean C_{max} ranged from 32.8–63.3 ng/mL fasted and from 25.1-43 ng/mL fed. Mean $AUC_{0-\infty}$ ranged from 163–270 ng.h/mL fasted and from 144-220 ng.h/mL fed. The mean estimate for half-life for these studies ranged from 3.38-3.85 h fasted and 2.54-3.36 h fed. Essentially similar results were obtained in patients with advanced carcinoma for the two formulations: there are no inherent differences in PK between healthy volunteers and patients.

Population PK analyses using pooled data from healthy volunteers and patients with advanced solid tumours including RCC did not demonstrate tumour type to be a significant covariate on axitinib clearance in the final model, thereby further supporting similar PK between healthy volunteers and patients. In addition inter- and intra-subject variability

for PK parameters were similar in patients with advanced solid tumours compared to those in healthy volunteers.

Multiple dose studies

Multiple dose PK of axitinib were evaluated in a total of five studies in patients with advanced solid tumours. Axitinib PK parameters following multiple doses of 5 mg bid axitinib in fasted or fed state studies, according to study treatment and study group, are presented in Table 5.

Table 5. Summary of axitinib PK parameters at steady state in patients with advanced solid tumours.

PK Parameter Mean (%CV)	Study A4060010 (Form IV)		Study A4060019 (Form IV)		Study A4061022 (Form IV)	Study A4061044 (Form XLI)	Study A4061046 (Form XLI)
	Fasted[a] C1D15 (n=12)	Fed[a] C1D15 (n=5)	Fed [b,d] C1D-1 (n=14)	Fed [c,d] C1D22 (n=5)	Fed[d,e] C1D15 (n=11)	Fed[d,e] C1D15 (n=6)	Fed C1D15 (n=20)
C_{max} (ng/mL)	64.6 (63)	29.6 (28)	38.6 (40)	44.6 (101)	32.1 (56)	25.9 (84)	37.9 (78)
$AUC_{0\text{-}24}$ (ng.hr/mL)	442 (93)	278 (36)	404 (68)	154 (19)	376 (67)	329 (78)	367 (77)
CL/F (L/hr)	42.6 (95)	41.4 (48)	39.2 (87)	65.7 (18)	42.7 (76)	41.0 (45)	53.1 (80)
V_z/F (L)	208 (158)	131 (46)	108 (42)	140 (37)	--	--	243 (105)
$t_{1/2}$ (hr)	4.04 (117)	2.22 (15)	2.83 (53)	1.45 (19)	--	--	4.09 (144)
T_{max} (hr)	1.02 (0.98-4.00)	2.00 (1.00-4.22)	2.06 (0.98-5.98)	2.74 (1.05-4.67)	4.00 (1.00-4.00)	4.04 (3.93-7.70)	2.00 (1.00-2.50)

Source: A4060010 CSR Table 30; Section 2.7.2, Appendix 1 Table 1.6; A4061019 CSR Table 13.8.3.1 and Table 13.8.5.1; A4061022 CSR Table 13.5.2.3; A4061044 CSR 13.5.2.3; A4061046 Interim Pharmacokinetic Report Table 2 (Module 5, Section 5.3.3.2.)

C_{max} = maximal plasma concentration; $AUC_{0\text{-}24}$ = area under the plasma concentration-time profile from time 0 to 24 hr; CL/F= apparent oral clearance; V_z/F = apparent volume of distribution during the elimination phase; $t_{1/2}$ = terminal half-life; T_{max} = time of maximal plasma concentration. All data is presented as arithmetic mean (% coefficient of variation) with the exception of T_{max} which is reported as median (range); C1D15= Cycle 1 Day 15; C1D-1 = Cycle 1 Day -1 (which represented day 3 of axitinib dosing); C1D22 = Cycle 1 Day 22.

Note: n represents the largest number of subjects for whom at least one pharmacokinetic parameter was estimated.

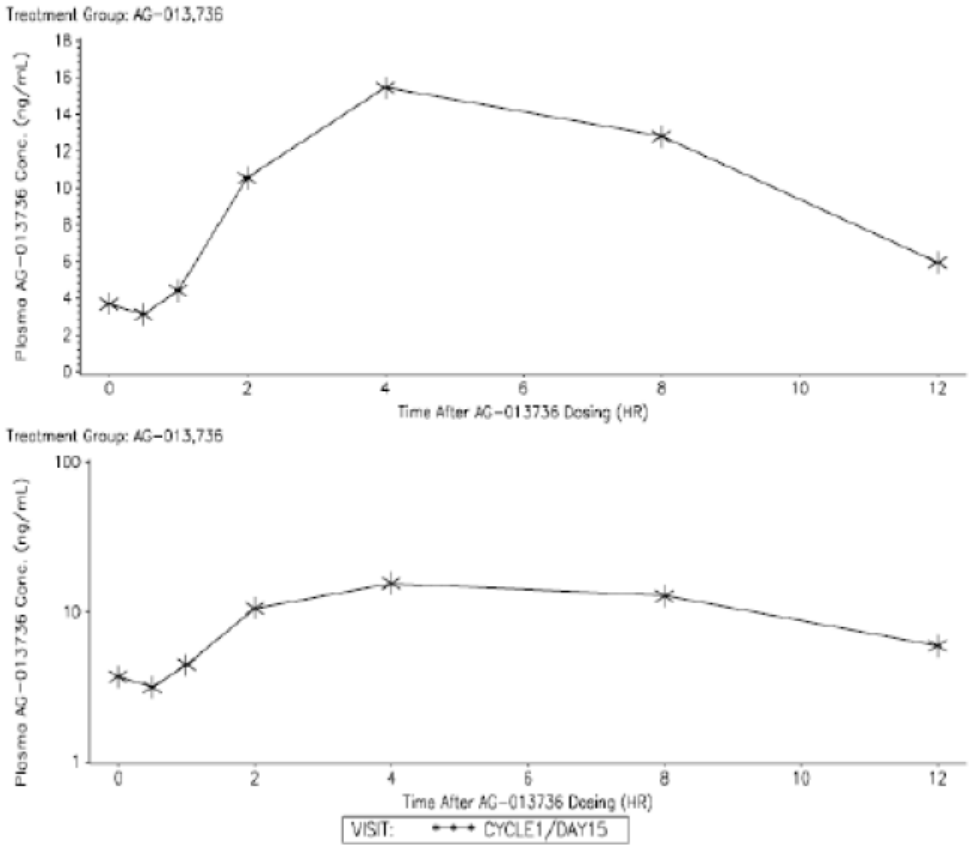
[a] Data from both cohort 5 and 6 in A4060010 study.

[b] A4061019: steady-state parameters when axitinib given alone in the cohort that evaluated combination with

Following multiple dosing with 5 mg Form-IV tablets bid, C_{max} was achieved by approximately 1.02 h post-dose in the fasted state and 2-4 h in the fed state. Axitinib exposure appeared comparable between studies. Mean C_{max} was 64.6 ng/mL in the fasted state and ranged from 29.6-44.6 ng/mL in the fed state. Mean $AUC_{0\text{-}24\,h}$ was 442 ng.h/mL fasted and ranged from 154-404 ng.h/mL in the fed state. Mean estimates of half-life in these states were 4.04 h fasted and ranged from 1.45-2.83 h fed.

Following multiple dosing with 5 mg bid of Form XLI tablets, maximum axitinib concentrations were achieved by approximately 2-4.04 h post-dose in the fed state. Axitinib exposure appeared comparable between studies. Mean C_{max} ranged from 25.9–37.9 ng/mL in the fed state. Mean $AUC_{0\text{-}24\,h}$ ranged from 330-367 ng.h/mL in the fed state. The mean estimate of half-life was 4.08 h in the fed state. Figure 2, below, from Study A4061044, presents representative linear and semi-logarithmic (semi-log) graphs of median concentration-time profiles for axitinib at steady state following multiple oral dosing.

Figure 2. Median plasma axitinib steady-state (Cycle 1 Day 15) concentration-time profiles.



Dose proportionality

Dose proportionality across the clinical 5-10 mg dose range for axitinib has been established. The dose proportionality of axitinib following administration of 5-30 mg is assessed in Study A4060010 and that between 5-10 mg is assessed in Studies A4061044 and A4061050.

In Study A4060010, the results indicate inconsistent changes in the plasma $AUC_{0-\infty}$ and C_{max} values with dose. A conclusive assessment regarding dose linearity could not be made. In Study A4061044, dose proportionality in axitinib PK was evaluated in 6 patients following a single dose of axitinib 5 mg, 7 mg and 10 mg. Results indicate a proportional increase in $AUC_{0-\infty}$ per dose increment. In Study A4061050 in 14 patients receiving a single oral dose of 5 mg, 7 mg and 10mg, proportionality was again observed.

Pooled data from these three studies showed axitinib PK (C_{max} and $AUC_{0-\infty}$) to be generally dose proportional over a range of 5 mg and 30 mg bid.

Dose proportionality following multiple doses at steady state was established in Study A4060010 at 10-40 mg total daily dose, and in A4061019 at 2-10 mg total daily dose. It was shown that the plasma PK of axitinib at steady state were linear, as indicated in Table 6, below. Similar dose proportionality was observed from Study A4061019. This suggests dose proportionality of 3-5 mg doses, but more than proportional $AUC_{0-24\,h}$ at 1-3 mg doses:

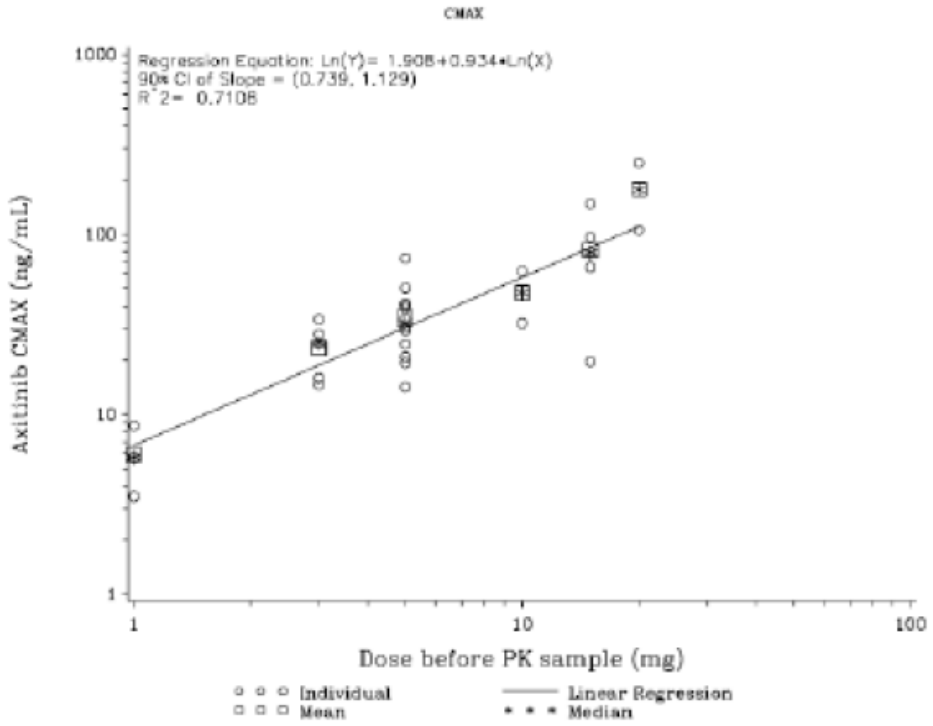
Table 6. Summary of axitinib PK parameters by dose following administration of multiple doses of axitinib (Studies A4060010 and A4061019).

Study	Dose	Total Daily Dose (mg)	CL/F (L/hr)	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/mL)
A4061019 Fed; day 3 post-dose[a]	1 mg BID; n=3	2	38.1 (70)	5.59 (43)	47.8 (89)
	3 mg BID; n=5	6	27.6 (26)	22.2 (35)	198 (55)
	5 mg BID; n=6	10	24.4 (62)	39.5 (43)	382 (80)
A4060010 Fed; day 15 post-dose	5 mg BID; n=5	10	38.3 (48)	28.7 (28)	261 (36)
	15 mg QD; n=6	15	30.6 (121)	67.1 (54)	458 (75)
	20 mg BID; n=3	40	32.7 (98)	94.8 (86)	971 (87)

Source: A4061019 CSR Table 13.8.2.1; A4060010 CSR Table 30
Geometric mean (%CV) reported.
Note: n represents the largest number of subjects for whom at least one pharmacokinetic parameter was estimated.
C_{max} = maximal plasma concentration; AUC_{0-24}= area under the plasma concentration-time profile from time 0 to 24 hr; CL/F= apparent oral clearance.
[a] Pharmacokinetic sampling done on Cycle 1 Day -1, which was day 3 after start of axitinib dosing.

Individual mean and median C_{max} and $AUC_{0-24\,h}$ values for axitinib dose plotted using a log–to-log scale are shown in Figure 3. These results indicate that the plasma PK of axitinib are linear following both single and multiple dosing across the 5-10 mg dose range which is intended for clinical use.

Figure 3. Log-Log plots of individual mean and median axitinib Cmax and AUC0-24 h values as a function of dose following administration of multiple doses of axitinib (Studies A4060010 and A4061019).



Repeated dosing

Evaluation of the degree of plasma accumulation of axitinib with continuous dosing was undertaken in Studies A4060010, A4061022 and A4061044. Within-patient accumulation ratios for $AUC_{0-12\,h}$ following continuous bid dosing indicate accumulation of axitinib in human plasma, consistent with the half-life of the drug. The mean observed accumulation ratio for axitinib plasma $AUC_{0-12\,h}$ with continuous dosing ranged from 1.35-1.48 across the three studies in the fed state. This is in agreement with what is expected based on the plasma half-life of the drug. There is no evidence that axitinib exhibits auto-inhibition or auto-induction with chronic dosing.

Absorption

As has previously been indicated, after PO administration C_{max} occurred within 4 h with a range of median T_{max} across studies of 2.5-4.1 h. It has also been demonstrated in earlier data that there is no influence on absorption as defined by plasma levels of axitinib following food. Accordingly it is recognised that axitinib can be administered either with or without food.

The aqueous solubility of axitinib is pH-dependent with a low pH resulting in the highest solubility. The sponsor assessed whether potent antacids could compromise the dissolution and absorption of the drug. In Study A4060010 the effect of the proton pump inhibitor rabeprazole was assessed on the steady state plasma PK of 5 mg bid axitinib. In the presence of rabeprazole the rapid rate of absorption of axitinib was decreased in the majority of patients, who had clinically insignificant changes in the $AUC_{0\text{-}24\ h}$.

Distribution and protein binding

The mean volume of distribution of axitinib was 68 L following 1 mg IV administration in the fasted state, as was demonstrated in Study A4061007. This value greatly exceeds the typical plasma volume of 3 L and indicates that axitinib is bound to plasma proteins and distributed into tissues from the plasma.

In vitro studies have demonstrated axitinib is highly bound to plasma proteins, that is, 99.5%. The results also demonstrated that mild to moderate hepatic impairment did not alter the plasma protein binding for axitinib.

