



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## CHMP assessment report

### Inlyta

International non-proprietary name: **axitinib**

Procedure No. **EMA/H/C/002406**

### Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



## Product information

|                                                         |                                                                                                                                                                 |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Name of the medicinal product:</b>                   | Inlyta                                                                                                                                                          |
| <b>Applicant:</b>                                       | Pfizer Ltd.<br>Ramsgate Road<br>Sandwich<br>Kent CT13 9NJ<br>United Kingdom                                                                                     |
| <b>Active substance:</b>                                | axitinib                                                                                                                                                        |
| <b>International Nonproprietary Name / Common Name:</b> | axitinib                                                                                                                                                        |
| <b>Pharmaco-therapeutic group (ATC Code):</b>           | Protein kinase inhibitors<br>(L01XE17)                                                                                                                          |
| <b>Therapeutic indication:</b>                          | Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. |
| <b>Pharmaceutical form:</b>                             | Film-coated tablet                                                                                                                                              |
| <b>Strengths:</b>                                       | 1 mg, 5 mg                                                                                                                                                      |
| <b>Route of administration:</b>                         | Oral use                                                                                                                                                        |
| <b>Packaging:</b>                                       | blister (Aluminium/aluminium), bottle (HDPE)                                                                                                                    |
| <b>Package sizes:</b>                                   | 1 mg : 28 tablets, 56 tablets and 180 tablets<br>5 mg: 28 tablets, 56 tablets and 60 tablets                                                                    |

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## List of abbreviations

|                     |                                                                          |
|---------------------|--------------------------------------------------------------------------|
| AE                  | Adverse event                                                            |
| AEM                 | Adverse event monitoring                                                 |
| ALT                 | alanine aminotransferase                                                 |
| ALP                 | alkaline phosphatase                                                     |
| AST                 | aspartate aminotransferase                                               |
| ATE                 | Arterial thromboembolic events                                           |
| ATP                 | Adenosine triphosphate                                                   |
| AUCt                | area under the plasma concentration-time curve to the last sampling time |
| AUC <sub>0-12</sub> | area under the plasma concentration-time curve from time zero to 12 h    |
| AUC <sub>0-24</sub> | area under the plasma concentration-time curve from time zero to 24 h    |
| AUC <sub>0-∞</sub>  | areas under the plasma concentration-time curves from zero to infinity   |
| AUC <sub>ss</sub>   | areas under the plasma concentration-time curves at steady state         |
| BID                 | "bis in die" (twice a day)                                               |
| BP                  | blood pressure                                                           |
| C <sub>eff</sub>    | minimum effective concentration                                          |
| C <sub>max</sub>    | maximum plasma concentration                                             |
| CI                  | confidence interval                                                      |
| CL                  | clearance                                                                |
| CMC                 | Carboxymethylcellulose                                                   |
| CR                  | controlled release                                                       |
| CR                  | Complete response                                                        |
| CRF                 | Case Report Form                                                         |
| CSR                 | clinical study report                                                    |
| CT                  | Computed Tomography                                                      |
| CTCAE               | Common Terminology Criteria for Adverse Events (Version 3.0)             |
| CV                  | coefficient of variation                                                 |
| CYP                 | cytochrome P450                                                          |
| dBp                 | Diastolic blood pressure                                                 |
| DCE-MRI             | Dynamic Contrast Enhanced Magnetic Resonance Imaging                     |
| DDPS                | Detailed description of the pharmacovigilance system                     |
| DILI                | Drug-induced liver injury                                                |
| DLT                 | Dose Limiting Toxicity                                                   |
| DMC                 | Data Monitoring Committee                                                |
| DR                  | Duration of response                                                     |
| EC50                | half maximal effective concentration                                     |
| ECG                 | Electrocardiogram                                                        |
| ECOG                | Eastern Cooperative Oncology Group                                       |
| ECOGPS              | ECOG performance status                                                  |
| EGFR                | Epidermal growth factor receptor                                         |
| EORTC               | Eastern Cooperative Oncology Group                                       |
| EuroQoL             | European Quality of Life                                                 |
| EQ-5D               | EuroQol EQ-5D self-report questionnaire                                  |
| EQ-VAS              | EuroQol EQ-5D visual analog scale                                        |
| FAS                 | Full Analysis Set                                                        |
| FCIR                | film-coated immediate release                                            |
| FIH                 | First in human                                                           |

|                  |                                                                                        |
|------------------|----------------------------------------------------------------------------------------|
| FGF              | Fibroblast growth factor                                                               |
| FGFR             | Fibroblast growth factor receptor                                                      |
| FKSI             | FACT-Advanced Kidney Cancer Symptom Index                                              |
| FKSI-DRS         | Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms |
| FLVK             | FGF like VEGF kinase                                                                   |
| GI               | Gastrointestinal                                                                       |
| GCP              | Good Clinical Practice                                                                 |
| GLP              | Good Laboratory Practice                                                               |
| hERG             | Human <i>Ether-à-go-go</i> related gene                                                |
| HPLC             | High-performance liquid chromatography                                                 |
| HUVEC            | Human umbilical vein endothelial cell                                                  |
| IAUC             | initial area under the curve                                                           |
| IC <sub>50</sub> | Half maximal inhibitory concentration                                                  |
| ICH              | International Conference on Harmonization                                              |
| ICSR             | Individual Case Safety Report                                                          |
| IEC              | Independent Ethics Committee                                                           |
| IFN-α            | interferon-alpha                                                                       |
| IL-2             | Interleukin-2                                                                          |
| IP               | Intraperitoneal                                                                        |
| IIR              | investigator-initiated research                                                        |
| IRC              | Independent Review Committee                                                           |
| IV               | Intravenous                                                                            |
| IVRS             | Interactive Voice Response System                                                      |
| LFT              | Liver function test                                                                    |
| LOAEL            | Lowest-observed-adverse-effect-level                                                   |
| MedDRA           | Medical Dictionary for Regulatory Activities                                           |
| MCH              | Mean corpuscular hemoglobin                                                            |
| MCV              | Mean corpuscular volume                                                                |
| mRCC             | Metastatic renal cell cancer                                                           |
| MRI              | Magnetic resonance imaging                                                             |
| MSKCC            | Memorial Sloan-Kettering Cancer Center                                                 |
| MTD              | Maximum tolerated dose                                                                 |
| mTOR             | Mammalian Target of Rapamycin                                                          |
| n                | number of patients                                                                     |
| NCI              | National Cancer Institute                                                              |
| NE               | not estimated                                                                          |
| NO               | Nitric oxide                                                                           |
| NOAEL            | No observed adverse effect level                                                       |
| NOEL             | No observed effect level                                                               |
| NRU              | Neutral Red Uptake                                                                     |
| NSCLC            | non-small cell lung cancer                                                             |
| OR               | Objective Response                                                                     |
| ORR              | objective response rate                                                                |
| OS               | overall survival                                                                       |
| PEC              | Predicted environmental concentration                                                  |
| PD               | progressive disease                                                                    |
| PFS              | progression-free survival                                                              |
| PDGF(R)          | Platelet-derived growth factor (receptor)                                              |