Metabolism

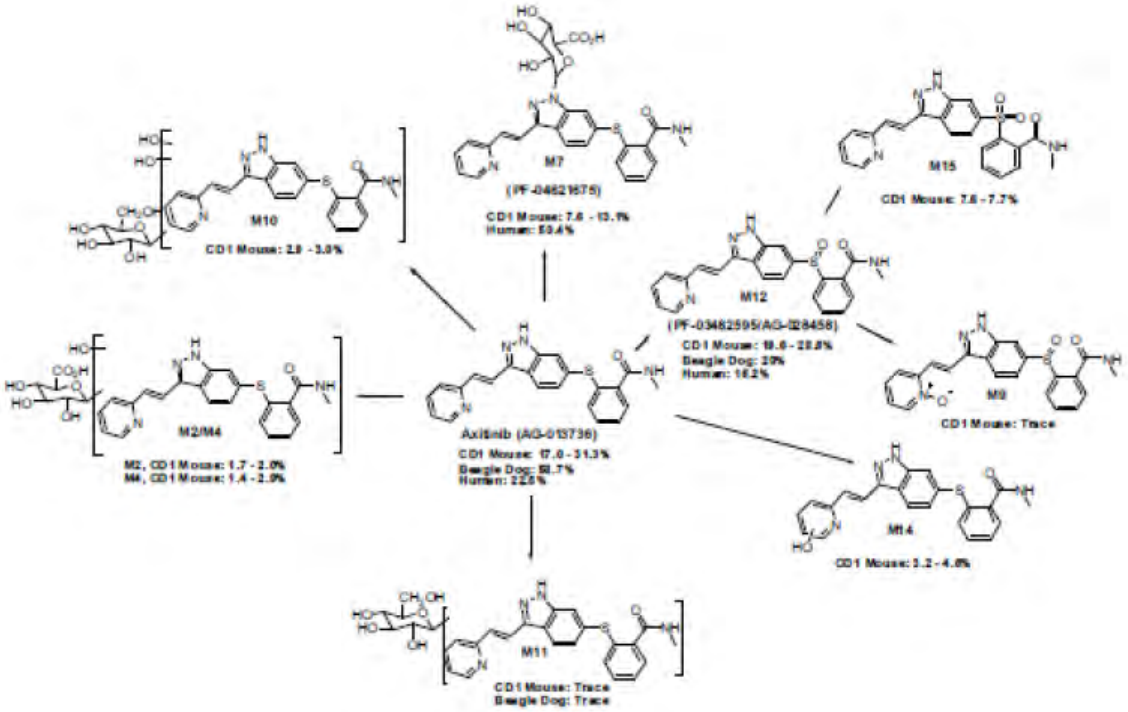
As determined from *in vitro* studies, axitinib is metabolised primarily in the liver by CYP3A4/5 and, to a lesser (< 10%) extent, by CYP1A2, CYP2C19 and UGT1A1. Following PO administration of a single 5 mg dose of ^{14}C-labelled axitinib to healthy volunteers in Study A4061003, the radioactivity profile for the drug related components, and structural characterisation of axitinib and its metabolites in human plasma, urine and faeces, indicated extensive metabolism to a variety of primary and secondary metabolites. These are illustrated in Figure 4, below.

In urine, the parent drug was not detected, while in faeces the parent drug represented the single most predominant radioactive component (12% of the dose). However, all faecal radioactive metabolite components together accounted for 16% of the dose.

As it is recognised that both absorption and metabolism contribute towards the overall variability when agents were administered PO, the relative contribution of absorption and metabolism to the observed inter-subject variability in axitinib plasma PK was assessed by an absolute bioavailability study (A4061007) conducted in 16 healthy volunteers. Similar variability estimates for plasma exposure following IV versus fasted PO dosing, that is, 44% versus 58%, indicated that metabolism was a major contributor towards the overall PK variability for axitinib. Food did not appear to contribute significantly towards variability.

The hepatic extraction ratio of axitinib in humans was estimated using data from Study A4061007, which revealed that axitinib is a low-extraction drug with approximately 32% of the drug being metabolised during a single pass though the liver.

Figure 4. Proposed *in vivo* axitinib metabolic schema



Effect of strong CYP3A4/5 inhibitors

An interaction study with ketoconazole was conducted in 35 healthy volunteers to identify the extent of increase in plasma axitinib exposure in the presence of metabolic inhibition (Study A4061004). There was mean 2 fold increase in plasma exposures and a 1.5 fold increase in peak plasma concentrations with a single 5 mg PO dose of axitinib in the presence of ketoconazole. This indicates that co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations.

Effect of strong CYP3A4/5 inducers

An interaction study with axitinib and rifampin, a strong CYP3A4/5 inducer, was conducted in 40 healthy volunteers to identify the extent of decrease in plasma axitinib exposures in the presence of metabolic induction (Study A4061026). Rifampin administered at a dose of 600 mg once daily for 9 days reduced the axitinib geometric mean $AUC_{0-\infty}$ by 79% and C_{max} by 71%.

Assessment of hepatic impairment on axitinib PK

The effect of hepatic impairment was evaluated in Study A4061036. Mild hepatic impairment did not alter axitinib plasma exposures compared to normal hepatic function. However there was an approximate 2 fold increase in axitinib $AUC_{0-\infty}$, both total and unbound, and an approximate 1.3 fold increase in axitinib C_{max} in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. This suggests a potential need to dose-reduce axitinib in the presence of moderate hepatic impairment.

Elimination

As previously indicated renal excretion does not contribute to excretion of axitinib parent drug, and axitinib elimination occurs primarily by hepatobiliary excretion. In the human mass balance Study A4061003, involving 8 healthy volunteers receiving ^{14}C-labelled axitinib as a single dose, variable faecal recovery was documented, with the overall radioactive recovery ranging from 51.3-77.9% of the dose in 6 of these subjects.

Half-life

Following peak plasma concentrations obtained after PO administration, the axitinib plasma profile demonstrated a multi-compartmental decline. In general, when serial PK samples were collected from healthy volunteers, a short initial distribution half-life was noted in the majority of subjects, followed by a longer half-life of 2.5-6.1 h in the fed state. The plasma half-life for axitinib of 2.5-6.1 h is consistent with the observed accumulation ratio of approximately 1.4 in patients after multiple dosing.

The half-life of axitinib measured in healthy volunteers and patients with advanced solid tumours was comparable being 2.5-6.1 h in healthy subjects and 2.3-4.8 h in patients with advanced solid tumours. In addition, the axitinib effective plasma half-life with the intended commercial formulation XLI ranged from 2.5-3.4 h in healthy volunteers after a single dose.

Population PK

Two primary, pooled population PK analyses were conducted to assess axitinib PK in healthy volunteers and patients with advanced solid tumours including advanced RCC.

The report (PMAR-00075), which is a population PK analysis of axitinib PK in healthy volunteers, involved an evaluation of data from 337 healthy volunteers receiving single dose axitinib in ten clinical studies. In this analysis the disposition of axitinib was described by a linear two-compartment model which included a lag-time and a first order absorption rate constant.

For Form-IV, the rate of absorption and absolute bioavailability of axitinib was significantly increased by 207% and 33.8% respectively in the fasted state compared to the fed state. The effect of food on Form XLI could not be assessed in this analysis as Study A4061053 was not available at the time of the analysis. Another covariate analysis of the effect of body weight on central volume of distribution (Vc) was statistically significant, but this effect was within the estimated inter-individual variability in axitinib Vc, and is not considered clinically relevant. None of the other study covariates, in particular genetic polymorphisms in UGT and CYP2C19, were significant.

The other population PK analysis (PMAR-00079) described analyses conducted in 12 healthy volunteer studies and five studies in patients with advanced solid tumours, including advanced RCC. Similar to the results from healthy volunteers, in analysis PMAR-00075 the disposition of axitinib was described by a linear two-compartment model which included a lag-time and first order absorption rate constant. For Form-IV the rate of absorption and absolute bioavailability for axitinib was increased by 197% and 33%, respectively, in the fasted and fed states. There was no food effect observed for Form XLI. When axitinib was administered as Form XLI in the fed state, absolute bioavailability of axitinib was reduced by 12.1% compared to Form-IV. The clearance (CL) of axitinib was estimated to be 14.6 L/h (inter-individual variance = 60%) and Vc was estimated to be 47.3 L (40%).

Covariate assessments

On reviewing various covariates, body weight was identified as a significant covariate for axitinib Vc in the final model. With lighter individuals, Vc was expected to be lower relative to heavy individuals, resulting in greater peak plasma concentrations. For a 58 kg individual the axitinib Vc was expected to decrease by 17% compared to a 74 kg individual. For a 94 kg individual the axitinib Vc was expected to increase by 20%. Overall, the effect of body weight on Vc was expected to have a minimal effect on the plasma concentration of axitinib.

In relation to age, the model predicted lower axitinib CL; an approximately 21% decrease in CL is expected in patients older than 60 years of age, resulting in modestly higher exposures for older subjects. The increase for CL was not considered clinically relevant.

The influence of Asian and Japanese ethnicity on axitinib CL was examined separately relative to all other races. The results showed that only Japanese ethnicity was associated with a 25% lower axitinib CL, resulting in correspondingly higher axitinib exposure. This could also be correlated with the overall lower body weight among Japanese patients in the study. The median age of Japanese patients was 63 years, compared to an overall median age of 42 years for the pooled data analysis set. This suggests confounding of results and therefore interpretation of the data with caution. It is also worth commenting that the overall 25% higher exposure in Japanese subjects predicted in the population PK analysis was within typical inter-subject variability in CL, that is, 60%, and hence is not considered clinically relevant.

Accordingly, the inclusion of all three significant covariates discussed above, namely, body weight, age, and Japanese race, resulted in no changes in residual variability between the final model and the base-model. Thus, they do not translate to clinically important descriptions of variability in axitinib PK and do not merit dose alterations.

A review of other intrinsic effects, including gender, performance status, tumour type, and mild to moderate renal impairment, failed to demonstrate any significant effect on axitinib PK, thereby not warranting consideration of potential dose adjustment. However as previously discussed in relation to hepatic impairment, moderate hepatic impairment resulted in an approximate 2 fold increase in axitinib $AUC_{0-\infty}$ and a 1.3 fold increase in axitinib C_{max} compared to patients with normal hepatic function. Accordingly, a study dose of 2 mg bid was recommended when administering to patients with moderate hepatic impairment.

The review of effect of extrinsic factors in the population PK models revealed that the concurrent administration of axitinib with strong CYP3A4/5 inhibitors resulted in an increased geometric mean $AUC_{0-\infty}$ and C_{max} of axitinib by approximately 2 fold in healthy volunteers, suggesting dose adjustments being required. Co-administration of axitinib and CYP3A4 inducers resulted in decreased geometric mean $AUC_{0-\infty}$ and C_{max} of approximately 79% and 71% in healthy volunteers, again recommending dose adjustment when there was co-administration of axitinib and strong inducers of CYP3A4/5.

Pharmacodynamics

PK/PD correlation studies

To assess correlations of clinical response endpoints, an extensive population based PK/PD analysis was conducted using data from the three Phase II advanced RCC studies (A4061012, A4061023 and A4061035). This data included results from a parametric exposure-response model relating tumour size to axitinib plasma exposure; and from time to event analyses evaluating progression-free survival (PFS) in relation to steady state AUC and diastolic blood pressure in patients with advanced RCC.

Tumour size

Considering the relationship between axitinib exposure and change in tumour size, study data showed the tumour size decreased over time in both cytokine-refractory patients (Studies A4061012 and A4061035) and sorafenib-refractory patients with advanced RCC (Study A4061023). The mean sum of lesion diameter percentage change from baseline reached a 30% decrease by approximately week 32 and approximately week 48 of treatments in cytokine-refractory and sorafenib-refractory patients, respectively. There was a trend towards a decrease in tumour size with increasing axitinib steady state AUC.

These data therefore suggest that the tumour dynamics model indicates that a decrease in tumour size over time correlated with increasing axitinib exposure for both cytokine–refractory and sorafenib-refractory patients.

Axitinib exposure and clinical response

To examine the relationship between axitinib exposure and clinical response, a Cox–proportional analysis was performed to investigate the relationship between axitinib exposure and PFS. Results of this Cox-proportional analysis showed that the higher AUCs are associated with a longer PFS in both cytokine-refractory and sorafenib-refractory patients.

Blood pressure and clinical response

A Cox-proportional analysis was performed to investigate the relationship between maximum diastolic blood pressure on study or at end of Cycle 1 and PFS in both cytokine-refractory and sorafenib-refractory patients. The Cox-proportional analysis showed that in both cytokine-refractory and sorafenib-refractory patients, those who had at least one diastolic blood pressure measurement ≥ 90 mmHg at any time during study treatment had a longer PFS than those who did not.

Blood pressure increases and axitinib exposure

In order to evaluate if axitinib-related blood pressure increase was associated with axitinib plasma exposure, the correlation between diastolic blood pressure and AUC was assessed. Results showed a weak correlation between axitinib exposure and diastolic blood pressure for all three Phase II advanced RCC studies, with the correlation (R^2) value < 0.10. This indicated that an axitinib related increase in diastolic blood pressure in individual subjects is an independent PD response that does not simply represent axitinib plasma exposure.

Axitinib exposure and adverse events

A correlation assessment between axitinib PK and safety was undertaken. A logistic regression analysis was conducted to assess the probability of having a ≥ Grade I adverse event as a function of axitinib exposure and dose. AUC and dose (that is, average total daily dose) were assessed at various time points over the previous day, week, month and study prior to the maximum Grade of adverse events for each patient. Exposure measures were calculated using the patient's total daily dose and individual *post hoc* clearance and bioavailability.

The exposure measures best correlated with safety endpoints were found to be the last daily dose and/or AUC before the observed highest Grade of the adverse event in each patient. In the logistic regression models, relationships between exposure and safety endpoints were shown for all adverse events except for hypertension. For patients with cytokine-refractory advanced RCC the probability of a ≥ Grade I adverse event for diarrhoea, hand-foot syndrome, fatigue, proteinuria or stomatitis was correlated with axitinib dose/exposure. For patients with sorafenib refractory advanced RCC, the probability of a ≥ Grade I adverse event for diarrhoea and stomatitis was correlated with axitinib dose/exposure.

QT interval

An analysis was undertaken to assess the effect of a single dose of axitinib on ECG derived QT intervals corrected for heart rate (QTc) when given alone and in the presence of metabolic inhibition with ketoconazole. The analyses represent pre-planned and structured assessment of the PK/PD modelling of the QTc signal for axitinib and plasma concentrations of the drug. Results from the study indicated that axitinib and plasma exposure exceeding those typically reported for RCC patients did not produce clinically significant QT prolongation.

Maximum tolerated dose (MTD) determination

In the first in-human Phase I study involving patients with advanced stage malignancies (Study A4060010), axitinib was administered at six different dose levels to six cohorts. The primary dose limiting toxicity was hypertension. Increases in blood pressure were noted in all 10 patients of the first two cohorts, at doses ranging from 10 mg once daily to 30 mg bid; five of them were Grade III or IV severity, which were responsive to antihypertensive medications and were also reversible when axitinib treatment was stopped. Two patients had seizures that both recovered without sequelae. The protocol was then amended to exclude patients with uncontrolled hypertension and to have patients monitor their blood pressure daily.

In subsequent cohorts where patients received doses ≤ 15 mg/day (n = 26), hypertension, considered a dose limiting toxicity, was observed in one patient receiving 15 mg/day. Six other patients developed hypertension that was not considered dose limiting and was managed by anti-hypertensive medication.

Based on the results of the first 10 patients, a dose of 20 mg bid exceeded the MTD. Dose limiting toxicities also occurred in patients in the first two cohorts who received 10 mg bid either as a starting dose or dose reduction and therefore this dose was also considered above the MTD.

Lower doses were then evaluated in subsequent cohorts, with the eventual MTD being defined as 5 mg bid in the fasted state. Of the 14 patients who received 5 mg bid in the fasted state, there were two dose limiting toxicities, being Grade II stomatitis and Grade III diarrhoea. Hypertension Grades I to III, which was not dose limiting and needed standard hypertensive therapy, was reported in 6 of 14 patients.

Associated measures of drug related PD changes in blood plasma and vascular permeability in selected lesions in individual patients was assessed in Study A4060010, which provided corroboration that the selected dose of 5 mg bid was an optimal dose and also agreed with PD assessment of drug-related changes in vascular permeability and flow.

Soluble protein changes

Since axitinib is a potent inhibitor of VEGFR 1, 2 and 3, changes in soluble proteins were assessed in several clinical studies. Soluble proteins assessed in the axitinib clinical development programme included plasma VEGF, VEGFR-2, VEGFR-3 and sKIT. Plasma samples were collected in a number of Phase II studies involving advanced malignancies and all the studies included 5 mg bid as the starting dose for axitinib.

Significant decreases in VEGFR-2 (mean percentage change from baseline ranging from −27 to -42%) and VEGFR-3 (mean percentage change from baseline ranging from -26 to −55%) concentrations, and increases in plasma VEGF (mean percentage change from baseline ranging from 152-460%) concentrations, were observed in these studies. This indicates that at the clinical axitinib starting dose of 5 mg bid there was evidence for mechanism-based changes in target related proteins.

Dosage selection for the pivotal trials

The recommended PO starting dose of axitinib for the treatment of patients with advanced RCC is 5 mg bid, with or without food. This is based on the analyses defining the MTD, discussed above, particularly related to Study A4060010.

As previously discussed, assessment of the food effect using Form XLI (the proposed commercial formulation) indicated an absence of clinically significant changes in axitinib plasma exposure in the presence of food compared to the fasted state.

Further support for the dose selection was based on the population PK modelling of clinical response, changes in soluble proteins, and changes in vascular permeability/blood flow, discussed above.

Efficacy

This submission involves presentation of data from four clinical studies, including the pivotal Phase III study, A4061032, a randomised, open label, multicentre study of axitinib versus sorafenib in patients with advanced RCC after failure of treatment with one prior systemic therapy containing one or more of the following agents: sunitinib, bevacizumab plus interferon alpha (IFN-α), temsirolimus, or cytokines.

There were three supportive Phase II, single arm studies in advanced RCC, two studies in cytokine-refractory advanced RCC (A4061012 and A4061035) and one study in sorafenib–refractory advanced RCC (A4061023). A4061012 was a Phase II, single arm, open-label, multicentre study of axitinib in patients with advanced RCC after failure of treatment with one prior cytokine-based therapy. Study A4061035 was a Phase II single arm, open-label, multicentre study of axitinib in Japanese patients with advanced RCC after failure of treatment with one prior cytokine-based therapy. Study A4061023 was a Phase II single arm, open-label, multicentre study of axitinib in patients with advanced RCC after failure of treatment with at least one prior sorafenib-based therapy; most subjects had additionally received prior treatment and/or other agents.

Pivotal Study A4061032

Study design, objectives, inclusion and exclusion criteria

The pivotal study was a Phase III randomised, open-label, multicentre study of axitinib compared with sorafenib in patients with advanced RCC after failure of treatment with one prior systemic therapy. The primary objective of the study was to compare PFS in patients with advanced RCC receiving either axitinib or sorafenib. Secondary objectives were to compare the overall survival and objective response rate in patients and to evaluate the duration of response, patient reported outcomes and safety within each treatment arm.

At the time this study was designed, sorafenib was the only approved treatment option in the second line treatment of advanced RCC. Although an open-label study design was used in this trial, disease progression was assessed using a blinded Independent Review Committee (IRC). Data cutoff date was the 31 August 2010 and the final analysis of PFS conducted on 15 November 2010.

Eligible patients were male or female, 18 years or older with histologically or cytologically confirmed diagnosis of RCC with a component of clear cell sub-type with evidence of metastatic disease. Patients required at least measurable target lesion documented radiographically and disease progression according to Response Evaluation Criteria In Solid Tumours (RECIST[28]) criteria after one prior systemic first-line regimen for advanced RCC. Prior systemic treatment, radiotherapy or surgical procedures should have ended at least two weeks prior to enrolment. Patients with evidence of uncontrolled hypertension were not eligible however patients whose hypertension was controlled by anti–hypertensive therapy were eligible. Patients required adequate organ function,

[28] RECIST is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response with X-ray, computer tomography and magnetic resonance imaging.

Eastern Cooperative Oncology Group ECOG performance status of 0 or 1[29] and a life expectancy of at least 12 weeks.

Treatment

Patients were randomised in a 1:1 ratio to either investigational treatment of single agent axitinib or to the control treatment of single agent sorafenib. Randomisation was stratified according to ECOG performance status, prior treatment regimen (sunitinib-containing regimen versus bevacizumab-containing regimen versus temsirolimus-containing regimen versus cytokine-containing regimens).

Treatment was administered continuously in four-week cycles. The starting dose for axitinib was 5 mg bid administered PO with food. The XLI tablets of axitinib were used in the study. Sorafenib was administered PO without food at a starting dose of 400 mg bid. Patients who tolerated axitinib with no related adverse effects above a Grade II level for two consecutive weeks were recommended to have their dose increased by one dose level, to 7 mg bid, and subsequently to a maximum of 10 mg bid. Special dose modifications for hypertension and proteinuria were undertaken, including a dose reduction to one lower dose level at 3 mg bid for these adverse events, and subsequently to a minimum of 2 mg bid in patients experiencing axitinib related Grade III non-haematological toxicity.

Treatment continued until patients experienced progressive disease, occurrence of unacceptable toxicity or death, or withdrawal of subject consent. Following discontinuation of study treatment, patients were followed for at least 28 calendar days after last dose of study drug for adverse events. All patients were followed for survival every three months following discontinuation of study treatment for at least three years after randomisation of the last subject.

Efficacy assessments

Baseline tumour assessments were performed within four weeks prior to randomisation. Imaging studies at screening included at least computer tomography (CT) or MRI scans and bone scans. Subsequent scans were required for all patients every six weeks for the first 12 weeks, then every eight weeks. Determination of tumour response progression was based on RECIST criteria. Review of tumour imaging was performed by an external IRC. Results of the IRC review of disease response progression were the basis for the primary analyses of efficacy endpoints. Review by IRC was performed in a blinded manner without knowledge of treatment assignment.

Reported outcomes of health related quality of life and disease related symptoms were assessed in the study using the Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index (FKSI) and time to deterioration of a composite endpoint of death, progression and a decrease in FKSI. FKSI includes 15 questions and a nine-question sub–scale, that specifically measured symptoms related to advanced RCC.

Statistical methods

In relation to statistical methods, the study was designed to test the hypothesis of whether treatment with single agent axitinib resulted in at least a 40% improvement in median PFS over single agent sorafenib. The initial target samples size was determined based on 90%

[29] ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 - Dead

power to demonstrate a 40% improvement in PFS using a one-sided stratified log-rank test and a significance (p) level of 0.025. The planned enrolment was 650 subjects. This number of subjects was required to observe 409 events of disease progression and deaths, assuming a five month follow up period after the last subject was enrolled. Other secondary and supportive efficacy analyses were tested at a significance level of 0.025 by a one-sided test.

Efficacy data was based on the Full Analysis Set, which included all patients randomised regardless of whether patients received study drug or received a different drug from that to which they were randomised.

Patient enrolment began on 15 September 2008 and a total of 723 patients were enrolled; 361 randomised to axitinib and 362 to the sorafenib. Two patients in the axitinib arm and seven in the sorafenib arm were randomised to study but were not treated. Thus 723 patients from the primary population were evaluated on efficacy endpoints and subject characteristics. Patients were enrolled from 175 sites in 22 countries.

Baseline data

Demographic and baseline characteristics for the pivotal study were similar between the axitinib and sorafenib treatment arms with regard to gender, age, race, performance status, geographic region and Memorial Sloan-Kettering Cancer Center (MSKCC) risk status. The MSKCC risk groups were derived using four risk factors, namely lactic dehydrogenase, serum haemoglobin, corrected serum calcium and absence of prior nephrectomy. The majority of patients in each treatment arm were < 65 years old, male and White. Slightly more than half the patients had an ECOG performance status of 0 and were in the intermediate MSKCC risk group.

Overall the baseline disease characteristics and prior treatment history were similar between the axitinib and sorafenib treatment arms. Nearly all patients in both treatment arms had a baseline histological classification of clear cell RCC and most patients were in Stage IV. Similar proportions of patients in the axitinib and sorafenib treatment arms had previous radiotherapy and previous surgery (nephrectomy). Most patients had previously experienced disease progression on either sunitinib based therapy (54%) or cytokine based interleukin-2 (IL-2) or IFN-α therapy (35%).

Discontinuations and dosing interruptions

In the pivotal study, 221 or 61.2% of patients were discontinued from treatment with axitinib, and 256 or 70.7% of patients discontinued from treatment with sorafenib. The most common reason for discontinuation of treatment with axitinib or sorafenib was objective progression or relapse and adverse events. A larger proportion of patients in the axitinib treatment arm compared with the sorafenib treatment arm started Cycle 10.

Overall patients on axitinib remained on treatment for longer median time than those on sorafenib. Dose interruptions due to adverse events were common in both treatment arms, but were slightly less frequent with axitinib. Most patients had their dose titrated up or down during the study: 132 patients or 36.8% had their dose titrated up, but 71 of these had their dose subsequently reduced; 110 patients or 30.6% had their dose reduced; while 139 subjects or 38.7% remained on the starting dose of 5 mg bid throughout study duration.

Primary efficacy endpoint - PFS

IRC analysis of PFS

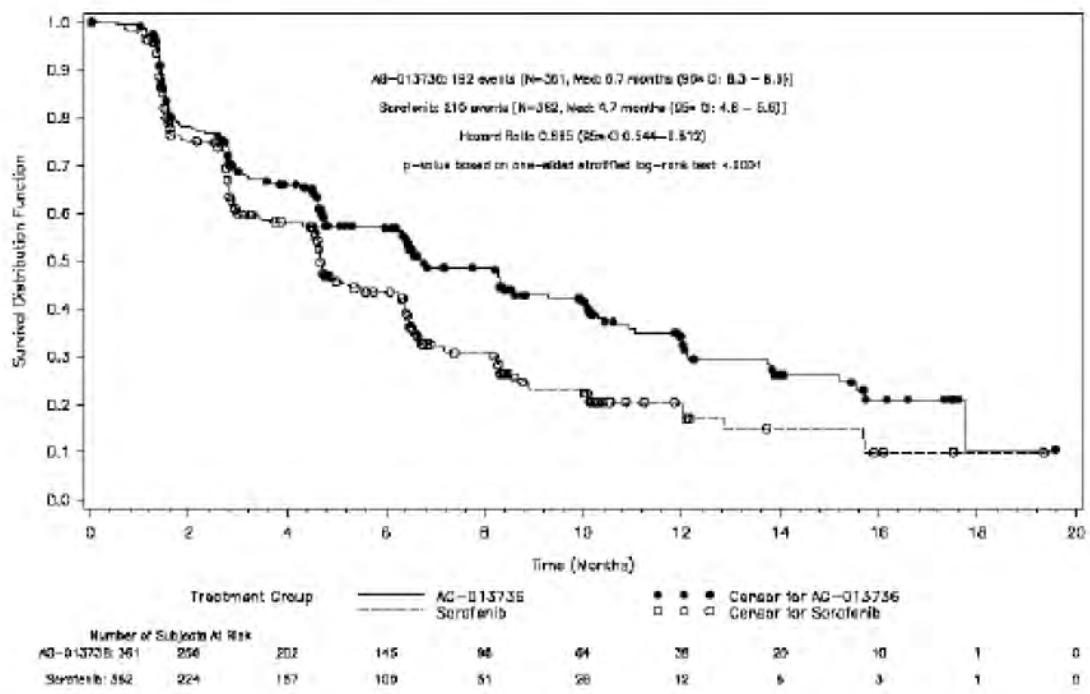
Reviewing the results of the primary efficacy endpoints, PFS as assessed by the IRC, a significant improvement in PFS was observed, favouring axitinib. This is summarised in Table 7:

Table 7. Pivotal Phase III Study A4061032: Summary of PFS by treatment and stratification factor (stratified analysis, IRC assessment; Full Analysis Set).

Progression-Free Survival Parameter	Axitinib (N = 361)	Sorafenib (N = 362)
Overall stratified analysis (N)	361	362
Progression Status [n (%)]		
Subject progressed or died due to any cause while on study[a]	192 (53.2)	210 (58.0)
Objective progression observed	180 (93.8)	200 (95.2)
Death without objective progression	12 (6.3)	10 (4.8)
Subject did not progress or die due to any cause while on study[a]	169 (46.8)	152 (42.0)
Progression-free survival (months)		
Quartiles (95% CI)[b]		
25%	2.7 (1.7, 2.9)	2.5 (1.6, 2.8)
50% (median)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)
75%	15.2 (12.1, NE)	8.8 (7.2, 12.0)
Axitinib vs. sorafenib		
Hazard ratio[c] (95% CI)	0.665 (0.544, 0.812)	NA
p-value[d]	<0.0001	NA
Prior sunitinib-containing regimen (N)	194	195
Progression Status [n (%)]		
Subject progressed or died due to any cause while on study[a]	117 (60.3)	120 (61.5)
Objective progression observed	109 (93.2)	114 (95.0)
Death without objective progression	8 (6.8)	6 (5.0)
Subject did not progress or die due to any cause while on study[a]	77 (39.7)	75 (38.5)
Progression-free survival (months)		
Quartiles (95% CI)[b]		

The primary analysis is based on 402 events, 192 events occurred in the axitinib treatment arm and 210 in the sorafenib treatment arm. 380 events (180 in the axitinib arm and 200 in the sorafenib arm) were disease progression, while 22 events (12 in the axitinib arm and 10 in the sorafenib arm) were deaths without objective tumour progression. Median PFS was 6.7 months in the axitinib treatment arm and 4.7 months in the sorafenib arm, with a hazard ratio (HR) of 0.665 and a p value of < 0.0001 based on log rank test. The Kaplan-Meier curves demonstrating this are given in Figure 5:

Figure 5. Pivotal Phase III Study A4061032: Kaplan-Meier curves of PFS (IRC assessment; Full Analysis Set)



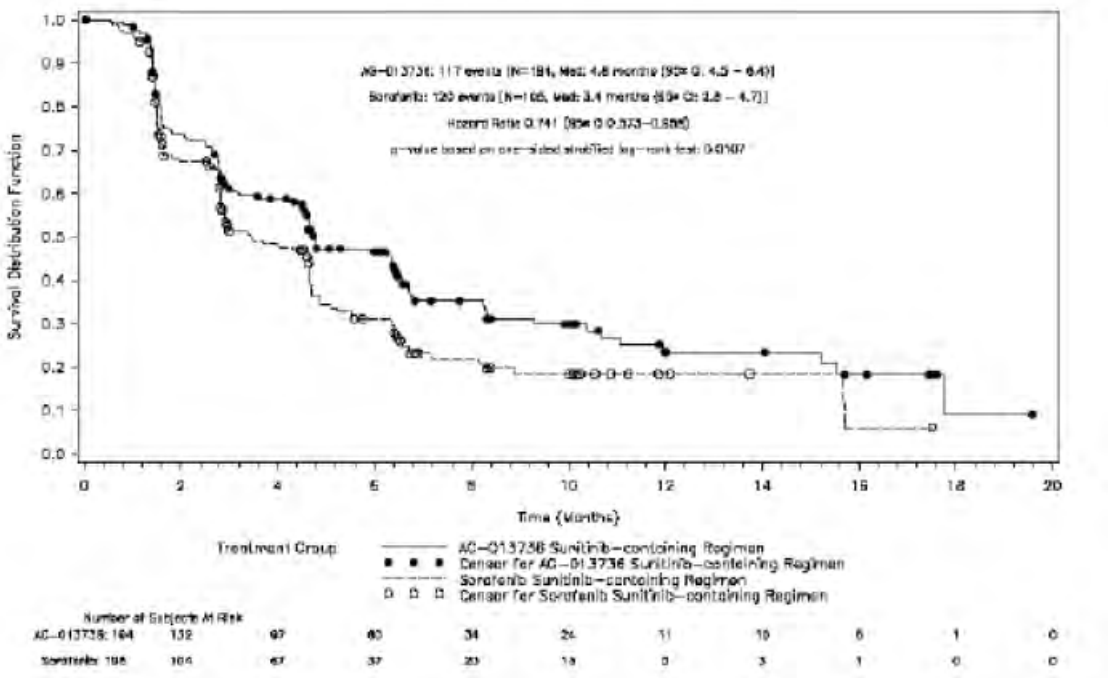
Source: A4061032 CSR Figure 14.1.1

Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test. For the overall stratified analysis, the p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status and prior treatment.

Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; Med=median; N=number of subjects

The clinical benefit of axitinib as measured by PFS was also similar in the sunitinib and cytokine prior therapy sub-groups. Among patients with prior sunitinib-containing regimens, 117 or 60.3% of patients in the axitinib treatment arm had a PFS event; 120 or 61.5% of patients had a PFS event in the sorafenib treatment arm. The median PFS was 4.8 months in the axitinib treatment arm and 3.4 months in the sorafenib treatment arm with a HR of 0.741 and a p value 0.0107. This is illustrated in Figure 6, below:

Figure 6. Pivotal Phase III Study A4061032: Kaplan-Meier curves of PFS by treatment and prior sunitinib-containing regimen (IRC assessment; Full Analysis Set)

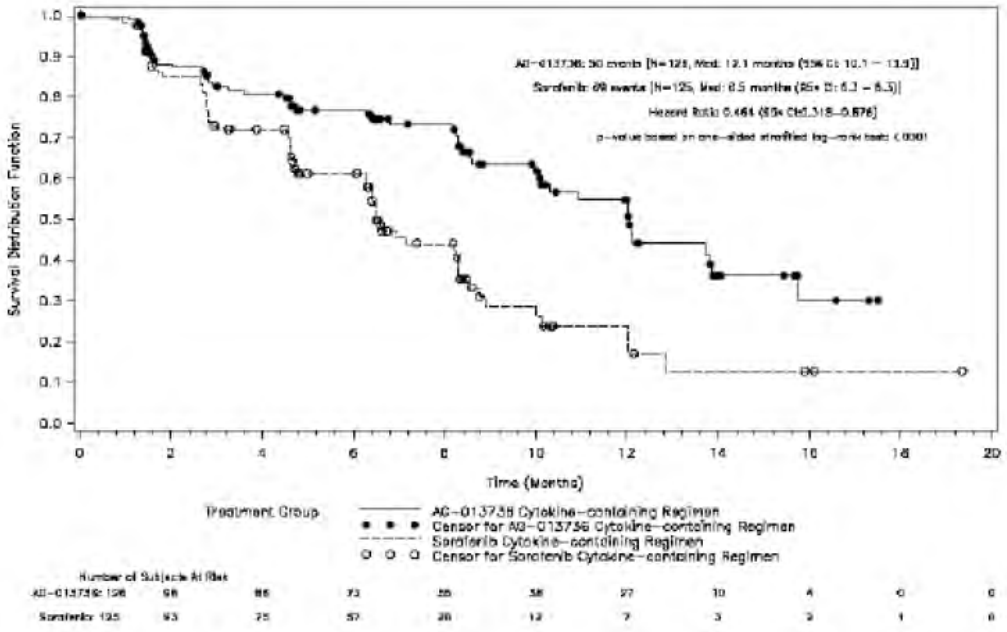


Source: A4061032 CSR Figure 14.1.2.1

Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test. For the stratified analysis, the p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status.
Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; Med=median; N=number of subjects

Among patients with prior cytokine-containing regimens, 50 or 39.7% of patients on the axitinib treatment arm had a PFS event, while 69 or 55.2% of patients in the sorafenib treatment arm had a PFS event. The median PFS was 12.1 months in the axitinib treatment arm and 6.5 months in the sorafenib treatment arm, with a HR of 0.464 and a p value < 0.0001. This is graphically illustrated in Figure 7.

Figure 7. Pivotal Phase III Study A4061032: Kaplan-Meier curves of PFS by treatment and prior cytokine-containing regimen (IRC assessment; Full Analysis Set)



Source: A4061032 CSR Figure 14.1.2.4

Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test. For the stratified analysis, the p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status.

Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; Med=median; N=number of subjects

The clinical benefit of axitinib as measured by PFS is supported by all sensitivity analyses which assessed the potential influence of the investigator assessment, disease assessment scheduling, and deviations in tumour lesion assessment. For each of these analyses, the HR was < 1 indicating a reduction in hazard progression in axitinib.

Study investigator analysis of PFS

For PFS as assessed by the study investigators, in both treatment arms in the overall stratified analysis, a total of 201 or 55.7% of patients in the axitinib treatment arm had a PFS event. The median PFS was 8.3 months in the axitinib treatment arm and 5.6 months in the sorafenib treatment arm, with a HR of 0.658 and a p value < 0.0001. In patients stratified by prior sunitinib-containing regimen, the median PFS was 6.5 months in the axitinib treatment arm and 4.5 months in the sorafenib treatment arm, with a p value < 0.0002. In patients stratified by prior cytokine-containing regimen, the median PFS was 12 months in the axitinib treatment arm and 8.3 months in the sorafenib treatment arm, with a HR of 0.636 and a p value = 0.0049, as illustrated in Table 8.

Table 8. Pivotal Phase III Study A4061032: Summary of PFS by treatment and stratification factor, stratified analysis, derived investigator analysis (Full Analysis Set)

Progression-Free Survival Parameter	Axitinib (N = 361)	Sorafenib (N = 362)
Overall stratified analysis (N)	361	362
Progression Status [n (%)]		
Subject progressed or died due to any cause while on study[a]	201 (55.7)	227 (62.7)
Objective progression observed	187 (93.0)	214 (94.3)
Death without objective progression	14 (7.0)	13 (5.7)
Subject did not progress or die due to any cause while on study[a]	160 (44.3)	135 (37.3)
Progression-free survival (months)		
Quartiles (95% CI)[b]		
25%	3.0 (2.8, 4.5)	2.8 (1.6, 2.9)
50% (median)	8.3 (6.6, 9.0)	5.6 (4.7, 6.5)
75%	14.1 (12.1, 15.9)	10.2 (8.4, 11.9)
Axitinib vs. sorafenib		
Hazard ratio[c] (95% CI)	0.658 (0.543, 0.798)	NA
p-value[d]	<0.0001	NA
Prior sunitinib-containing regimen (N)	194	195
Progression-Free Survival Parameter	**Axitinib (N = 361)**	**Sorafenib (N = 362)**
Progression Status [n (%)]		
Subject progressed or died due to any cause while on study[a]	120 (61.9)	129 (66.2)
Objective progression observed	109 (90.8)	121 (93.8)
Death without objective progression	11 (9.2)	8 (6.2)
Subject did not progress or die due to any cause while on study[a]	74 (38.1)	66 (33.8)
Progression-free survival (months)		
Quartiles (95% CI)[b]		
25%	2.8 (2.2, 4.3)	1.6 (1.5, 2.0)
50% (median)	6.5 (4.8, 7.6)	4.5 (3.0, 4.7)
75%	12.0 (10.1, 15.8)	8.1 (6.4, 10.1)
Axitinib vs. sorafenib		
Hazard ratio[c] (95% CI)	0.636 (0.494, 0.818)	NA
p-value[e]	0.0002	NA
Prior cytokine-containing regimen (N)	126	125
Progression Status [n (%)]		
Subject progressed or died due to any cause while on study[a]	57 (45.2)	74 (59.2)
Objective progression observed	55 (96.5)	69 (93.2)
Death without objective progression	2 (3.5)	5 (6.8)
Subject did not progress or die due to any cause while on study[a]	69 (54.8)	51 (40.8)
Progression-free survival (months)		
Quartiles (95% CI)[b]		
25%	6.6 (4.7, 8.6)	4.8 (4.6, 6.4)
50% (median)	12.0 (10.1, 13.8)	8.3 (6.6, 9.9)
75%	15.9 (13.8, 17.7)	12.0 (10.2, 17.4)
Axitinib vs. sorafenib		
Hazard ratio[c] (95% CI)	0.636 (0.449, 0.900)	NA
p-value[e]	0.0049	NA

Source: A4061032 CSR Table 13.4.1.13.2
% = n/N x 100
Abbreviations: CI=confidence interval; IRC=Independent Review Committee; N=number of subjects; n=number of subjects meeting prespecified criteria; NA=not applicable
[a] On study includes treatment plus 28-day follow-up period.
[b] Based on the Brookmeyer and Crowley method.
[c] Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test.
[d] For the Overall Stratified Analysis, the p-value is from a log-rank test of treatment stratified by ECOG performance status and prior treatment regimen.
[e] P-value was from a 1-sided log-rank test stratified by ECOG performance status.

Secondary endpoints

Overall survival

Overall survival on the pivotal trial: the data were not mature enough to draw conclusions, as only approximately 30% of patients had experienced overall survival events. However the survival probability at 12 months in the axitinib treatment arm was 66% and the survival probability at 12 months in the sorafenib treatment arm was 67.8%. The observed HR was 1.008 with a p value 0.5253 adjusted for ECOG performance status and prior treatment regimen. It is worth noting that 28% of patients on the axitinib treated arm and 37% of patients on the sorafenib treatment arm went on to receive subsequent systemic therapy upon progression, which may influence the overall survival data.

Objective response rate

In relation to objective response rate for the pivotal study, a statistically significant difference in the overall tumour response rate favouring axitinib over sorafenib was observed. Based on the IRC review, 70 or 19.4% of patients in the axitinib treatment arm had either a complete response (CR) or partial response (PR), compared with 34 9.4% in the sorafenib treatment arm, with a risk ratio of 2.056 and a p value of 0.0001 favouring axitinib. A similar response rate result was obtained with the investigator assessment, with an overall response rate of 19.4% for axitinib versus 11% for sorafenib and a risk ratio of 1.748 and p = 0.007 favouring axitinib.

Overall response rate data favoured axitinib over sorafenib in the sunitinib-refractory and the cytokine-refractory sub-groups. Based on the blinded IRC review, in the cytokine refractory sub-group, the overall response rate is 33% in the axitinib arm versus 14% sorafenib, with a p value 0.0002; the sunitinib refractory group overall response rate was 11% for axitinib and 8% for sorafenib. The study investigator assessments were similar to the IRC assessments.

Response duration and quality of life

The median duration of response in the axitinib versus sorafenib treatment arms were 11 months versus 10.6 months, respectively. Similar data were also observed in the cytokine-refractory and sunitinib-refractory sub-groups.

In relation to patient-reported outcome results, axitinib provided patients with a benefit in PFS and generally enabled them to maintain their quality of life, as compared with sorafenib. Patients in the axitinib arm were able to tolerate the treatment as well as those patients on sorafenib. There was no difference in the overall estimated mean FKSI-15 scores between the two treatment arms over time, being 42.21 versus 41.86 mean post-baseline scores for axitinib and sorafenib, respectively, with a p value of 0.4833.

Efficacy in subpopulations

A review of the results in sub-populations revealed that efficacy was independent of axitinib total daily dose as well as demographic and other baseline characteristics.

Evaluator's conclusion regarding efficacy

Data from this quite large trial has clearly demonstrated a significant benefit for PFS and other secondary endpoints for axitinib versus sorafenib. This was demonstrated in patients who had received at least one line of prior therapy. Sorafenib is presently recognised as one of the principal available therapies for second-line treatment of RCC. This demonstrated significant benefit for PFS indicates a favourable degree of efficacy for axitinib. It is difficult to judge whether this represents a clear advantage over sorafenib, as overall survival data is not available. There is certainly some considerable potential that follow up therapy in patients who have progressed with other treatment may well

mitigate against an overall survival advantage. Nevertheless, the at-least equivalent evidence of benefit for axitinib in patients with advanced stage RCC receiving second-line therapy supports its approval.

Evaluator's addendum: An updated analysis provides an extra dimension of outcome, mainly time to deterioration with this being defined as the pre-specified composite endpoint of death or disease progression, or FKSI-15 decrease of at least five points, whichever occurred first. Results indicate superiority of axitinib over sorafenib, with a 17% risk reduction and an HR 0.829 (one-sided p value = 0.0141). Median time to deterioration was 3.1 months for axitinib versus 2.8 months for sorafenib, and a 75% time to deterioration was 8.4 months for axitinib versus 6.5 months for sorafenib. These data represent a further endpoint supporting the clinical superiority of axitinib versus sorafenib in this trial.

Supportive studies

Three supportive studies are provided in this submission: Studies A4061012, A4061035 and A4061023.

Study A4061012

This was a single arm, two-stage, multicentre, open label Phase II clinical study evaluating single agent axitinib as second-line treatment in subjects with advanced RCC whose disease was refractory to cytokine therapy. The primary objective of this study was to determine the activity of axitinib in patients with advanced RCC who had received one prior cytokine-based therapy, as measured by overall response rate. Secondary objectives include the assessment of time to tumour progression, PFS, duration of response, and overall survival.

This study included patients with histologically documented RCC with metastases after failure of one prior cytokine based therapy, either IL-2 or IFN-α. Subjects were excluded if they had had prior systemic treatment for RCC, other than indicated above. Evidence of measurable disease was required for eligibility, as was adequate bone marrow, hepatic and renal function and an ECOG performance status of 0 or 1.

All patients received axitinib in a dose of 5 mg bid in crystal polymorph Form-IV tablets. Subjects who tolerated axitinib with no adverse events ≥ Grade II for eight weeks could have their dosing increased by 20%, unless responding to therapy at the starting dose. Dose reductions for adverse events were performed by 20% decrement.

Study A4061035

This was a single stage, open-label, non-randomised, multicentre Phase II study of single agent axitinib in Japanese subjects with advanced RCC whose disease was refractory to cytokine therapy. The primary objective of the study was to determine the objective tumour response of axitinib in advanced RCC, as measured by the overall response rate according to RECIST criteria. Secondary objectives include the assessment of PFS, time to tumour progression, duration of response, and overall survival.

The study included patients with histologically documented advanced RCC with a component of clear cell cancer and nephrectomy who were refractory to first-line treatment with cytokine therapy or a cytokine based regimen due to disease progression or intolerance to the drug. Evidence of measurable disease was required, together with ECOG performance status of 0 or 1 and adequate organ function. The study treatment involved axitinib at a dose of 5 mg bid on a continuous schedule, again using the crystal polymorph Form-IV axitinib tablets.

Study A4061023

This was a single-stage, open label, multicentre Phase II clinical study evaluating the safety and anti-tumour activity of single agent axitinib in patients with advanced RCC after failure of prior treatment with sorafenib. The primary objective of the study was to determine the activity of axitinib in advanced and refractory RCC, as measured by overall response rate according to RECIST criteria. Secondary objectives included the assessment of PFS, duration of response and overall survival.

Eligible patients included those with histologically documented RCC with metastases or nephrectomy for whom prior sorafenib-based therapy had failed due to progression according to RECIST criteria. Patients with unresectable primary tumours were excluded. Evidence of measurable disease by RECIST criteria, adequate organ function and ECOG performance status of 0 or 1 were required for eligibility. The starting dose of axitinib was 5 mg bid using the polymorph Form-IV axitinib tablets.

Baseline data

Sample size for Study A4061012 (with a two stage design and a null hypothesis of the true overall response rate being at least 5%) required 30 subjects to be enrolled, whereas for Study A4061035 utilising the same design, the requirement for a true overall response rate of at least 10% was 63 subjects, and similarly for A4061023.

The majority of the patients were male in all three supportive studies and most often white, although in Study A4061035 all subjects were Japanese. More than 50% of patients had an ECOG performance status 0 except in the sorafenib-refractory Study A4061023, with the majority of patients reaching ECOG performance status 1.

In the supportive studies (and in the pivotal Phase III Study A4061032), the majority of patients had a baseline histological classification of clear cell RCC with Stage IV disease. All patients experienced disease progression on either the cytokine-based therapy for Studies A4061028 and A4061035 or on sorafenib therapy for A4061023.