|                  |                                                                       |
|------------------|-----------------------------------------------------------------------|
| PK               | pharmacokinetic                                                       |
| PO               | peros                                                                 |
| PNEC             | Predicted no-effect concentration                                     |
| PPES             | Palmar-plantar erythrodysaesthesia syndrome                           |
| PRES             | Posterior reversible encephalopathy syndrome                          |
| PR               | partial response                                                      |
| PRO              | patient-reported outcome                                              |
| PT               | Preferred term                                                        |
| PV               | Pharmacovigilance                                                     |
| PV               | Perivascular                                                          |
| QA               | Quality Assurance                                                     |
| QC               | quality control                                                       |
| QD               | “quaque die” (once a day)                                             |
| QOD              | every other day                                                       |
| QoL              | quality of life                                                       |
| QPPV             | Qualified person for pharmacovigilance                                |
| QTc              | heart rate corrected QT interval length                               |
| QTcB             | Bazett's correction of the QT interval                                |
| QTcF             | Fridericia's correction of the QT interval                            |
| RCC              | renal cell carcinoma                                                  |
| RECIST           | Response Evaluation Criteria in Solid Tumours                         |
| RMP              | Risk management plan                                                  |
| RTK              | Receptor tyrosine kinase                                              |
| SAE              | Serious adverse event                                                 |
| SAP              | Statistical Analysis Plan                                             |
| sBP              | Systolic blood pressure                                               |
| SD               | Standard deviation                                                    |
| SDD              | spray-dried dispersion                                                |
| SE               | standard error                                                        |
| SEDDS            | self-emulsifying drug delivery system                                 |
| SGOT             | serum glutamic oxaloacetic transaminase                               |
| SGPT             | serum glutamic pyruvic transaminase                                   |
| SLD              | sum of longest diameters                                              |
| SMQ              | Standardized MedDRA Query                                             |
| SOC              | system organ class                                                    |
| SPC              | Summary of product characteristics                                    |
| TBL              | total bilirubin                                                       |
| TGI              | tumour growth inhibition                                              |
| T <sub>max</sub> | time of maximal plasma concentration                                  |
| T <sub>½</sub>   | terminal half life                                                    |
| TKI              | Tyrosine kinase inhibitor                                             |
| TSH              | thyroid-stimulating hormone                                           |
| TTP              | time to progression                                                   |
| UGT              | Uridine diphosphate-glucuronosyltransferase                           |
| UGT1A1           | uridine 5'-diphospho-glucuronosyltransferase 1 family, polypeptide A1 |
| ULN              | Upper limit of normal                                                 |
| VAS              | visual analog scale                                                   |
| Vc               | volume of distribution of the central department                      |

|                   |                                                              |
|-------------------|--------------------------------------------------------------|
| VEGF              | Vascular endothelial growth factor                           |
| VEGFR             | Vascular endothelial growth factor receptor                  |
| VMD               | volume median diameter                                       |
| VTE               | Venous thromboembolic events                                 |
| V <sub>z</sub>    | volume of distribution during the elimination phase          |
| V <sub>z</sub> /F | apparent volume of distribution during the elimination phase |

# **1. Background information on the procedure**

## ***1.1. Submission of the dossier***

The applicant Pfizer Ltd. submitted on 19 April 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Inlyta, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 September 2010.

Inlyta was designated as an orphan medicinal product EU/3/10/844 on 23 February 2011 in the following indication: treatment of renal cell carcinoma. The Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 11 July 2012.

The applicant applied for the following indication: Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior systemic treatment.

### **The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

### ***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/63/2010 on the granting of a class waiver.

### ***Information relating to orphan market exclusivity***

#### **Similarity**

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

#### **New active Substance status**

The applicant requested the active substance axitinib contained in the above medicinal product to be considered as a new active substance in itself.

#### **Scientific Advice**

The applicant did not seek Scientific Advice at the CHMP.

#### **Licensing status**

Inlyta has been given a Marketing Authorisation in the USA on 27 January 2012.

## **1.2. Steps taken for the assessment of the product**

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Karsten Bruins Slot**      Co-Rapporteur: **Jens Ersbøll**

- The application was received by the EMA on 19 April 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2011 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2011 .
- During the meeting on 22 September 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 September 2012 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 January 2012.
- During the CHMP meeting on 16 February 2012 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 March 2012.
- The applicant submitted the responses to the Rapporteurs Joint Assessment Report on 12 April 2012
- During a meeting of a SAG on 2 March 2012, experts were convened to address questions raised by the CHMP .
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 19 April 2012.
- The applicant submitted the responses to the Rapporteurs updated Joint Assessment Report on 15 May 2012.
- The Rapporteurs circulated an updated Joint Assessment Report on 21 May 2012.
- During the meeting on 21-24 May 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Inlyta on 24 May 2012.
- The CHMP adopted a report on similarity for Inlyta with Afinitor, Nexavar and Torisel on 17 November 2011.

## 2. Scientific discussion

### 2.1. Introduction

#### Problem statement

Renal cell carcinoma is the third leading urologic cancer. About 30% of patients with RCC have metastatic disease at the time of diagnosis, and a significant proportion of patients with localized disease treated with curative nephrectomy relapse subsequently with metastatic disease. Metastatic RCC is associated with a high quality-of-life burden, based on physical, psychological, and social criteria, and drastically reduced survival; only about 8% to 22.5% of mRCC patients survive for five years or more as compared to 90% of patients with localized renal cancer. Despite substantial progress in the understanding and treatment of mRCC in recent years, its incidence is increasing, and the disease is still considered incurable. The most frequent locations of metastases are the lungs, mediastinum, bone, liver, and brain.

Until the development of agents that target tumour angiogenesis and other signaling pathways, systemic therapy with the cytokines interleukin 2 (IL-2) or interferon (IFN)- $\alpha$  was the main treatment for advanced RCC. Currently, eight drugs are approved for the treatment of advanced RCC, including IL-2, IFN- $\alpha$ , sorafenib, sunitinib, everolimus, temsirolimus, bevacizumab in combination with IFN- $\alpha$ , and pazopanib. Systemic therapy with the cytokines IFN- $\alpha$  and/or IL-2 was until recently the main treatment of advanced RCC, however, the use of both agents has declined substantially since the introduction of therapies targeting angiogenic pathways.

#### About the product

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

The Applicant applied for the indication: *Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior systemic treatment.*

The CHMP adopted a positive opinion for the following indication:

*Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.*

Axitinib should be taken orally twice daily approximately 12 hours apart with or without food. Axitinib tablets should be swallowed whole with a glass of water. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs, that cannot be managed by concomitant medicines or dose adjustments. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

### 2.2. Quality aspects

#### 2.2.1 Introduction

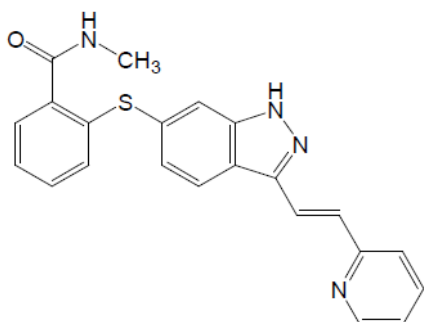
Inlyta is available as 1 mg and 5 mg film-coated tablets containing axitinib as the active substance. The 1 mg strength tablets are red, oval, debossed with "Pfizer" on one side and "1 XNB" on the other,

whereas the 5 mg film-coated tablets are red, triangular, debossed with "Pfizer" on one side and "5XNB" on the other. The drug product is packaged in Al/Al blisters or HDPE bottles with desiccant.

The full list of ingredients is defined in section 6.1 of the SmPC.