In Study A4061012, all patients had previously experienced disease progression on one prior cytokine-based therapy. Previous cancer treatments included immunologic/biologic therapy (51 subjects, 98.1%), surgery (other than nephrectomy; 15 subjects, 28.8%), radiotherapy (12 subjects, 23.1%), and chemotherapy (6 subjects, 11.5%). For Study A4061035, all 64 patients had received prior treatment for RCC, which included at least one or two systemic therapy regimens and surgery. Six patients had received prior radiotherapy. All patients had had disease progression on the first line cytokine based therapy.

In Study A4061023 all patients had prior surgery and cancer therapy for RCC and prior radiation therapy in 48%. All patients had received prior sorafenib therapy, with 25.8% receiving sorafenib alone, 46.8% receiving sorafenib with cytokines, and 22.6% receiving sorafenib and sunitinib.

Considering patient disposition, a total of 52 patients were enrolled in Study A4061012, 64 in Study A4061035 and 62 in A4061023. 98% of patients in A4061012 had discontinued therapy, while 57.8% in A4061035 and 98.4% in A4061023 had discontinued treatment. Principal reason for discontinuation of therapy was objective disease progression in 25 patients in A4061012, 24 patients in A4061035 and 34 patients in A4061023, with adverse events causing treatment discontinuation in 10, 13 and 22 patients, respectively, while death was only documented as a reason for discontinuation in one patient (in Study A4061012).

Efficacy

PFS, tumour progression, and overall survival

Progression free survival is a secondary endpoint in the study of cytokine-refractory patients. Based on investigator assessment, median PFS was 13.7 months in Study A4061012 and 12 months in Study A4061035. A similar result was obtained with IRC assessment in Study A4061035, with a median PFS of 11 months. In sorafenib-refractory patients, the median PFS was 7.4 months in Study A4061023.

In addition, time to tumour progression was a secondary endpoint; in A4061012 the median time to tumour progression was 15.7 months whereas in Study A4061035 the mean time to tumour progression was identical to the PFS outcome and no patients had died prior to progressive disease in this study.

In relation to overall survival, again a secondary endpoint for the three studies, overall survival was only available for A4061012 and A4061023, with median survival being 29.9 months for A4061012 and 13.6 months for A4061023.

Overall response rate

Overall response rate was the primary efficacy endpoint for the three Phase II studies. In patients with cytokine-refractory advanced RCC, axitinib treatment resulted in an overall response rate of 44.2% in Study A4061012 and 54.7% in Study A4061035, based on investigator assessment. For Study A4061035, IRC assessment was 50%, or similar to that observed in the investigator assessment. In patients with sorafenib-refractory advanced RCC (Study A4061023), axitinib resulted in an overall response rate of 22.6% based on investigator assessment.

Response duration

Another secondary endpoint for the three studies was duration of response. The median duration of response for Study A4061012 was 23 months, while for Study A4061035 it was 12.8 months and for Study A4061023 it was 17.4 months.

Patient reported outcomes

In relation to patient reported outcomes, in Study A4061012 there was little change from baseline in mean Health-Related Quality of Life (HRQoL) scores (measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30). The EORTC QLQ-C30 consists of 30 questions that measure functional status, symptoms, and global health), with results for up to 40 weeks of treatment.

> ***Evaluator comment:*** The supportive Phase II studies have indicated a definite evidence of activity for axitinib in patients who have previously received either cytokine therapy or sorafenib therapy. The response observed is in line with those documented in the pivotal trial for axitinib based therapy and also at least equivalent if not superior to those for other cytokine kinase inhibitors.

Safety

This evaluation involves a safety analysis for forty one clinical studies involving 3655 patients, of which thirty one were completed studies and ten were ongoing. Of the 3655, subjects, 2507 received at least one dose of axitinib either as a single agent or as a component of combination therapy. A total of 699 subjects received single agent axitinib at a 5 mg bid starting dose in completed single agent studies, including 537 patients who received single agent axitinib in the four completed advanced RCC studies. The safety data cutoff point was 31 August 2010.

Previous nonclinical safety data analyses conducted with axitinib had identified the gastrointestinal and haematopoietic systems (erythroid primarily) and the musculoskeletal and reproductive systems as potential targets for toxicity. Other findings related to administration of axitinib included the potential for developmental effects, haemodynamic changes (blood pressure and heart rate) following repeated dose administration, effects on the exocrine pancreas, clinical chemistry changes attributed to the liver, and aneugenicity.

Drug exposure

All patients receiving at least one dose of study medication, regardless of whether the treatment assigned was the actual study treatment received, were included in the analyses of safety. The pooled safety analyses for completed single agent studies included patients who had received a 5 mg bid starting dose of axitinib. Routine safety analyses included summaries of the frequency and severity of adverse effects in patients who discontinued treatment.

The incidence of laboratory test abnormalities and assessment of changes in vital signs and QTc intervals from baseline were included. All definitions related to adverse events were by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and were graded accordingly. Clinical laboratory assessments for the vast majority of stages were conducted at least every four weeks. Vital signs including temperature, blood pressure and heart rate were recorded at each clinic visit. Quarterly tracings for all ECGs were utilised, and QT interval values summarised from data sheets. QTc intervals and changes from baseline were summarised using descriptive statistics by treatment cycle and study days.

In relation to drug exposure, of the 3655 subjects, 2507 received at least one dose of axitinib either as a single agent or as a component of combination therapy. A total of 885 subjects with various solid tumours received axitinib as a single agent at a 5 mg bid starting dose and 1059 subjects received axitinib as a component of combination therapy.

Single agent studies

Of the 2507 axitinib treated subjects, 699 received single agent axitinib at the 5 mg bid recommended starting dose in the completed studies, with 537 of these subjects receiving single agent axitinib to treat advanced RCC. 359 subjects received axitinib and 355 received sorafenib in the pivotal Phase III Study A4061032.

For exposure to axitinib and sorafenib in the pivotal Study A4061032: overall, subjects on axitinib had a higher number of median days on treatment than patients on sorafenib (196 days versus 152 days); there were more days on study drug for axitinib (186 days) versus sorafenib (141 days); a smaller proportion of subjects with dose interruptions on axitinib (276 subjects) than sorefenib (285 subjects); a smaller percentage of doses with interruptions for axitinib (3.2%) than for sorefenib (4.8%); and a higher relative dose intensity for those on axitinib (98.6%) than subjects on sorafenib (91.7%).

Overall, 38.7% of axitinib treated subjects remained on the total daily dose of 10 mg (5 mg bid) throughout the study duration, 8.4% of patients in axitinib group had at least one total daily dose of < 6mg and never increased above a total daily dose of 10 mg, and 19.8% had at least one total daily dose of 20 mg. Overall 71 patients in the axitinib group had their dose increased above 5 mg bid and then reduced.

In relation to the supportive Phase II RCC studies, the mean duration of exposure in Study A4061012 was 287 days with a range of 3-973 days. The median daily dose administered was 8.83 mg with a range of 3.9-11.7 mg and a median cumulative dose of 2576 mg (range 25-9543 mg). For Study A4061035, the mean duration of study treatment was 326 days with a range of 13-696 days. The overall mean of the individual average daily dose was 7.08 mg (range of 1.6-16.4 mg) and the mean cumulative dose was 2474.1 mg, ranging

from 97-7307 mg. In Study A4061023, the median duration of exposure was 189 days with a range of 5-1009 days. The mean average daily dose administered was 10 mg (range 6–19.7 mg) and the median cumulative dose was 1966 mg (range 50-16,598 mg).

Duration of exposure to axitinib for the overall completed single agent studies was a mean of 197 days with a range of 1-1538 days. The median daily dose administered was 9.89 mg with a range of 1.96-19.7 mg, and the median cumulative dose was 2030 mg with a range of 5-44,000 mg.

Combination studies

Pooled data from the completed pancreatic cancer studies showed a median duration of exposure to axitinib of 99.5 days with a range of 1-556 days. The median total daily dose of axitinib was 10 mg with a range of 3.95-18.7 mg, and the median cumulative dose was 835 mg with a range of 10-8560 mg.

Demographic and baseline characteristics

Regarding demographic and baseline characteristics for all axitinib treated subjects in the completed single agent studies, the mean age of subjects in the completed single agent studies was 59.9 years, 68.7% were male and 71.8% were white.

In relation to malignancy diagnoses in the completed single agent studies, patients with a primary diagnosis of advanced RCC was 77.5%, followed by thyroid cancers (8.7%), non–small-cell lung cancer (4.9%), and metastatic malignant melanoma (4.6%).

Adverse events

Pivotal trial

Treatment-emergent adverse events – all causality

In the pivotal Phase III RCC study 342 subjects or 95.3% of the axitinib group and 347 subjects or 97.7% in the sorafenib group reported adverse events; and 236 subjects or 65.7% of the axitinib group and 242 subjects or 68.2% in the sorafenib group reported Grade III or greater adverse events.

Adverse events reported more frequently in the axitinib group included hypertension, fatigue, decreased appetite, nausea, dysphonia, vomiting, asthenia, hypothyroidism, dyspepsia and dizziness. Reported more frequently in the sorafenib group were palmar-plantar erythodysesthesia syndrome (red hand syndrome), rash, pruritus, anaemia, erythema and alopecia.

Grade III or greater events reported by at least 5% of subjects in the axitinib group were hypertension, fatigue, diarrhoea, disease progression, asthenia, decreased appetite and red hand syndrome; whereas Grade III or greater events in the sorafenib group were red hand syndrome, hypertension, fatigue and diarrhoea. Fatigue was the only Grade III or greater adverse event reported more frequently in the axitinib group, whereas red hand syndrome was the only Grade III event reported more frequently in the sorafenib group. Diarrhoea was the most commonly reported adverse event in both treatment groups with a similar incidence for the two groups. It was generally mild to moderate and rarely led to discontinuation of study.

Hypertension was one of the most common adverse events reported in the axitinib group and was more frequently reported in the axitinib group (40.4%) than the sorafenib group (29%). It was most often Grade I–III although one patient had Grade IV events that led to discontinuation of treatment. Hypertensive crisis was reported in two subjects in the axitinib group.

Fatigue was more frequently reported in the axitinib group (39%) than the sorafenib group (31.5%) and Grade III fatigue was reported by 10.9% of patients in the axitinib

group and 4.8% of patients in the sorafenib group. Grade IV fatigue was reported in 0.6% of patients in the axitinib group and 0.3% in the sorafenib group. Fatigue led to permanent discontinuation of treatment in four patients in the axitinib group and one in the sorafenib group.

Treatment-related adverse events

Overall 325 patients or 90.5% in the axitinib group and 336 or 94.6% in the sorafenib group reported treatment-related adverse events and 177 subjects in the axitinib group and 189 in the sorafenib group reported Grade III or greater treatment-related adverse events in the pivotal Phase III study. The most commonly reported treatment-related adverse events are given in Table 9.

Table 9. Treatment-related adverse events summarised by maximum severity Grade for ≥ 5% (all Grades; decreasing frequency) of subjects in either treatment group in the pivotal Phase III study (A4061032)

	Axitinib (N=359)		Sorafenib (N=355)	
Preferred Term[a]	Grade 3+[b] n (%)	All Grades[c] n (%)	Grade 3+[b] n (%)	All Grades[c] n (%)
Any AEs	177 (49.3)	325 (90.5)	189 (53.2)	336 (94.6)
Diarrhea	36 (10.0)	184 (51.3)	25 (7.0)	179 (50.4)
Hypertension	56 (15.6)	141 (39.3)	39 (11.0)	103 (29.0)
Fatigue	35 (9.7)	125 (34.8)	13 (3.7)	93 (26.2)
Nausea	5 (1.4)	103 (28.7)	3 (0.8)	65 (18.3)
Decreased appetite	13 (3.6)	102 (28.4)	6 (1.7)	88 (24.8)
Dysphonia	0	101 (28.1)	0	42 (11.8)
Palmar-plantar erythrodysesthesia syndrome	18 (5.0)	98 (27.3)	57 (16.1)	181 (51.0)
Hypothyroidism	1 (0.3)	66 (18.4)	0	24 (6.8)
Asthenia	15 (4.2)	63 (17.5)	8 (2.3)	44 (12.4)
Vomiting	5 (1.4)	60 (16.7)	0	44 (12.4)
Weight decreased	5 (1.4)	59 (16.4)	4 (1.1)	54 (15.2)
Mucosal inflammation	5 (1.4)	54 (15.0)	2 (0.6)	43 (12.1)
Stomatitis	5 (1.4)	52 (14.5)	1 (0.3)	42 (11.8)
Constipation	0	44 (12.3)	1 (0.3)	45 (12.7)
Rash	1 (0.3)	42 (11.7)	13 (3.7)	109 (30.7)
Headache	2 (0.6)	37 (10.3)	0	24 (6.8)
Dysgeusia	0	37 (10.3)	0	29 (8.2)
Proteinuria	11 (3.1)	37 (10.3)	4 (1.1)	23 (6.5)
Dry skin	0	36 (10.0)	0	35 (9.9)
Pain in extremity	1 (0.3)	32 (8.9)	2 (0.6)	35 (9.9)
Arthralgia	2 (0.6)	31 (8.6)	1 (0.3)	17 (4.8)
Abdominal pain	3 (0.8)	30 (8.4)	1 (0.3)	16 (4.5)
Dyspepsia	0	28 (7.8)	0	6 (1.7)
Dyspnea	1 (0.3)	25 (7.0)	1 (0.3)	13 (3.7)
Abdominal pain upper	1 (0.3)	22 (6.1)	0	7 (2.0)
Pruritus	0	21 (5.8)	0	43 (12.1)
Dizziness	0	20 (5.6)	0	5 (1.4)
Cough	0	19 (5.3)	1 (0.3)	16 (4.5)
Epistaxis	0	19 (5.3)	0	10 (2.8)
Myalgia	3 (0.8)	19 (5.3)	0	7 (2.0)
Alopecia	0	12 (3.3)	0	112 (31.5)
Anemia	1 (0.3)	10 (2.8)	5 (1.4)	20 (5.6)
Erythema	0	8 (2.2)	1 (0.3)	35 (9.9)
Lipase increased	2 (0.6)	8 (2.2)	11 (3.1)	18 (5.1)

Source: A4061032 CSR Table 13.6.3.4

AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects fitting specified criteria

[a] MedDRA (version 13.1) coding dictionary applied.

[b] Grade 3+ includes Grades 3, 4 and 5.

[c] All Grades includes Grades 1-5

The most common treatment-related adverse events included diarrhoea in the axitinib group and red hand syndrome in the sorafenib group. Treatment related adverse events were reported more frequently in axitinib group compared to sorafenib and included hypertension, fatigue, nausea dysphonia, hypothyroidism, asthenia and dyspepsia, whereas for the sorafenib group more common was red hand syndrome, rash, pruritus, alopecia and erythema.

Grade III or greater treatment related adverse events reported in at least 5% of patients in the axitinib group were hypertension, fatigue, diarrhoea and red hand syndrome, whereas for the sorafenib group this included red hand syndrome, hypertension and diarrhoea. Again, the only Grade III or greater treatment related adverse event reported more frequently in the axitinib group was fatigue and the only Grade III or greater treatment related adverse event reported more frequently for sorafenib was red hand syndrome.

In relation to prior anti-cancer therapy, in general the most common adverse events were the same for all axitinib treated subjects who received either prior cytokine therapy or prior sunitinib therapy. The same could be said for the adverse events that were considered treatment related.

Median time to onset

In relation to median time to adverse event onset, for those who experienced at least Grade III events the time to onset was 85 days in axitinib group and 41 days in the sorafenib group. Rash was the earliest Grade III or greater adverse event in the axitinib group, with onset being 19 days; the adverse event with the earliest time to onset in the sorafenib group was hypertension (9 days). The median time to onset for hypertension in the axitinib group was 22 days. The median time to onset for diarrhoea was 113 days for axitinib and 76 days for sorafenib; for fatigue, it was 74 days for axitinib and 70.5 days for sorafenib; and for red hand syndrome it was and 89.5 days for the axitinib group and 85 days for the sorafenib group.

Other studies

Completed single agent studies

In relation to the total 699 axitinib treated subjects who received this agent for single therapy, 97.3% reported adverse events and these were generally Grade I or II. Regarding the all causality adverse events, the most common were diarrhoea, fatigue, hypertension and decreased appetite. Overall these were generally similar to the pivotal study except for headache (21.6% versus 13.9%) and fatigue (52.6% versus 39%). On the other hand, asthenia was more common in the pivotal study than in the completed single agent studies, being 20.6% versus 13.7%.

Almost 70% of subjects experienced at least one Grade III or greater event in the completed single agent studies. The most common of these were hypertension, fatigue and diarrhoea. Treatment-related adverse events were reported in 93% of patients in these studies with the most common of these being generally similar to those associated in the pivotal trial.

Combination studies

The data in relation to the completed, pooled pancreatic cancer studies involving the combination of axitinib and gemcitabine showed adverse events most commonly being hypertension, neutropenia, thrombocytopenia, diarrhoea, nausea, stomatitis, asthenia, fatigue, mucosal inflammation, decreased weight, headache, dysphonia and alopecia. This represents an indication of the combination of both axitinib and gemcitabine. Overall 53.2% of patients in the axitinib plus gemcitabine group experienced Grade III or greater treatment related adverse events. The median onset time to treatment-related Grade III or greater adverse events was 35 days and the shortest time to onset was 15 days for events including neutropenia, thrombocytopenia and leukopenia. Adverse events with the longest time to onset were hypertension and vomiting.

Healthy volunteer studies

In relation to healthy volunteer studies in which the volunteers only received a single dose of axitinib, 170 of the 511 axitinib treated subjects reported adverse events. All were

Grade I and II with the exception of one Grade III headache. The most commonly reported events were headache in 43 subjects, fatigue in 13 subjects, oropharyngeal pain in 11 subjects, and diarrhoea in 10 subjects.

Deaths

In relation to deaths in the four RCC studies, a total of 62 subjects, 39 axitinib treated patients and 23 sorafenib treated patients, experienced events with a fatal outcome on treatment or within 28 days of treatment. It is noteworthy that four deaths occurred in the axitinib group in the pivotal trial. Causes included asthenia, gastrointestinal haemorrhage, sepsis and disease progression/metastatic RCC. For the four deaths associated with sorafenib, one was unknown cause, another showed increased creatinine, one had gastrointestinal haemorrhage, another had retroperitoneal haemorrhage and one had circulatory collapse.

For the total 699 patients who had received axitinib as a single agent, 64.9% experienced a fatal outcome on treatment. Again the most common reason for this being disease progression followed by dyspnoea in seven events and general physical health deterioration in three events. Two of these deaths were considered potentially treatment related, including one intestinal perforation and one haemoptysis and cardiac arrest.

Serious adverse events

In relation to serious adverse events in the Phase III pivotal study, these were reported in 106 patients or 29.5% of those receiving axitinib and in 31% of those receiving sorafenib. The most common were disease progression and metastatic RCC. It is noteworthy that were five events of pulmonary embolism, seven of diarrhoea and nine of dehydration.

The most common treatment related serious adverse events were dehydration (7 events), diarrhoea (6), fatigue (3), pneumonia (3) and transient ischaemic attack (TIA; 3) in the axitinib group; and anaemia (4), diarrhoea (3), pyrexia (3) and erythema multiforme (3) in the sorafenib group.

In relation to the completed single agent studies, there were 281 serious adverse events. The most common included dehydration, diarrhoea, hypertension and fatigue.

In relation to all Pfizer sponsored studies, involving a total of 2498 subjects, 838 or 33.5%, experienced a serious adverse event. The most commonly reported treatment related serious adverse events in these subjects were dehydration (52 events), vomiting (32), hypertension (31), diarrhoea (27) and nausea (23).

Discontinuations and dose reductions

In the pivotal study, 33 or 9.2% of patients in the axitinib group discontinued treatment due to adverse events, and 14, or 3.9%, discontinued due to treatment related adverse events. This is compared to 46 or 13% of the patients on the sorafenib group discontinuing therapy and 29 or 8.2% discontinuing therapy because of treatment related adverse events. Overall discontinuation of treatment for adverse events involving the skin and subcutaneous tissue and gastrointestinal disorders were more frequent in the sorafenib group than the axitinib group.

The only treatment related adverse event that led to discontinuation in more than one patient in the axitinib group was fatigue in four patients, TIA in three patients and asthenia in two patients. Red hand syndrome in four patients, diarrhoea, nausea, asthenia, erythema multiforme and rash, in two patients each, were treatment related adverse events that led to discontinuation of treatment in the sorafenib group.

Some 127 or 18.2% of the 699 patients who had completed single agent studies discontinued axitinib due to adverse events and 9.3% of these were due to treatment related adverse events. The most common events were fatigue and proteinuria.

In relation to temporary discontinuation or dose reductions in the Phase III study, a total of 199 or 55.4% of patients in the axitinib group and 220 or 62% of patients in the sorafenib group had dose modification or temporarily discontinued treatment. There were more dose modifications or temporary delays due to diarrhoea, hypertension and proteinuria in the axitinib group than in the sorafenib group and more dose reductions or temporary discontinuation due to red hand syndrome and rash in the sorafenib group.

For the total completed single agent studies, 177 or 25.3% of patients had their dose reduced and 405 or 57.9% had doses temporarily discontinued. The most common adverse events leading to dose reduction or temporary discontinuation were similar to those in the pivotal study, the only difference between this study and that of the pivotal study was a higher incidence of fatigue in the completed single agent studies (11.4%) compared to the pivotal study (6.1%). Treatment related adverse events that led to dose reduction or temporary discontinuation of axitinib were diarrhoea in 17.7%, hypertension in 16% and fatigue in 10.9% of patients.

Adverse events of special interest

Adverse events of special interest included hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events (VTEs), elevation of haemoglobin/haematocrit, haemorrhage, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) and proteinuria. Also considered were potential risks such as hepatic disorders and wound healing complications, as well as asthenia and skin reactions.

Hypertension

In relation to the pivotal Phase III trial, during the study, hypertension was reported in 145 or 40.4% of patients receiving axitinib and 103 or 29% of patients receiving sorafenib. Grade III hypertension was reported in 55 subjects (15.3%) receiving axitinib and 38 subjects (10.7%) receiving sorafenib. Grade IV hypertension was reported in one patient receiving axitinib and one receiving sorafenib. One patient discontinued therapy on axitinib because of hypertension while two patients experienced hypertensive crises.

For the completed single agent studies, hypertension was reported in 318 or 40.5% of patients receiving axitinib, Grade III/IV hypertension was observed in 134 or 19.2% of patients and two of these experienced hypertensive crises.

Based on the data from the RCC studies in which rigorous 24 h blood pressure monitoring was undertaken, it was noted median increase in diastolic blood pressure occurred from approximately Day 4 and by Day 15 had reached the highest potential level. After initial elevation, BPs tended to stabilise.

In the pivotal Phase III study the incidence of hypertension with axitinib treatment ranged from about 16 to 40%. In terms of requirement for antihypertensive medication about half of the subjects receiving axitinib required some adjustment of already ongoing antihypertensive medication or a commencement of antihypertensive treatment.

Thyroid dysfunction

In the pivotal Phase III study hypothyroidism was reported at baseline for 18% and 17.1% of patients in the axitinib and sorafenib groups, respectively. There were similar numbers of patients in each treatment group who were receiving thyroid medication. During the study hypothyroidism was reported more commonly for axitinib treated patients, being 69, or 19.2% of patients, compared to sorafenib (29 or 8.2%). The incidence of

hyperthyroidism was the same, being four in each treatment group. There were no events of Grade V severity or discontinuations due to thyroid dysfunction in either treatment group. Among the patients who had an initial normal thyroid stimulating hormone (TSH) level, levels of TSH greater than twice normal occurred in 79 or 32.2% of patients receiving axitinib and in 25 (10.8%) of patients receiving sorafenib. The findings of the incidence of hyperthyroidism and hypothyroidism were consistent throughout the remaining pooled data analyses.

Arterial thromboembolic events

In the pivotal Phase III study the overall incidence of arterial thromboembolic events (ATEs) was similar in the two treatment groups, being four patients receiving axitinib (including a TIA and a retinal artery occlusion) and three patients receiving sorafenib. The ATEs in the axitinib treated patients were TIA in three patients and retinal artery occlusion in one. All were Grade III/IV. The ATEs in the sorafenib patients were myocardial infarction in two and ischaemic stroke in one. These were also Grade III/IV.

These findings were consistent across the pooled data for all completed single agent studies. Overall, in the monotherapy phase of axitinib ATEs were reported in 11/699 patients or 1.6%, and included TIA, arterial embolism, lacunar infarction, myocardial infarction and retinal artery occlusions.

Venous thromboembolic events

In the pivotal study, the incidence of VTEs was higher in subjects receiving axitinib (11 subjects) compared to sorafenib (2 subjects). The most common VTEs on axitinib treatment were pulmonary embolism in seven subjects and deep vein thrombosis in two. Grade III/IV VTEs were reported in 9 or 2.5% of axitinib patients and one axitinib treated patient experienced Grade V severity (pulmonary embolism). This was not considered related to study treatment as it occurred some three weeks after discontinuation of axitinib. These data were consistent with the pooled data from all completed single agent studies, where VTEs were reported in 2.8% of patients who received axitinib. There were two fatal pulmonary embolisms reported in patients who received axitinib, including the one from the pivotal study.

Elevation of haemoglobin

In the pivotal study elevated haemoglobin above the upper limit of normal (ULN) was observed in 31 or 8.6% of axitinib patients, compared to 3 or 0.8% of sorafenib patients. This is consistent with pooled data from all completed single agent studies where the haemoglobin level was elevated in 73 or 13.6% of axitinib treated patients.

Haemorrhage

In the pivotal Phase III study, patients who had evidence of untreated brain metastases or recent active gastrointestinal bleeding were excluded. Haemorrhagic events were reported with similar incidence in the two treatment groups, being 58 or 16.2% of patients receiving axitinib and 64 or 18% of patients receiving sorafenib. The most common individual haemorrhagic events for those receiving axitinib were epistaxis in 22 patients, haematuria in 12, haemoptysis in 8 and rectal haemorrhage in 8. Epistaxis, haemoptysis and haematuria were also the most common haemorrhagic events for those receiving sorafenib.

Grade III or IV haemorrhagic events were reported in 1.4% of patients receiving axitinib (including a cerebral haemorrhage, haematuria, haemoptysis, lower gastrointestinal haemorrhage and melena in one patient each) and in 3.1% of patients receiving sorafenib. Fatal haemorrhage was reported in one patient receiving axitinib, being a gastric haemorrhage, and in 3 patients receiving sorafenib. Again, pooled data from all completed single agent studies were consistent.

Gastrointestinal perforation

In the pivotal Phase III study, gastrointestinal perforations, including abdominal abscess, anal abscess, anal fistula, gastrointestinal and anastomotic leak, and gastrointestinal perforation, were reported in 5 or 1.4% of patients receiving axitinib and in none receiving sorafenib. In all completed single agent axitinib studies, a fatal gastrointestinal perforation was reported in one patient receiving axitinib.

Wound healing complications

No formal studies of the effect of axitinib on wound healing have been conducted. In all axitinib studies, investigators were instructed to interrupt treatment with axitinib at least 24 h before a major surgical intervention or procedure and resume treatment after the wound had completely healed and there were no wound healing complications. In the pivotal study, 4 patients, all of whom were treated with axitinib, experienced adverse events involving wound healing. All patients recovered and no cases were considered serious, although one was a Grade III/IV wound healing delay. These findings were consistent with the pooled data.

Reversible Posterior Leukoencephalopathy Syndrome

In the pivotal Phase III study, RPLS was reported in one patient receiving axitinib and in none receiving sorafenib. This was Grade III/IV in intensity. For the completed single agent studies, 3 patients receiving axitinib experienced RPLS and two of these (including the pivotal trial patient) were Grade III/IV in intensity.

Proteinuria

In the pivotal Phase III study, proteinuria was reported as an adverse event in 39 or 10.9% of patients receiving axitinib and in 26 or 7.3% of patients receiving sorafenib. Most events were Grade I or II in severity. Grade III proteinuria was reported in 11 or 3.1% of axitinib patients and in 6 or 1.7% of patients receiving sorafenib. There were no reports of Grade IV or V proteinuria. There was no discontinuation from axitinib or sorafenib due to proteinuria. The incidence of protein in urine based on urine analysis was similar in the two treatment groups, being 52.9% for axitinib and 50% for sorafenib. The incidence of Grade III urine protein abnormalities was similar in the two treatment groups, being 2.6% versus 2.3%, and there were no events of Grade IV severity. The data from the pooled studies were consistent.

Hepatotoxicity

In view of the fact that hepatotoxicity had been associated with sunitinib and pazopanib, a thorough evaluation was undertaken in relation to reviewing possible cases of hepatotoxicity among patients receiving axitinib. The clinical assessment was based on 2409 patients from all completed clinical studies, including 1838 patients receiving axitinib and revealed no severe case of drug induced liver injury attributable to axitinib with the recommended starting dose of 5 mg bid. In the pivotal Phase III study, no concurrent elevations of ALT and bilirubin were observed for axitinib or sorafenib. In the early Phase I studies, one patient who received axitinib at a starting dose of 20 mg bid was observed to have elevated liver function tests at least 10 times above normal, which was considered to be drug related.

Asthenia

Asthenia and fatigue were more frequently reported in axitinib treated patients (20.6% and 39%, respectively) than in the sorafenib treated patients (14.1% and 31.5%, respectively). There were 4 patients with Grade IV and one with Grade V asthenia in the axitinib group, compared to 2 in the sorafenib group. Two patients discontinued axitinib due to asthenia and 4 discontinued axitinib due to fatigue. In the completed single agent studies, treatment related asthenic conditions were reported in 55.1% of axitinib treated

patients and fatigue in 45.1%. Six patients experienced Grade IV asthenia and one had a Grade V event. The Grade V asthenia event was in the pivotal study. Three patients discontinued due to asthenia and 12 due to fatigue.

Skin reactions

In relation to rash, in the pivotal study these were reported more frequently in the sorafenib patients (59.2%) than in the axitinib patients (31.5%). Grade III or greater rashes were more frequently reported in sorafenib patients, being 8.2% for Grade III and 0.3% for Grade IV, compared to axitinib (1.4% for Grade III and 0% for Grade IV). The most common of these included dry skin, pruritus and rash in both treatment groups. The data from completed single agent studies revealed 38.2% of axitinib patients experienced rash, dry skin, pruritus and skin exfoliation.

In relation to the incidence of hand-foot syndrome for the Phase III study, this was higher in the sorafenib treated patients, being 51%, compared to axitinib, being 27.3%. The majority of these in the axitinib patients were Grade I or II. There was more Grade III or greater red hand syndrome in the sorafenib treated patients, being 16.1%, compared to axitinib, being 5%. One patient discontinued axitinib because of red hand syndrome. Single agent studies were consistent with these findings.

Clinical laboratory evaluations

Pivotal trial

In relation to haematology, for the pivotal study, similar proportions of patients in the axitinib and sorafenib groups experienced haematology test abnormalities, except for decreased haemoglobin, which was seen less often in axitinib patients (34.9%) than in sorafenib patients (52.5%). Elevated haemoglobin above normal occurred in 31 or 8.6% of patients in the axitinib group and in 3 or 0.8% in the sorafenib group; and 3 patients had polycythemia reported while receiving axitinib.