### 2.2.2. Active Substance

Axitinib is an indazole derivative obtained by chemical synthesis and is chemically designated as Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]



Axitinib is a white to light yellow powder, weak base, non-hygroscopic, classified as Biopharmaceutics Classification System (BCS) class II (low solubility, high permeability), and exhibits polymorphism. Five crystalline anhydrous forms have been identified (Form I, Form IV, Form VI, Form XXV and Form XLI). A number of crystalline solvates and hydrate forms have been observed and an amorphous form has been prepared. The polymorphic form intended for marketing is Form XLI.

Full information on the active substance axitinib is provided in the dossier.

### Manufacture

The active substance is manufactured in five synthetic steps followed by recrystallisation. A design space has been developed for steps 4, 5 6 and milling and operational boundaries are proposed for all process parameters. The development has been widely discussed. An extensive impurity discussion is provided on each step of the synthesis including both results of purging and spiking studies. The structure of each possible impurity is provided in a flow-chart showing where in the synthesis each possible impurity can be formed and the fate of each possible impurity. Flexibility has been granted for synthetic routes of starting materials.

### Specification

The active substance specification is set based on the critical quality attributes (CQA), historical data, toxicological and clinical evaluation, validation data and stability data and is considered acceptable.

Both the polymorphic form and the particle size distribution are critical quality attributes (CQA) for the dissolution of the active substance, which is classified as BCS class II drug (low solubility, high permeability). Both the polymorphic form and the particle size distribution are limited in the active substance specification.

The specification includes tests for appearance, identification by Infrared (IR) and by High Performance Liquid Chromatography (HPLC), assay by High Performance Liquid Chromatography (HPLC), polymorphic form by X-Ray diffraction, impurities by High Performance Liquid Chromatography (HPLC),

residue on ignition, heavy metals, particle size by laser diffraction and residual solvents by Gas Chromatography (HPLC/GC).

Impurities have been evaluated and found to be acceptable from the point of view of safety.

Satisfactory justification for the chosen parameters and related limits in the active substance specification and analytical procedures are presented in the dossier according to relevant guidelines (ICH Q6a and Q3A) and European Pharmacopoeia (Ph. Eur.) standards.

The descriptions of the analytical methods are considered acceptable and their validations are performed in accordance with ICH standards and Ph. Eur. requirements. The concept of Quality by Design (QbD) is used in the development of the HPLC method selected for determination of identification, assay and purity of axitinib. As a result of this a Method Operable Design Region (MODR) has been proposed defining ranges for certain method parameters which have been found acceptable.

Batch data from three commercial batches of pilot scale synthesised using the proposed route and supporting data from a number of development batches is provided. Results confirm batch to batch consistency and support uniformity of the quality of the active substance.

## ***Stability***

Satisfactory stability data on three commercial batches stored at ICH long-term conditions (25°C/60% RH) for 36 months and at accelerated conditions (40°C/75% RH) for 6 months has been provided.

The parameters tested were appearance, water content, assay (HPLC), impurities (HPLC), polymorphic form by Powder X-ray diffraction and microbial quality.

Forced degradation studies exposing the active substance to acid, base, free radical initiator, hydrogen peroxide, heat, humidity or high intensity light conditions have also been performed demonstrating that the active substance is sensitive to light.

The photo stability study was performed according to ICH Q1B and also demonstrated that axitinib is photolabile.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

### **2.2.3 Finished Medicinal Product**

#### ***Pharmaceutical Development***

Axitinib is a non-hygroscopic, white to light yellow powder, classified as BCS II (low solubility and high permeability). Polymorphic form XLI was chosen as it is the most thermodynamically stable polymorphic form. The drug substance has generally low solubility, but is highly soluble in the gastric (pH 1.7). The particle size is limited to ensure bioperformance.

The excipients used in Inlyta are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and film coating Opadry II red (hypromellose, titanium dioxide, lactose monohydrate, triacetin and red iron oxide). All excipients are well-known and commonly used in tablet formulations and meet the corresponding requirement of the European Pharmacopoeia, where appropriate.

The compatibility of the active substance with the excipients has been investigated by performing stress studies (high temperature and humidity). The tablet core formulation was tested to confirm

acceptable chemical stability and various film coating systems were also tested. The active substance, the excipients and the coating were directly mixed to enhance the possible affect of the coating. The hypromellose based coating system is more compatible with axitinib than the PVA/PEG (polyethylene glycol) based coating systems. During development, the hypromellose white coating system was adjusted to include red iron oxide to improve photo-stability. During this time a switch was made from the less photo-stable form IV drug substance to a more stable form, form XLI and changing the colour of the coating from white to red gave better protection against light.

The purposeful degradation test demonstrated that the polymorphic form change and modification in coating system resulted in a chemically more stable formulation.

The tablets used in early clinical trials were manufactured by a wet granulation process and were subsequently modified to dry granulation formulation to reduce processing time and material costs. A design space was developed for the manufacturing process. The critical quality attributes identified were uniformity of dosage units, dissolution and photo-stability.

Three packaging system were investigated during development. A HDPE bottle with desiccant and Al/AL blister were chosen.

### ***Adventitious agents***

An extensive TSE/BSE assessment was completed on the excipients used to manufacture axitinib tablets in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01, Revision 2). All excipients are of non-animal origin except for the lactose monohydrate used in the core tablet and in the coating. It is certified by the manufacturers that the lactose monohydrate used in this formulation is produced in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01, Revision 2).

### ***Manufacture of the product***

Inlyta 1 and 5mg tablets are manufactured by a dry granulation process. The manufacturing process consists in blending, milling, dry granulation, tableting, film-coating and packaging.

The manufacturing formula, flow chart and description of the manufacturing process are presented.

A design space was developed for the milling, dry granulation and milling and the film coating steps of the manufacturing process and the critical quality attributes identified were uniformity of dosage units, dissolution and photo-stability. A process validation scheme is presented and is considered acceptable.

### ***Product specification***

Satisfactory specification has been presented for the finished product and includes tests for appearance, identification (UV & HPLC), pH, assay (HPLC), impurities (HPLC), uniformity of dosage units (HPLC), microbiological control and dissolution.

The proposed test procedures and acceptance criteria comply with the requirements of the Ph. Eur. and current ICH guidelines. Analytical procedures are described and validated.

The concept of Quality by Design (QbD) is used in the development of the HPLC method selected for determination of identification, assay, purity and uniformity of dosage units. As a result of this a Method Operable Design Region (MODR) has been proposed defining ranges for certain method parameters which have been found acceptable.

Batch analysis data are provided for 6 batches of 1 mg tablets and 6 batches of 5 mg tablets, all of which were manufactured using the intended commercial route. All except one of the batches were at the commercial scale and two batches of the 1 mg batches had the proposed oval shape, while the tablets in four of the batches were triangular in shape. Batch data confirms consistency and uniformity of the product indicating that the process is capable to produce a finished medicinal product of the intended quality and is adequately under control.

### **Stability of the product**

Stability data for 24 months at the ICH long term storage condition of 30°C/75% RH and 6 months at the accelerated storage condition of 40°C/75% RH for 3 batches of 1 mg (triangular) and 3 batches of 5 mg (triangular) tablets and up to 18 months at 30°C/75% RH and 6 months at 40°C/75% RH for 1 batch of 1 mg tablets (oval) have been presented. All batches were of production scale. In addition, photo-stability, in accordance with ICH guideline Q1B, and in-use studies were evaluated on one batch of each strength and tablet shape.

The results of the following tests were submitted: appearance, assay by HPLC, and degradation products as well as dissolution, water content, hardness, disintegration time and microbial enumeration.

Analysis of the stability samples has been performed by applying the validated and stability indicating test methods.

Based on the stability results provided, the proposed shelf-life and storage conditions as defined in the Summary of Product Characteristics (SmPC) are acceptable.

### **2.2.4. Discussion on chemical, pharmaceutical and biological aspects**

The new active substance is an indazole derivative obtained by chemical synthesis. Information on development, manufacture and control of the active substance and finished medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

### **2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The applicant has applied QbD principles in the development of the active substance and finished product and has demonstrated to a very high level of knowledge about their product and especially the manufacturing processes involved in the drug substance and product. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Documentation has been presented to give reassurance on TSE safety.

## **2.3. Non-clinical aspects**

### **2.3.1. Introduction**

Non-clinical studies were conducted in mice, rats, monkeys, rabbits and dogs.

The absorption, distribution, metabolism, excretion and toxicokinetics of axitinib have been investigated mainly in mice, dogs and in limited studies in rats and monkeys.

The nonclinical safety profile of axitinib has been evaluated *in vitro*, and *in vivo* in rodent (mice, rats) and non-rodent species (rabbits, dogs). The *in vivo* safety pharmacology and toxicology studies were conducted in mice and dogs.

All pivotal safety pharmacology and toxicology studies were conducted in compliance with GLP. Non-pivotal studies were non-GLP. These studies were conducted by laboratories that operate in compliance with GLP or in accordance with standard operating procedures at the conducting site.

### 2.3.2. Pharmacology

#### **Primary pharmacodynamic studies**

Axitinib was evaluated for its inhibitory activity against its intended target kinases, the kinase domains of VEGFRs. Both the phosphorylated and non-phosphorylated FLVK (FGFlkeVEGF kinase) were used in the assays. In addition, axitinib was also tested for its potency against a panel of closely related kinases in the Type III, IV, and V receptor tyrosine kinase family. These tests showed that axitinib is a potent, ATP-competitive inhibitor of the following protein kinases: VEGFR-1, -2 (both the non-phosphorylated and phosphorylated FLVK), murine VEGFR-2 and PDGFR- $\beta$ .  $K_i$  values ranged from 0.7 to 22 nM (data not shown).

Axitinib is more potent against the non-phosphorylated form than against the phosphorylated form of VEGFR kinases because it binds to the “DFG-out” conformation, which is more predominant in the unphosphorylated structure.

Further, the selectivity of axitinib was tested in a panel including approximately 100 different kinases. Axitinib at 1  $\mu$ M concentration was reported to inhibit 10 non-PDGFR family kinases by more than 50%. The circulating plasma sulfoxide metabolite of axitinib (M12) was evaluated for kinase selectivity against a panel of 52 kinases. Two kinases (Aur-2 and AMPK) were inhibited by more than 50% at 1  $\mu$ M of M12.

In endothelial cells, axitinib inhibited VEGF-mediated autophosphorylation of VEGFRs with IC50s of 0.09-0.12 nM for VEGFR-1,  $0.2 \pm 0.06$  nM for VEGFR-2, and 0.1-0.29 nM for VEGFR-3. Axitinib showed weaker inhibitory activity against the autophosphorylation of PDGFR- $\alpha$ , PDGFR- $\beta$  and KIT, with IC50s of  $5.0 \pm 1.0$  nM,  $1.6 \pm 0.4$  nM, and  $1.7 \pm 0.6$  nM, respectively. Furthermore, axitinib inhibited VEGF-mediated human umbilical vein endothelial cells (HUVECs) survival with an IC50 of  $0.24 \pm 0.09$  nM; in the same assay, axitinib demonstrated approximately 1000-fold selectivity for VEGFR-2 versus FGFR-1.

Axitinib was not potent against the cellular activities of other RTKs tested, including CSF-1R, Flt-3, RET, EGFR and cMet (protein encoding the mesenchymal-epithelial transition factor, proto-oncogene).

Axitinib dose-dependently inhibited 3-D tubule formation of spheroidal endothelial cells embedded in the fibrin matrix. Axitinib also blocked VEGF-mediated endothelial cell adhesion and migration on extracellular matrix proteins, and it induced endothelial cell apoptosis as early as 6 hours after exposed to the compound in cell culture. The treatment of HUVECs with axitinib produced a rapid, potent and dose-dependent inhibition of eNOS, Akt, and ERK1/2 phosphorylation with concentrations similar to that required for VEGFR inhibition. The inhibition of eNOS and Akt phosphorylation by axitinib was fully reversible only 0.5 to 2 hours after the withdrawal of the compound. In contrast, under the same experimental conditions, the VEGFR-2 phosphorylation remained partially suppressed for at least 24 hours.

Axitinib also has functional effects on tumour cells that express PDGFRs and KIT. For instance, in PDGFR- $\beta$  positive human glioma U87MG cells, axitinib dose-dependently inhibited PDGF-BB-stimulated

cell migration (but not proliferation). Axitinib dose dependently inhibited KIT phosphorylation in KIT+ human SCLC NCI-H526 cells.

However, the concentrations required for modulating PDGFR- $\beta$  and KIT mediated cellular activity were greater than that required for modulating VEGFR activity, consistent with the potency and selectivity profile of axitinib. Finally, with as high as 1 to 10  $\mu$ M concentrations, axitinib had little anti-proliferative effect on tumour cells that do not express VEGFRs, PDGFRs, and/or KIT.

The two major human metabolites of axitinib M12 (sulfoxide) and M7 (N-glucuronide) were evaluated for VEGFR-2, PDGFR- $\beta$ , and KIT cell activity. In cells, M12 had minimal effect on VEGF mediated HUVEC survival, and PDGFR- $\beta$  and KIT autophosphorylation until its concentrations were at least 400-, 470- and 290-fold higher, respectively, than those required by its parent compound axitinib (average values). The N-glucuronide metabolite showed approximately 8300-fold less activity against VEGFR-2 autophosphorylation compared to axitinib. M7 is also expected to have little activity against PDGFR- $\beta$  and KIT based on activity test results using a structurally homologous analog compound. Furthermore, the computer modelling of the co-crystal structure of M7 and the kinase domain of VEGFR2 suggested that N-glucuronidation at the NH position of axitinib disrupted a key hydrogen bond and significantly compromised an appropriate fit in the ATP binding site.

The *in vivo* effects of anti-angiogenesis of axitinib were investigated in retinal tissues of rats and xenograft tumours in mice.

Newborn rats were treated with two IP injections of axitinib hydrochloride of 10 or 30 mg/kg before the retinal tissues were collected and processed. Immunoprecipitation and Western blot (IP/IB) experiments were performed for the determination of rat VEGFR-2 phosphorylation. Compared to vehicle-treated tissues in the control group, VEGFR-2 phosphorylation in the axitinib-treated tissues was reduced by 80 – 90% one hour after the second injection of the compound of both dose levels. In the low-dose group, the signal fully rebounded at 6 hours post-dose, when the unbound plasma drug concentration was  $0.017 \pm 0.02$  ng/mL (or  $0.04 \pm 0.06$  nM), much below the value of IC<sub>50</sub> for VEGFR-2 ( $0.20 \pm 0.04$  nM). In the high-dose group, a 50 – 60% recovery of phospho-VEGFR-2 signal occurred 6 – 24 hours postdose. This was associated with an unbound plasma drug concentration of  $0.57 \pm 0.14$  ng/mL (6 hour) and  $0.066 \pm 0.008$  ng/mL (24 hour), which translated to  $1.5 \pm 0.36$  nM (6 hour) and  $0.17 \pm 0.02$  nM (24 hour), respectively. The full activity of VEGFR-2 rebounded between 24–32 hours postdosing. Overall, the degree of target inhibition correlated to the plasma concentration across the time points. A non-linear regression analysis of the 30 mg/kg group in Prism (Graphpad) using the sigmoidal doseresponse model revealed an EC<sub>50</sub> for target inhibition of  $0.49 (\pm 3.1)$  nM or 0.19 ng/mL.