Shifts in white blood cell counts were more frequent in the sorafenib group both in terms of neutrophils and lymphocytes.

In relation to clinical chemistry in the pivotal study, in general the incidence of Grade III or IV clinical chemistry laboratory test abnormalities were similar for the two groups, except for elevations of lipase and hypophosphatemia, which were less often seen in the axitinib patients compared to sorafenib. Hypercalcemia was more common in the axitinib group and hypocalcemia more common in the sorafenib group, while the incidence of Grade III or IV abnormalities were similar for the two groups.

In relation to urine analysis, 52.9% of patients in the axitinib group and 50% in the sorafenib group had urine/protein abnormalities during the study. The majority of these were Grade I or II. In the axitinib group, Grade III abnormalities in urine and protein were experienced by 9 patients and there were no Grade IV abnormalities. Shifts in urine protein were similar in the axitinib and sorafenib groups.

Other studies

Considering the completed single agent studies, again the majority of haematological abnormalities were Grade I or III, although 7.9% of axitinib treated subjects assessed for absolute lymphocytes in completed single agent studies had a Grade III abnormality.

In relation to clinical chemistry abnormalities, the majority were Grade I or II except for Grade III/IV hyperkalemia in 2.9%, hyponatremia in 4.7%, hypoglycaemia in 3.2% and elevations of lipase in 6.2% and amylase 2.4%.

In relation to urine analysis 52% of axitinib treated patients who completed single agent studies had abnormalities in urine protein, the majority of which were Grade I or II.

Vital signs

The data summarising heart rates, temperature and body weight, and changes in blood pressure have been separately discussed.

A higher proportion of axitinib treated subjects than sorafenib treated subjects had pulse rates of < 50 beats per minute (15.9% versus 5.1%, respectively) and pulse rates of at least 30 beats per minute increase from baseline (15.3% versus 9.3%, respectively). There is no evidence of clinically meaningful changes in temperature or body weight, although it is noted that a higher proportion of subjects in the axitinib treatment group reported weight decrease as an adverse event compared to the sorafenib group, being 24.8% versus 20.8%.

In relation to ECG analyses, an evaluation of the QT interval based on results from 152 subjects who had post-baseline triplicate QT measurements (collected from the three completed single agent studies including the pivotal trial and the two RCC Studies A4061035 and A4061044), 4 patients, all of whom were in the pivotal Phase III study, had clinically noteworthy values, defined as a post-baseline absolute value of > 500 msec and/or a change from baseline of > 60 msec, in the QT interval. Three of these 4 subjects had abnormalities noted in their baseline ECG prior to the start of study. None of these patients had relevant clinical signs or symptoms in association with the QTc findings.

Two further studies conducted (A4061028 and A4061004) failed to reveal any significant differences in mean QTc values. Across all completed single agent axitinib studies there were no reports of adverse events of torsade de pointes, ventricular fibrillation, ventricular flutter, sudden death or ventricular tachycardia, and the incidence of other adverse event terms that could be associated with an effect on QTc ranged from 0.1%-1.4%.

In general these data support the lack of a definite effect of axitinib on the QT interval.

Safety in special groups

Use in the elderly

In the pivotal Phase III study, the majority of patients were < 65 years but a total of 123 (34.3%) of axitinib treated patients and 121 (34.1%) of sorafenib treated patients aged 65 years or older were included in the safety evaluation. Although greater sensitivity to drug in some older patients cannot be ruled out, no overall differences were observed in the safety and effectiveness of axitinib between patients who were >65 years and those younger.

Race

For the pivotal study in the axitinib group, the overall incidences of adverse events were similar for White and Asians subjects. There was some difference, however, with a greater incidence of abdominal pain, nausea, vomiting, asthenia, decreased weight, arthralgia, anxiety and dry skin for White patients. Hypothyroidism, stomatitis, fatigue, insomnia, proteinuria, dysphonia, epistaxis, red hand syndrome and hypertension were more common in the Asian subjects. The incidence of Grade III or greater adverse events was higher in the Asian subjects, being 71.4% versus 63.4%. This particularly related to hypertension, decreased appetite and red hand syndrome. Similar results were also observed in the Phase II studies. Nevertheless the overall incidence and severity of these adverse effects was generally such that it was considered not automatically appropriate to recommend dose adjustment based on race.

Gender

There is no evidence of a difference in incidence and severity of adverse events in relation to gender.

Hepatic and renal impairment

Previous discussion has been given with regards to hepatic impairment and requirement for consideration of dose adjustment in relation to moderate hepatic impairment. There is no evidence for requirement for dose adjustment in relation to renal impairment.

Evaluator's conclusions regarding safety

As described above, the most common adverse effects associated with axitinib involved diarrhoea, hypertension, fatigue, decreased appetite, nausea, dysphonia and red hand syndrome. Overall these findings were consistent with the recognised mechanism of action and were generally clinically manageable though the use of dose interruptions, dose reductions and relevant standard medical management.

First round benefit/risk assessment

First round assessment of benefits

The pivotal Phase III study (A4061032), involving administration of axitinib in a starting dose of 5 mg bid compared to sorafenib, resulted in a clinically significant improvement in PFS for patients with advanced stage RCC who failed either cytokines or prior sunitinib. The improvement in PFS was significant, with $p < 0.0001$, and there was a 33% reduction in risk of disease progression. This PFS benefit was independent of demographics and baseline characteristics.

It was noted that a significant improvement of PFS was also apparent in sub-group analyses involving prior sunitinib and cytokine-containing treatment of patients, with a 26% and 54% reduction in the risk of disease progression, respectively. Axitinib was also associated with a clinically significant increase in overall response rate compared to sorafenib, being 19.4% versus 9.4%, respectively, with a p value of 0.0001. Evaluation of overall survival is still too immature and unfortunately the dossier does not give data in relation to this.

The data from the three Phase II studies in advanced stage RCC support moderate efficacy in terms of significant overall response rates, ranging from 19-50%, together with PFS comparable to that seen with axitinib in the pivotal study.

Overall, the data therefore support the fact that axitinib has activity at least comparable to sorafenib as based on the pivotal Phase III study which is robust and well conducted. It is unfortunate that overall survival data remains extant and subsequent reporting of this will be important.

As the efficacy of axitinib has been demonstrated in these studies to be at least comparable to that for sorafenib, a currently approved agent for the treatment of advanced stage RCC in Australia, and also appears to be comparable to the other TKIs as well as mTOR inhibitors and monoclonal antibodies currently approved for marketing, the overall benefits for axitinib warrant approval for marketing in at a starting dose of 5 mg bid with the option of increasing the dose depending on tolerance.

First round assessment of risks

The most common adverse events observed following treatment with axitinib included diarrhoea, hypertension, fatigue, decreased appetite, nausea, dysphonia, red hand syndrome, decreased weight, vomiting, asthenia and constipation. Overall these were most often mild to moderate in severity and generally manageable with appropriate dose reduction or interruption and relevant standard medical therapy. Very few patients required treatment discontinuation because of adverse events, and individual risks associated with specific side effects, such as hypertension, gastrointestinal perforation, haemorrhage, and wound healing complications, require relevant monitoring and

management. This adverse effect profile is essentially comparable to that observed with other TKIs, without any undue new adverse effects being reported.

First round assessment of benefit-risk balance

The evaluator considers that the robust data from the Phase III study, which clearly indicate benefit for axitinib versus sorafenib in terms of PFS in patients with advanced stage RCC who had failed one prior line of therapy including either cytokines or sunitinib, support the role of axitinib in the management of this condition. The Phase II data also support this. In terms of adverse effects, the overall profile generally appears to be manageable in terms of relevant approaches and therefore appears reasonable to support axitinib for treatment of advanced stage RCC.

List of questions

1. Please advise whether an updated analysis of the overall survival data from the pivotal Study A4061032 has been conducted. If so, please provide a summary of the results.

Summary of Sponsor's response to the clinical evaluator's question

At the time the final PFS analysis was conducted for the pivotal Study A4061032 (data cutoff of 31 August 2010; the data were included in the initial application/submission), only 223 patients out of the 723 patients with metastatic RCC (mRCC) had died (approximately 30% of the total number of patients enrolled and 50% of the protocol required 417 events for the final Overall Survival (OS) analysis). The interim OS analysis, based on the immature data, showed an observed HR (axitinib relative to sorafenib) of 1.008 with a 95% CI of 0.774-1.313 and a 1-sided p-value of 0.525 adjusted for ECOG performance status and prior treatment regimen.

Following the final PFS analysis, patients remained in the treatment arms to which they had been randomised and were followed for evaluation of safety and efficacy, including OS.

Clinical Study Report Supplement 3 for Study A4061032 is provided and includes the final OS data, as well as a summary of subsequent treatment, based on 723 patients as of the data cutoff date of 01 November 2011. As of that cutoff date for the final OS analysis, there were 211 deaths (58.4%) in the axitinib arm and 214 deaths (59.1%) in the sorafenib arm.

The final OS results were largely consistent with the interim OS results reported previously for the data cutoff of 31 August 2010. Based on the final analysis, there was no difference between axitinib and the active comparator, sorafenib, in OS in the overall population (HR = 0.969 [95% CI: 0.800-1.174] with a 1-sided p-value of 0.3744 adjusted for ECOG performance status and prior treatment regimen). In addition, there was no difference in OS between axitinib and sorafenib in the subgroup of patients previously treated with a sunitinib-containing regimen (HR = 0.997 [95% CI: 0.782-1.270] with a 1–sided p-value of 0.4902). In the subgroup of patients previously treated with a cytokine-containing regimen, the HR (0.813 [95% CI: 0.555-1.191] with a 1-sided p-value of 0.1435) favoured axitinib. The results in the subgroups of patients previously treated with bevacizumab or temsirolimus are difficult to interpret due to the low numbers of patients in each treatment group (59 and 24 patients, respectively) and the wide confidence intervals.

The above response is taken into account in the *Delegate's overview*, below.

Clinical summary and conclusions

The evaluator considers that, on the basis of the results of the pivotal Phase III study together with supportive data from the Phase II trials, there is sufficient evidence to support axitinib as treatment for advanced stage RCC. The proposed indication is for the treatment of patients with advanced RCC. It is recognised that the pivotal study involves treatment of patients who have failed one prior line of approved treatment for RCC. Nevertheless in view of the fact that the data from the pivotal study has demonstrated at least equivalent efficacy for axitinib versus sorafenib, a commonly used first line treatment for advanced RCC in Australia today, it is considered reasonable to support the proposed indication as it stands rather than any limitation in relation to prior treatment.

V. Pharmacovigilance findings

Risk management plan

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* are proposed to monitor all the specified Ongoing safety concerns.

Given the proposed indications and the target population, there is no objection to the sponsor implementing only routine pharmacovigilance activities to monitor all the specified Ongoing safety concerns.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns.

Given the proposed indications, the target population and the likely prescribers of this medication, the sponsor's conclusion would appear to be reasonable and therefore acceptable.

Summary of recommendations

- The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:
- Given the proposed indications and the target population, there is no objection to the sponsor implementing only routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.
- Given the proposed indications, the target population and the likely prescribers of this medication, the sponsor's conclusion that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns would appear to be reasonable and therefore acceptable.
- The sponsor's proposed application of routine risk minimisation activities would appear to be reasonable and therefore acceptable. The table on *'Overall Summary of the Risk Management Plan'* does not appear to describe all of the routine activity in the proposed Australian PI related to the specified ongoing safety concerns (for example,

no description of routine activity for lactating women). This part of the RMP should be amended accordingly.

- In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft Consumer Medicine Information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections to registration on chemistry and quality grounds. At the time of writing, details of an acceptable tablet assay were still being finalised. However, this issue is not expected to delay registration. The application was reviewed by the PSC at its November 2011 meeting. No objections to registration were raised.

Nonclinical

There are no nonclinical objections to registration. Toxicity was studied in mice and dogs. Major toxicities included:

- Gastrointestinal effects – abnormal faeces, inflammation, ulceration and mucosal haemorrhage;
- Haematopoietic effects – decreased reticulocytes and red cells parameters, lymphoid depletion;
- Effects on growing teeth and bone;
- Toxic effects on male and female reproductive systems;
- Increased blood pressure;
- Hepatic effects;
- Pancreatic toxicity.

The observed toxicities were consistent with the pharmacological action of axitinib and were similar to those observed with other VEGFR inhibitors.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics

The absolute bioavailability of axitinib was shown to be approximately 60%, T_{max} was approximately 1.5-4.1 h and the drug had approximately dose-proportional PK over the 5–10 mg dose range. There was modest accumulation, with accumulation ratios up to 1.48 with repeated dosing. With the formulation proposed for marketing (Form XLI) there did not appear to be a clinically significant effect of food on absorption, with a decrease in AUC

of 10% with a moderately high fat meal and an increase in AUC of 19% with a high fat meal. A pilot study suggested that gastric acid suppression did not have a major effect on the absorption of the drug.

Following IV administration axitinib had a volume of distribution of 67.9 L. Nonclinical data indicate that the drug is highly protein bound (99.5%).

A mass balance study demonstrated that no unchanged drug was excreted in the urine, indicating that the drug is metabolically cleared. Nonclinical data suggest that the drug is predominantly metabolised by CYP3A4/5, with lesser contributions from CYP1A2, CYP2C19 and UGT1A1, and that the metabolites are inactive. After IV administration, clearance was 20.7 L/h (345 mL/min) and half-life was 2.3 h. Elimination was mainly *via* faeces.

Mild hepatic impairment (Child-Pugh Class A[30]) did not significantly alter the PK of axitinib. Moderate impairment (Child-Pugh Class B) resulted in a 100% (2 fold) increase in AUC. The effect of severe hepatic impairment was not studied.

Co-administration with the CYP3A4/5 inhibitor ketoconazole resulted in a 100% (2 fold) increase in AUC. Co-administration with the CYP3A4/5 inducer rifampicin resulted in an 80% decrease in AUC.

Pharmacodynamics

The submission contained population PK/PD analyses examining correlations between axitinib systemic exposure and various PD endpoints. Increasing axitinib AUC was associated with several adverse events.

A Phase I dose finding study established that the maximum tolerated starting dose was 5 mg bid, with hypertension being the dose-limiting toxicity.

Axitinib treatment was also associated with decreases in soluble VEGFR-2 and soluble VEGFR-3, and increases in plasma VEGF. These changes in soluble proteins are consistent with those previously observed with other VEGF inhibitors.

Efficacy

Evidence to support efficacy comes primarily from one pivotal, randomised controlled trial – Study A4061032, also known as the AXIS trial. The study has been published[31].

The study enrolled subjects with mRCC which had a component of clear cell histology. Subjects were required to have progressive disease after one prior systemic first-line regimen. The first-line regimen had to contain one or more of the following 4 agents: sunitinib, bevacizumab with IFN-α, temsirolimus, or a cytokine.

Subjects were randomised (1:1) to receive axitinib (5 mg bid starting dose) or sorafenib (400 mg bid). Sorafenib is registered in Australia for the treatment of advanced RCC with a starting dose of 400 mg bid.