In the M24met human melanoma xenograft model it was found that a single oral dose of axitinib (50 mg/kg) suppressed murine VEGFR- 2 phosphorylation in tumour tissues for up to 7 hours compared to the vehicle-treated tumours. In the 30 mg/kg dose group, the level of VEGFR-2 phosphorylation in the tumours inversely correlated with axitinib plasma concentrations. The same study also measured the phosphorylation of tumour ERK (MAPK44/42) by Western blot. The ERK signal was partially inhibited by axitinib treatment. The inhibition quickly reached a plateau (30 minutes after the dose) and the signal remained partially inhibited for at least 7 hours.

The effect of axitinib on PDGFR- $\beta$  phosphorylation was examined in a rat C6 glioma tumour model. Mice with large tumours were administered axitinib at 10, 30 and 100 mg/kg (po; 3 doses in 1.5 days). At 10 or 30 mg/kg, axitinib produced partial inhibition of PDGFR- $\beta$  phosphorylation, whereas significant (90%) and more sustained inhibition of PDGFR- $\beta$  activity was observed at 100 mg/kg. The unbound plasma exposure in the 10 mg/kg group did not reach the IC<sub>50</sub> for PDGFRs, and axitinib plasma exposure in the 30 mg/kg dose levels reached the IC<sub>50</sub> for PDGFR- $\beta$  only transiently. In all dose groups the full activity of PDGFR- $\beta$  did not return within 48 hours, although the drug concentration in the plasma was no longer detectable at 24 hours.

Based on chronic treatment studies of MV522 human colon carcinoma xenografts, the pharmacologically efficacious concentration,  $C_{\text{eff}}$ , was estimated to be 22–66 ng/mL in plasma of humans.

In a TGI study in the MV522 model in mice, the  $ED_{50}$  was 8.7 mg/kg (BID). The  $ED_{70}$  and  $ED_{80}$  doses in mice were 30 mg/kg (BID) and 60 mg/kg (BID), respectively. Correlating plasma exposure with length of exposure for the 10 mg/kg BID dose level (i.e. approximately  $ED_{50}$ ) showed that a 50% TGI would be achieved if: 1) the unbound plasma concentration was maintained at or above 0.85 nM (or a total concentration of 66 ng/mL in humans) for  $\geq 10$  hours/day; or 2) the unbound plasma concentration was maintained at or above 0.65 nM (or a total concentration of 50 ng/mL in humans) for  $\geq 16$  hours/day; or 3) the unbound plasma concentration was maintained at or above 0.28 nM (or a total concentration of 22 ng/mL in humans) for 24 hours.

Axitinib showed dose-dependent primary TGI (45-87% at 30 mg/kg) in the SC or orthotopically implanted human xenograft and rodent tumour models including tumour models of breast, colon, lung, pancreas, kidney, brain, skin and liver with marked inhibitory effect on local and distant tumour metastasis in the orthotopically grown and spontaneous metastasis models of HCT-116 GFP (human colon carcinoma), SN12C-GFP (human renal cell carcinoma) and M24met (human melanoma).

In the MV522 tumour model, a prolonged dosing break ( $>1$  week) between treatment cycles caused a significant compromise in anti-tumour efficacy of axitinib while similar efficacy was obtained with QD and BID dosing.

Axitinib was evaluated for its ability to enhance anti-tumour efficacy of chemotherapeutic agents, radiation therapy or targeted therapy. Axitinib was combined with docetaxel in the subcutaneously implanted tumours of the human xenograft of breast cancer model MDA-MB-231 and MDAMB-435\HAL-Luc; and in the murine LLC model; with carboplatin in the human ovarian carcinoma model A2780; with gemcitabine in the human pancreatic carcinoma model BxPC-3; with radiation therapy in the human prostate carcinoma model DU145, with the MEK inhibitor PD-0325901 in the human melanoma model A2058; and with bevacizumab in the human colon carcinoma model MV522 and the human melanoma model M24met. The combination therapies resulted in improvement in efficacy consistently across models, ranging from efficacy enhancement (less than additive), to an additive effect, and to synergism (more than additive effect). Significant anti-tumour effect was also observed with axitinib in tumour populations that were insensitive to bevacizumab (data not shown).

## **Secondary pharmacodynamic studies**

Axitinib was evaluated in radioligand displacement assays against the following receptors or ion channels at up to 10  $\mu\text{M}$ : adenosine  $A_1$  and  $A_{2A}$ ; adrenergic  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$ ; bradykinin  $B_2$ ; calcium channel type L; dopamine  $D_1$  and  $D_{2L}$ ; estrogen  $ER\alpha$ ; GABA<sub>A</sub> (agonist and chloride channel); glucocorticoid; glutamate (*N*-methyl *D*-aspartate); glutamate (non-selective); glycine (strychnine-sensitive); histamine  $H_1$  and  $H_3$ ; insulin; muscarinic  $M_1$ ,  $M_2$ , and  $M_3$ ; and neuropeptide  $Y_2$ , nicotinic acetylcholine (central); opiate ( $\delta$ ,  $\kappa$ ,  $\mu$ ); phorbol ester; purinergic ( $P_{2X}$ ,  $P_{2Y}$ ); serotonin (5-HT<sub>1</sub>, 5-HT<sub>2</sub>);  $\text{ig}$ ma (non-selective); sodium channel (site 2); tachykinin  $NK_1$ ; testosterone.

Modest binding affinity in the low  $\mu\text{M}$  range was observed for the adenosine  $A_{2A}$  ( $K_i$  of 2.76  $\mu\text{M}$ ), muscarinic  $M_2$  ( $K_i$  of 2.23  $\mu\text{M}$ ), and neuropeptide  $Y_2$  ( $IC_{50}$  of 10  $\mu\text{M}$ ) receptors. In secondary functional assays, the effect of axitinib on the  $A_{2A}$ ,  $M_2$ , or  $Y_2$  receptors at concentrations up to 30  $\mu\text{M}$  was less than the predefined effect criterium of  $\geq 50\%$  agonistic or antagonistic activity. Results were in the range 0-19%. The highest response detected was a 19% antagonistic effect on  $M_2$  receptors in atria from guinea pig.

## **Safety pharmacology programme**

Axitinib was evaluated for potential effects on the central nervous system, cardiovascular and respiratory system and gastrointestinal system *in vitro* and/or *in vivo*.

Axitinib was administered as an oral suspension (0.5% w/v aqueous CMC) in all *in vivo* studies. Studies with repeat-dose administration were conducted with BID dosing, approximately 6 hours apart.

Plasma protein binding values of 97.0%, 98.1%, and 98.0% were used to calculate the unbound  $C_{\max}$  or AUC in mouse, rat, and dog, respectively, in those safety pharmacology studies where exposure values were available.

The results of the safety pharmacology studies are summarised in table 1.

**Table 1. Overview of safety pharmacology studies**

| Organ System Evaluated<br>(Study Report No.)<br>GLP-status                                                                                                         | Species / Number                                                                           | Method of Administration / Dose / Compound                                                | Results                                                                                                                                                                                                                                                                 | NOAEL                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| <b>CENTRAL NERVOUS SYSTEM</b>                                                                                                                                      |                                                                                            |                                                                                           |                                                                                                                                                                                                                                                                         |                               |
| Neurobehavioural evaluation (Irwin test)<br>(VFF/488)<br><br>GLP                                                                                                   | CD-1 Mice / 4 ♂ / group                                                                    | PO / 0, 3, 10, 30 mg/kg / Axitinib                                                        | No treatment-related effects                                                                                                                                                                                                                                            | 30 mg/kg PO                   |
| <b>CARDIOVASCULAR and RESPIRATORY SYSTEM</b>                                                                                                                       |                                                                                            |                                                                                           |                                                                                                                                                                                                                                                                         |                               |
| hERG current<br>(AG013736HERG)<br><br>Non-GLP                                                                                                                      | Stably transfected HEK293 cells / 6 cells pr. concentration                                | <i>In vitro</i> / 3 µM <sup>a</sup> / Axitinib                                            | 7.0±0.6% inhibition (mean ± SEM).                                                                                                                                                                                                                                       | ND                            |
| K <sub>i</sub> Determination for hERG channel<br>(DOF_GBLFP1_E - 02102006)<br><br>Non-GLP                                                                          | Dofetilide Fluorescence Polarization Binding Assay                                         | <i>In vitro</i> / 0.002–200 µM / AG-028458 <sup>b</sup> (sulfoxide metabolite)            | K <sub>i</sub> >79 µM.<br>IC <sub>50</sub> >200 µM.                                                                                                                                                                                                                     | 200 µM                        |
| hERG current<br>(SP1307)<br><br>Non-GLP                                                                                                                            | Stably transfected HEK293 cells / 9 cells pr. concentration                                | <i>In vitro</i> / 1, 3, 10, 30 µM / PF-04621675 (metabolite)                              | 1.7±3.4% inhibition (mean ± SEM) at 30 µM.<br>hERG inhibition IC <sub>50</sub> > 30 µM.                                                                                                                                                                                 | 30 µM                         |
| Cardiovascular effects (Blood pressure, heart rate)<br>(SP4009)<br><br>Non-GLP                                                                                     | C57/BL6 Mice / 9 ♂ / group                                                                 | PO / 3, 30, 100 mg/kg/day for 4 days / Axitinib                                           | <b>30 and 100 mg/kg/day:</b><br>↑BP 6% and 9%, respectively.<br>↑BP in vehicle group also.<br>Inconclusive.                                                                                                                                                             | ND                            |
| Cardiovascular effects (Blood pressure, heart rate)<br>(SP4009-2)<br><br>Non-GLP                                                                                   | C57/BL6 Mice / 6 ♂ / group                                                                 | PO / 30 mg/kg/day for 4 days / Axitinib                                                   | <b>30 mg/kg/day:</b><br>↑BP (SBP 9-16%, DBP 13-20%, MAP 11-18%).<br>↓HR (-10 to -13%, 1-8 hours post-dose).<br>↑HR (10-14%, 16-24 hours post-dose).<br>↑HR and BP (10-20%) at times during recovery days 1 and 2. Began to return to baseline values on recovery day 3. | ND                            |
| Cardiovascular effects (Blood pressure, heart rate)<br>(SP0304)<br><br>Non-GLP Cardiovascular Effects<br>(Blood pressure, heart rate, ECG)<br>(VFF/492)<br><br>GLP | Telemetered rats / 9-11 ♂ / group<br><br>Telemetered dogs / 1 ♂ + 3 ♀ / group <sup>c</sup> | PO / 100, 300, 500 mg/kg/day for 7 days / Axitinib<br><br>PO / 3, 10, 30 mg/kg / Axitinib | <b>≥300 mg/kg/day:</b><br>↑SBP (2-3%)<br><br>No treatment-related effects                                                                                                                                                                                               | 100 mg/kg/day<br><br>30 mg/kg |

|                                                                                  |                                   |                                                           |                                  |             |
|----------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------|----------------------------------|-------------|
| Cardiovascular Effects<br>(Blood pressure, heart rate)<br>(SPT04-029)            | Telemetered dogs<br>/ 6 ♂ / group | PO /<br>10, 50, 150 mg/kg/day<br>for 3 days /<br>Axitinib | Inconclusive                     | ND          |
| GLP                                                                              |                                   |                                                           |                                  |             |
| Respiratory function<br>(Respiration rate, tidal and minute volume)<br>(VFF/491) | Wistar rats /<br>8 ♂ / group      | PO /<br>50, 250, 500 mg/kg /<br>Axitinib                  | No treatment-related effects     | 500 mg/kg   |
| GLP                                                                              |                                   |                                                           |                                  |             |
| <b>GASTROINTESTINAL SYSTEM</b>                                                   |                                   |                                                           |                                  |             |
| Charcoal Propulsion Test<br>(VFF/489)                                            | CD-1 Mice /<br>10 ♂ / group       | PO /<br>3, 10, 30 mg/kg /<br>Axitinib                     | No treatment-related effects     | 30 mg/kg PO |
| GLP                                                                              |                                   |                                                           |                                  |             |
| Gastric Emptying<br>(Phenol Red Method)<br>(VFF/490)                             | Wistar Rats /<br>8 ♂ / group      | PO /<br>5, 10, 30 mg/kg /<br>Axitinib                     | ≥10 mg/kg:<br>↑Gastric emptying. | 5 mg/kg PO  |
| GLP                                                                              |                                   |                                                           |                                  |             |

Note: Studies with repeat-dose administration were conducted with BID dosing, approximately 6 hours apart.  
BP: Blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; SBP: systolic blood pressure; ECG: Electrocardiography; SEM: Standard error of mean.

a Higher concentrations could not be tested because 3 µM is the limit of axitinib solubility in hERG extracellular recording saline.

b Also referred to as PF-03482595.

c Four animals in total.

## Pharmacodynamic drug interactions

No relevant studies were submitted (see discussion on non-clinical aspects).

### 2.3.3. Pharmacokinetics

The pharmacokinetics has been studied in mice, rats, beagle dogs and cynomolgus monkeys following IV and PO administration.

Bioavailability following PO administration was low to moderate in all animal species and humans: 16% in mice, 3-31% in rats, 10-59% in dogs, 3% in monkeys and 58% in human patients.

The peak plasma concentration following PO administration was generally observed within 8 hours in mice, 5 hours in rats, 7 hours in dogs, 5 hours in monkeys and 4 hours in human patients.

The terminal half-life following PO administration was 1-10 hours in mice, 1-4 hours in rats, 0.4-6 hours in dogs, 10 hours in monkeys and 3 hours in healthy humans.

Volume of distribution and clearance following PO administration were 0.8 L/kg and 0.7 L/hr/kg in mice, 0.8 L/kg and 0.7 L/hr/kg in monkeys and 1 L/kg and 0.4 L/hr/kg in humans. Following IV administration, volume of distribution and clearance were 2 L/kg and 2 L/hr/kg in mice, 32 L/kg and 24 L/hr/kg in rats and 1 L/kg and 0.7 L/hr/kg in dogs.

Following single dose IV or PO (monkeys and humans) administration, axitinib showed a volume of distribution that was comparable to the total body water in all species tested including humans (mouse: 3-fold, rat: 48-fold, dog: 1.7-fold, monkey: 1.2-fold and human: 1.7-fold relative to total body water of the respective species).