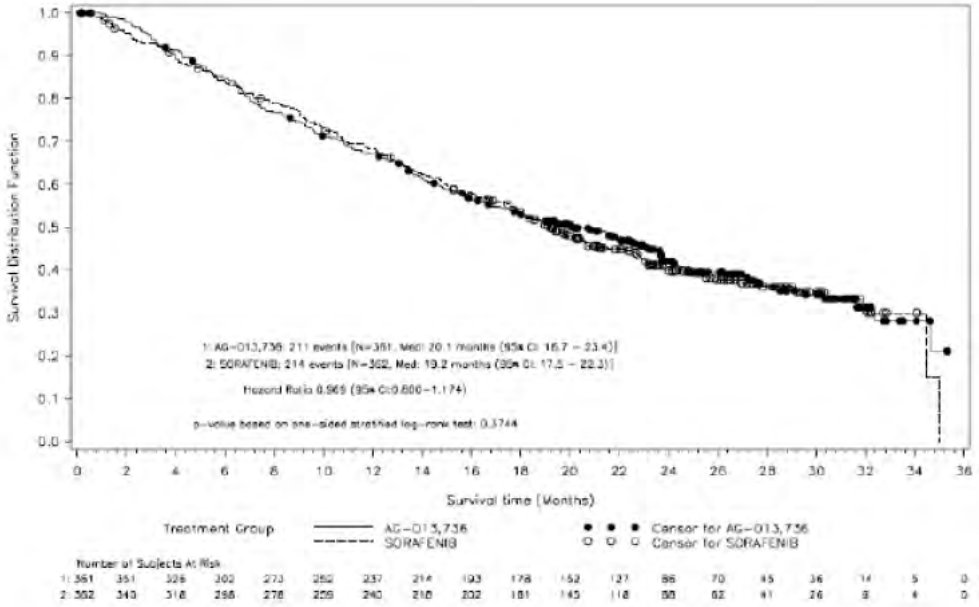
The primary efficacy endpoint was PFS as assessed by a blinded IRC. Treatment with axitinib was associated with a significant improvement in PFS (HR = 0.665; 95%CI: 0.544–0.812; p < 0.0001). Median PFS was increased by 2 months (6.7 versus 4.7). Efficacy appeared greater in patients who had received a cytokine as first-line therapy (median PFS increase of 5.6 months) than in those who had received sunitinib (median PFS increase of 1.4 months).

[30] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

[31] Rini B., Escudier B., Tomczak P., *et al*. Compariative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; 378:1931-1939.

At the time of the initial study report, overall survival data were not mature as only 30% of subjects had died at the time of data cutoff. In response to a question raised by the evaluator, the sponsor has provided data from the final analysis of survival. The Kaplan–Meier curves of these data are shown in Figure 8.

Figure 8. Pivotal Phase III Study A4061032: Kaplan-Meier curves of overall survival by treatment (Full Analysis Set)



Source: Figure 14.2.1
Data cutoff date: 01 November 2011
Note: Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicates a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test. For the overall stratified analysis, the p-value was from a 1-sided log-rank test stratified by ECOG performance status and prior treatment.
AG-013,736 = axitinib, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, Med = median, N = number of patients

There was no significant difference between the two study treatments in terms of overall survival. Crossover between the two drugs at the time of disease progression was not permitted, and would therefore not explain the lack of a survival benefit.

Response rate was significantly increased in the axitinib arm (19.4% versus 9.4%). Duration of response was comparable in the two arms. There were no significant differences in quality of life.

Other studies

The submission included three single-arm, Phase II studies of axitinib in RCC patients, using overall response rate as the primary endpoint. All three studies examined efficacy in the second-line setting. Response rates were somewhat higher than those obtained in the pivotal study. Cross-trial comparison of the results from the three studies again suggested that efficacy is greater in patients previously treated with cytokines (Studies A4061012 and A4061035) compared to patients previously treated with sorafenib (Study A4061023).

Safety

A total of 2507 subjects were exposed to axitinib in the submitted studies. Of these, 537 were patients who received the drug for the treatment of RCC at the recommended starting dose of 5 mg bid. In the pivotal study, the median duration of treatment was 196 days (6.4 months).

The overall safety profile of the drug compared to sorafenib in the pivotal study, in terms of incidences of adverse events deaths and discontinuations, is summarised in Table 11.

Table 10. Overall safety profile of axitinib compared to sorafenib

	Axitinib	sorafenib
Adverse events (AEs)	95.3 %	97.7 %
Treatment – related AEs	90.5 %	94.6 %
Grade 3 or 4 AEs	65.7 %	68.2 %
Treatment – related Grade 3 or 4 AEs	49.3 %	53.2 %
Serious adverse events (SAEs)	29.5 %	31.0 %
Treatment – related SAEs	12.8 %	12.4 %
Deaths on treatment / within 28 days	31	23
Deaths due to study drug	n = 4	n = 4
Discontinuations due to AEs	9.2 %	13.0 %

Specific axitinib toxicities with an increased incidence compared to sorafenib included the following:

- Gastrointestinal – diarrhoea, nausea, vomiting, decreased appetite, abdominal pain, dyspepsia;
- Fatigue and asthenia;
- Hypertension (40.4% versus 29.0%);
- Proteinuria (10.9% versus 7.3%);
- Dysphonia (30.9% versus 13.5%);
- Hypothyroidism (19.2% versus 8.2%);
- Hypercalcaemia (30.1% versus 7.1%).

The majority of these events were of Grade I or II in severity.

Axitinib was associated with a *decreased* incidence compared to sorafenib of the following:

- Skin toxicity – palmar-plantar erythodysaesthesia (PPE), rash, pruritus, alopecia;
- Hypophosphataemia (12.8% versus 49.5%);
- Hypocalcaemia (9.3% versus 28.0%)
- Increased lipase (26.6% versus 46.0%).

These findings suggest that the two drugs have comparable overall toxicity, although with a somewhat different pattern of adverse events. Many of the adverse events observed with axitinib have been described with other TK VEGFR inhibitors. The evaluator considered the toxicity of the drug to be manageable.

Another randomised controlled trial compared the combination of axitinib plus gemcitabine with gemcitabine alone in patients with pancreatic cancer. The pattern of adverse events with axitinib was similar to that seen in the pivotal study. Toxicity

observed in the single-arm Phase II studies was consistent with that observed in the pivotal study.

Risk management plan

The RMP proposed by the sponsor has been found to be acceptable by the TGA's OPR.

Risk-benefit analysis

Delegate considerations

Overall risk-benefit balance

The pivotal study has demonstrated some evidence of superior efficacy (in terms of PFS) over sorafenib, an agent which is currently registered for the treatment of advanced RCC. The overall safety profile of the two drugs appeared comparable, although there were differences in the patterns of toxicity. Overall, the Delegate considers that axitinib has a comparable risk-benefit balance compared to sorafenib, and therefore proposed to approve the application.

Indication

The pivotal study, and the three Phase II studies, examined the efficacy of axitinib in the second line setting. The indication sought by the sponsor includes treatment in the first line setting. Sorafenib was granted a broad indication (including both first and second line treatment) on the basis of a pivotal study conducted in the second line setting. However this approval was granted at a time when the available therapies for RCC were very limited. As there are now multiple approved therapies for use in the first line setting, the Delegate proposed to restrict the axitinib indication to second line use, the setting for which there is adequate evidence.

Product Information

Revisions proposed to the PI are beyond the scope of this AusPAR.

Delegate's proposed recommendation

The Delegate proposed to approve the application for the following indication:

> *Inlyta is indicated for the treatment of patients with advanced RCC, after failure of one prior systemic therapy.*

General advice on this application was requested from the ACPM.

Sponsor's response to the Delegate's overview

Overall risk benefit

Pfizer concurs with the Delegate's overall assessment.

Indication

The Delegate has recommended the proposed indication *"Inlyta is indicated for the treatment of patients with advanced RCC"* be amended to *"Inlyta is indicated for the treatment of patients with advanced RCC, after failure of one prior systemic therapy"*.

Pfizer requests the Delegate and the ACPM further consider the proposed indication *"Inlyta is indicated for the treatment of patients with advanced RCC"*.

Pivotal Study A4061032 compared axitinib to sorafenib, and is the first Phase III study conducted in advanced RCC (aRCC) patients to evaluate an experimental agent against an

approved active VEGFR TKI. Previous Phase III studies that supported registration of currently approved therapies in RCC compared the new agent to either placebo (registration studies for pazopanib, sorafenib, everolimus) or to IFN-α (registration studies for sunitinib, bevacizumab and temsirolimus).

Sorafenib was granted a broad indication *"For the treatment of advanced RCC"* on the basis of a pivotal study conducted in the second line setting, and was the second VEGFR TKI available first line for the treatment of advanced RCC in Australia.

In assessing this application the clinical evaluator supported axitinib for the treatment of advanced RCC. This recommendation was made on the basis that while the pivotal study treated patients who had failed one prior line of approved therapy, the data clearly *"demonstrated at least equivalent efficacy for axitinib versus sorafenib, a commonly used first line treatment for advanced RCC in Australia today."*

Pfizer agrees with the Delegate that the pivotal study *"demonstrated some evidence of superior efficacy (in terms of PFS) over sorafenib,"* and overall a comparable safety profile with different patterns of toxicity. In pivotal Study A4061032 a statistically significant and clinically meaningful improvement was observed in favour of axitinib with median PFS of 6.7 months in the axitinib treatment arm and 4.7 months in the sorafenib arm.

The HR was 0.665 (95% CI: 0.544-0.812) $p < 0.0001$ for the overall study population, representing a 33% reduction in the risk of progression or death on the axitinib arm relative to the sorafenib arm. This reduction represents a clinically important benefit relative to sorafenib, an approved agent for the treatment of patients with advanced RCC.

As shown in Table 11 below, based on indirect comparisons of clinical data in different patient populations, the median PFS of 12.1 months associated with axitinib in cytokine-refractory patients with advanced RCC in Phase III Study A4061032 was comparable to that of pazopanib, sunitinib, and bevacizumab in combination with IFN-α in treatment-naïve patients (11.1 months, 10.9 months and 10.2 months respectively).

A pivotal Phase III study (A4061051) is currently ongoing to determine the efficacy of axitinib in treatment-naïve patients. Historically, the efficacy of anticancer drugs in treatment naïve patients with mRCC (that is, first line setting) is higher than that observed in previously treated patients with mRCC (that is, second line setting). Therefore, it is expected that in treatment naïve patients in Study A4061051, the PFS associated with axitinib will be superior to that observed in cytokine-refractory patients (> 12.1 months).

Table 11. Efficacy results from the pivotal Phase II studies for axitinib and approved mRCC therapies

Patients studied	Therapy	Control	Median PFS (mo)	HR (p-value)	Median OS (mo)	HR (p-value)
First-line (good or intermediate risk)	Pazopanib[1]	Placebo	11.1 vs 2.8	0.40 (<0.0001)	22.9 vs 23.5[2]	1.01 (0.525)
	Sunitinib[3,4]	IFN-α	10.9 vs 5.1	0.42 (<0.001)	26.4 vs 21.8	0.82 (0.051)
	Bevacizumab/IFN-α[5,6]	IFN-α	10.2 vs 5.4	0.63 (<0.0001)	23.3 vs 21.3	0.91 (0.336)
First-line (poor risk)	Temsirolimus[7]	IFN-α	5.6 vs 3.2	0.74 (0.0042)	10.9 vs 7.3	0.78 (0.025)
Prior cytokine	Pazopanib[1]	Placebo	7.4 vs 4.2	0.54 (<0.001)	NR	NR
	Sorafenib[8,9]	Placebo	5.5 vs 2.8	0.44 (<0.000001)	17.8 vs 15.2	0.88 (0.146)
	Axitinib[11,12]	Sorafenib	12.1 vs 6.5	0.46 (<0.0001*)	29.4 vs 27.8	0.81 (0.14*)
Prior TKI	Everolimus[10]	Placebo	4.9 vs 1.9	0.33 (<0.001)	14.8 vs 14.4	0.87 (0.162)
	Axitinib[11,12]	Sorafenib	4.8 vs 3.4	0.74 (0.01*)	15.2 vs 16.5	0.997 (0.49*)

* One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

NR: not reported; [1]Sternberg CN et al. J Clin Oncol. 28(6) Feb 2010; [2]NICE Final Appraisal Determination document issue date: December 2010 (see section 3.3 page 5); [3]Sutent (sunitinib) SmPC; [4]Motzer RJ et al. J Clin Oncol, 2009; [5]Avastin (bevacizumab) SmPC; [6]Escudier B et al. J Clin Oncol, 2010; [7]Torisel (temsirolimus) SmPC; [8]Nexavar (sorafenib) SmPC; [9]Escudier B et al. J Clin Oncol 2009, 27(20):3312-8; [10]Motzer RJ et al. Cancer 2010, 116:4256-65; [11]A4061032 CSR Table 24; [12]A4061032 CSR Supplement 3 (23 December 2011) Table 1.

While the clinical landscape has shifted rapidly with the advent of new therapies, none are curative and new treatment options are warranted to further advance the treatment and management of RCC. The first therapy in RCC to be investigated against an approved active comparator, axitinib is well placed to continue this advance after demonstrating superior efficacy and a comparable safety profile to sorafenib, a registered first line therapy in advanced RCC. Pfizer respectfully requests the Delegate and the ACPM consider axitinib *"for the treatment of patients with advanced RCC."*

Product Information

Details regarding revisions to the PI are beyond the scope of this AusPAR.

Clinical data

Pfizer refers to the summary Adverse Event Table in the Delegate's overview, which was reviewed against the Clinical Evaluation Report references and the Clinical Study Report for A4061032. From this review Pfizer identified minor descriptive errors in two Adverse Event headings in the summary table, as described below:

	Axitinib	Sorafenib	CER page
Adverse events (AEs)	95.3%	97.7%	124
Treatment – related AEs	90.5%	94.6%	125
Grade 3 – 5 ~~or 4~~ AEs	65.7%	68.2%	124
Treatment-related Grade 3 – 5 ~~or 4~~ AEs	49.3%	53.2%	125
Serious adverse event (SAEs)	29.5%	31.0%	34
Treatment – related SAEs	12.8%	12.4%	-
Deaths on treatment / within 28 days	31	23	129
Deaths due to study drug	n=4	n=4	129
Discontinuations due to AEs	9.2%	13.0%	130

Note: Changes reflect data reported in clinical study report for Phase 3 RCC study A4061032

The "Grade 3 or 4 AEs" and "Treatment-related Grade 3 or 4 AEs" headers listed in the summary table actually also include incidence rates for Grade 5 AEs. In the summary table (above), insertions are marked with underline and deletions with strikethrough.

Conclusion

Axitinib is an effective treatment for patients with advanced RCC and has shown a statistically significant and clinically meaningful improvement over sorafenib, a VEGFR TKI approved for the treatment of advanced RCC. Furthermore, the efficacy of axitinib was shown among patients who were refractory to prior treatment with sunitinib and to be of even greater magnitude among patients who were refractory to cytokine treatment – the population that was studied as the basis of the sorafenib approval. This improvement in efficacy is independent of demographics and baseline characteristics and is robust, as demonstrated by the results across subgroups. Adverse effects were generally managed, with a safety profile comparable to those agents targeting VEGF signalling that are approved for the treatment of advanced RCC.

Both the clinical evaluator and TGA Delegate consider the benefits of axitinib in advanced RCC patients outweigh its risks and recommend the approval of this application. As the first therapy in RCC to be investigated against an approved active comparator, axitinib is well placed to advance the treatment of kidney cancer after demonstrating superior efficacy compared to sorafenib, a registered first line therapy in advanced RCC. Accordingly, Pfizer requests further consideration by the Delegate and the ACPM for the approval of axitinib for the treatment of patients with advanced RCC.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit–risk profile for the following indication**:**

> ***For the treatment of patients with advanced RCC after failure of one prior systemic therapy.***

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

A statement in the appropriate sections of the PI and CMI to accurately reflect that studies in patients with impaired renal function had not been conducted and significant caution is warranted with use in this population.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Inlyta, axitinib 1 mg and 5 mg tablet for oral administration at a dose of 5 mg bid, up to a maximum of 10 mg bid, indicated:

> *For the treatment of patients with advanced RCC after failure of one prior systemic therapy.*

Specific conditions of registration applicable to these goods:

- The implementation in Australia of the axitinib Risk Management Plan (RMP) Version 1.0, dated 22 March 2011, included with submission PM-2011-00876-3-4, to be revised as specified in the sponsor's correspondence dated 13 April 2012.
- Batches of axitinib tablets released in Australia must, in addition to meeting submitted release specification limits, have the TGA required acceptance value in the test for uniformity of dosage units.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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