Exposure exceeded dose-proportionality in mice, rats and (possibly) dogs following repeated dosing but was not investigated in monkeys. Overall, no accumulation was found in mice and dogs following repeated dosing, while it was not investigated in rats and monkeys. In clinical studies, minimal accumulation was observed.

Oral administration of axitinib to fed dogs resulted in higher exposure than when administered to fasted dogs, whereas in mice, no apparent effect of food on exposure was observed. In healthy humans, a high-fat, high-calorie meal produced a 19% increase in axitinib (Form XLI) exposure (based on AUC) compared to an overnight fast. However, a moderate-fat, standard-calorie meal decreased axitinib exposure by 10-fold when compared to axitinib exposure in fasted healthy humans (based on AUC).

Axitinib has moderate to high passive permeability with evidence of efflux in Caco-2 cells. In transfected cells, axitinib was shown to be a weak substrate for both P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2).

In OATPs, substrate activity was noted for OATP1B1 and OATP1B3. However, the passive permeability of axitinib is expected to greatly exceed the active uptake component.

The tissue distribution of axitinib has been evaluated in male (pigmented) B6C3F1/Crl BR mice following single PO administration of [<sup>14</sup>C]-axitinib (50 mg/kg). Radioactivity was rapidly absorbed and well distributed into the tissues. All tissues exhibited maximal tissue concentration at a time point before or equal to the time point for T<sub>max</sub> suggesting rapid distribution. The tissues that reached peak concentration at the latest time point (4 hours) were preputial gland, uveal tract and mucosae of the small intestine, caecum and large intestine.

The highest levels of radioactivity were associated with the gall bladder, kidney cortex, kidney medulla, liver, exorbital lachrymal, intra-orbital lachrymal and Harderian glands, brown fat, bulbo-urethral gland myocardium, pancreas, uveal tract and the mucosae of the gastrointestinal tract (excluding the mucosa of the rectum). The lowest measured concentrations were in the brain and spinal cord.

Peak concentrations of radioactivity occurred at 1 hour post-dose in most tissues, after which levels declined rapidly such that by 24 hours, most no longer contained quantifiable radioactivity. At 48 hours post-dose, quantifiable radioactivity was only present in the liver, gall bladder and uveal tract. Drug-related material was bound to melanin, substantiated by the high levels of radioactivity present in the uveal tract of the eye at all sampling times.

Axitinib distributed to bone marrow, skin and eyes.

At concentrations ranging from 0.2 to 20 µg/mL, axitinib was strongly bound to plasma protein (96-99%) in plasma from mice, dogs and humans. Plasma protein binding was found not to be entirely concentration independent. With a mean binding value of 99%, axitinib was highly bound to human serum albumin. A definitive value for the binding to α1-acid glycoprotein could not be determined. However, the best estimates suggested only moderate binding of axitinib to this protein.

The metabolism of axitinib was been studied *in vivo* in mice, dogs and humans and *in vitro* in microsomes and hepatocytes from mice, rats, dogs, monkeys and humans. The primary metabolic pathways of axitinib involve oxidations and direct glucuronidation/ glucosylation followed by secondary oxidations and glucuronidation/glucosylation of the primary metabolites.

Metabolism in man was investigated in a mass balance study, where 5 mg [<sup>14</sup>C]-axitinib was administered PO to healthy males. The N-glucuronide (M7) was the predominant metabolite and accounted for approximately 50% of the circulating radioactivity. The sulfoxide metabolite (M12) and unchanged parent drug accounted for 16% and 23%, respectively, of the circulating radioactivity. In

faeces, the parent drug represented the single most predominant radioactive component (12% of the dose).

The combined *in vivo* metabolic data indicated some species differences. Nevertheless, all human metabolites were found in one or both of the animal species used for toxicological testing except for three metabolites (M8a, M12a and UNK). These three metabolites were found in human urine or faeces and not in plasma.

Quantitative differences in axitinib metabolism in liver microsomes were found between mice, dogs and humans with regard to the circulating metabolites M7 and M12. While M12 was found at lower-to-comparable levels in humans as compared to mice and dogs, M7 was found in humans at levels 3-5-fold higher than in mice while it was not detected in dog plasma.

*In vitro*, axitinib was shown to be a substrate for CYP3A4/5 and to a lesser extent for CYP2D6, CYP2C19, CYP2C9, CYP2C8 and CYP1A2. At therapeutically relevant concentrations, axitinib did not cause significant inhibition or induction of CYP P450 enzymes in human liver microsomes.

Faecal excretion was the primary route of elimination of [<sup>14</sup>C]-axitinib, accounting for the majority of the administered dose (66-83%) following PO administration to mice and dogs. Faecal excretion was relatively rapid, occurring largely within the first 48 hours in both species. Urinary excretion accounted for 6-13% of the administered dose in both species. Trace amounts of unchanged parent drug was found in mouse and dog urine. No gender differences were observed.

In bile duct cannulated dogs, 53% of the dose was recovered from the faeces and an additional 8% was recovered from bile at 240 hours post-dose.

In healthy humans, elimination of axitinib with faeces generally accounted for 30-60% of the total dose while 14-28% of the dose was detected in the urine with only trace amounts of unchanged axitinib in the urine.

## 2.3.4. Toxicology

### ***Single dose toxicity***

The single-dose toxicity of axitinib was examined following oral administration in mice and dogs.

The studies are summarised in table 2.

**Table 2. Summary of single dose toxicity studies**

| Study ID    | Species | Number / Sex / Group | Dose (mg / kg)                  | NOAEL      | Major findings                                                                                                            |
|-------------|---------|----------------------|---------------------------------|------------|---------------------------------------------------------------------------------------------------------------------------|
| 22337-0-800 | Mouse   | 5/sex                | 2000<br>(po, gavage)            | 2000 mg/kg | None                                                                                                                      |
| 6348-505    | Dog     | 3/sex/gr             | 0, 500, 1000, 2000 (po, gavage) | 2000 mg/kg | <u>500 mg/kg</u> : nonformed, mucoid, discoloured feces (1m)<br><u>2000 mg/kg</u> : nonformed, mucoid, discoloured feces. |

### ***Repeat dose toxicity***

The toxicity of axitinib after repeated p.o. administration was studied in toxicity studies in CD-1 mice and Beagle dogs following treatment for up to 6 and 9 months, respectively. The design and results of the repeat-dose toxicity studies are summarised in table 3.

**Table 3. Summary of repeat dose toxicity studies**

| Study ID | Species<br>(N/ Sex/Gr) | Duration                                     | Dose /<br>NOAEL<br>(mg/kg/day)                                                                                        | Major findings<br>NOAEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------|------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6750-144 | Mouse<br>(15/sex/gr)   | 14 days                                      | 0, 50, 250,<br>500<br>(0, 25, 125,<br>250 mg/kg<br>BID)<br>(po, gavage)                                               | <u>0 mg/kg</u> : 1 death (f).<br><u>50 mg/kg</u> : 2 deaths (1m, 1f).<br><u>≥ 50 mg/kg</u> : ↓body weight gain (f).<br><u>≥250 mg/kg</u> : ↓reticulocyte count (f). ↓ thymic weights (m).<br><u>500 mg/kg</u> : 4 deaths (m). ↓body weight gain (m), ↓ testis/epididymis weights. ↓mean total protein and albumin (f). ↓mean red blood cell (RBC) count, hemoglobin, hematocrit, and reticulocyte count. ↑poikilocytosis.<br><u>NOAEL</u> : male - 250 mg/kg/day, female - 50 mg/kg/day                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 6750-145 | Mouse<br>(16/sex/gr)   | 28 days                                      | 0, 10, 30, 250<br>(0, 5, 15, 125<br>mg/kg, BID)<br>(po, gavage)                                                       | <u>≥ 30 mg/kg</u> : ↑mean corpuscular hemoglobin (MCH) and volume (MCV). Thickening of physeal cartilage in femur.<br><u>250 mg/kg</u> : ↑reticulocytes (f). Slight ↑ALP. ↓thymus weight, ↓testis/epididymis weight. Minimal bilateral testicular atrophy. ↓corpora lutea.<br><u>NOAEL</u> 10 mg/kg/day                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 6750-148 | Mouse<br>(15/sex/gr)   | 13 / 26<br>weeks<br>+ 4<br>weeks<br>recovery | 0, 10, 30, 100,<br>250 (5, 15,<br>50, 125<br>mg/kg, BID)<br>(po, gavage)                                              | <u>≥ 10 mg/kg</u> : dose related odontopathy.<br><u>30 mg/kg</u> : one death (m).<br><u>≥ 30 mg/kg</u> :<br>13 weeks: Malocclusion, ↑ MCH, MCV. ↓corpora lutea.<br>26 weeks: Poor clinical condition, ↓RBC. Mucosal inflammation and hyperplasia (cecum), ↑hepatocellular and spleen pigmentation.<br><u>≥100 mg/kg</u> :<br>13 weeks: onset of mortality. Hunched, thin appearance, hypoactivity. Missing, broken teeth. Rough hair coat. ↓testes weight. Hypospermia<br>26 weeks: ↓reticulocytes, mucosal hyperplasia in colon, uterus atrophy.<br><u>250 mg/kg</u> :<br>13 weeks: ↓food consumption and body weight, ↓spleen and uterus weight, broken incisors, thickened growth plate (femur/tibia). GI hyperplasia, inflammation. Pigmentation in liver and spleen, uterine atrophy, lymphoid depletion (thymus, spleen).<br>26 weeks: dosing group terminated at week22 due to unscheduled deaths (11m, 12f)<br><u>Recovery</u> : Growth plate thickening, hyperplasia in the colon, hepatocellular and splenic pigment, and lymphoid depletion were reversed. All other findings were partially reversed.<br><u>NOAEL</u> : < 10 mg/kg/day |
| 6750-142 | Dog<br>(4/sex/gr)      | 14 days                                      | Days1-9:<br>0, 25, 50, 150<br>(12.5, 25, 75<br>BID)<br><br>Days 10-14:<br>0, 50, 100,<br>300<br>(25, 50, 150,<br>BID) | <u>≥25/50 mg/kg</u> : ↓body weight, gum reddening.<br><u>≥50/100 mg/kg</u> : ↓food consumption. ↑cholesterol and triglyceride levels. Dark pigmentation in GI-tract.<br><u>150/300 mg/kg</u> : 1f euthanized prescheduled. Thin appearance, hypoactivity, dehydration, discolored and liquid feces, oral mucosal ulcers. ↓reticulocytes, slight ↑MCH (m). ↓eosinophil (m) and lymphocyte counts. ↓PT, ↑APTT. ↑total protein and globulin. ↓thymus weight<br><u>NOAEL</u> : 25/50 mg/kg/day                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 6750-143 | Dog<br>(4/sex/gr)      | 28 days                                      | 0, 10, 30 100<br>(5, 15, 50,<br>BID)                                                                                  | <u>≥ 10 mg/kg</u> : ↓body weight and food consumption. Abnormal stool (mucoïd, nonformed, liquid, and/or discolored), hyperemic oral mucosa. Delayed sexual maturity (f). Chronic oral inflammation.<br><u>≥ 30 mg/kg</u> : ↓reticulocytes (m), ↑triglycerides.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

Haematuria (f, potential contamination). Dark GI-mucosa. Oral reddening, inflammation and ulcers. Gastric inflammation/necrosis. ↓thymus and pituitary weight (f). Growth plate thickening (m, ribs). Mucosal inflammation. Minimal to slight GI fibrinosis. Intestinal congestion/hemorrhage (1f). ↓zymogen granules/↑acinar cells in pancreas. Thymic lymphoid depletion.

100 mg/kg: 6 animals (4m, 2f) euthanized in moribundity (days 15-18). Hair shedding, dehydration, thin appearance, hypoactivity, ↑ salivation. Dark GI-mucosa. Inflammation/necrosis of tongue, GI mucosa and submucosal vessels. Intestinal congestion/hemorrhage. Bone marrow hypocellularity. ↑cholesterol, ↑ALAT.

NOAEL: < 10 mg/kg/day

|          |                     |                                           |                                            |                                                                                                                                                                                                                                                                                                                                                                                             |
|----------|---------------------|-------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6750-150 | Dog<br>(3-4/sex/gr) | 13 / 26<br>weeks +<br>4 weeks<br>recovery | 0, 1, 3, 6, 10<br>(0.5, 1.5, 3, 5,<br>BID) | <p><u>&gt;1 mg/kg</u>: abnormal feces (discoloured, liquid, mucoid).</p> <p><u>≥6 mg/kg</u>: small and inconsistent haematuria</p> <p><u>10 mg/kg</u>: 3 deaths (1m/2f; with bone marrow hypocellularity, lymphoid depletion in thymus, zymogen depletion in pancreas). ↓body weight, thin appearance.</p> <p><u>Recovery</u>: all findings reversed.</p> <p><u>NOAEL</u>: 6 mg/kg/day.</p> |
| 6348-470 | Dog<br>(4/sex/gr)   | 39 weeks<br>+ 8<br>weeks<br>recovery      | 0, 1, 3, 6<br>(0.5, 1.5, 3,<br>BID)        | <p><u>All doses</u>: Fecal abnormalities.</p> <p><u>≥3 mg/kg</u>: ↓testis weight, testis atrophy, ↑syncytial cells in testis.</p> <p><u>6 mg/kg</u>: slight ↑cholesterol (f). Hypospermia, epididymal cellular debris.</p> <p><u>Recovery</u>: All findings reversed</p> <p><u>NOAEL</u>: male – 1 mg/kg/day, female – 6 mg/kg/day.</p>                                                     |

ALP – alkaline phosphatase; ALAT – alanine aminotransferase; GI - gastrointestinal ; f - female; m - male; PT – prothrombin time; APTT – activated partial thromboplastin time; MCH – mean corpuscular hemoglobin; MCV - mean corpuscular volume; RBC – red blood cells;

## Genotoxicity

Axitinib was evaluated for potential genotoxicity *in vitro* and *in vivo* studies. The design and results of the genotoxicity studies are summarized in table 4.

**Table 4. Genotoxicity studies with axitinib**

| Study ID   | Test              | Test system                                               | Concentrations/<br>Dose | Metabolic<br>activation | Results                                                    |
|------------|-------------------|-----------------------------------------------------------|-------------------------|-------------------------|------------------------------------------------------------|
| 01-2191-02 | Ames test         | <i>S. typhimurium</i><br>(TA98, TA100,<br>TA1535, TA1537) | 50-5000 µg/plate        | ± S9                    | Negative                                                   |
|            |                   | <i>E. coli</i><br>(WP2 uvrA pKM101)                       | 50-5000 µg/plate        | ± S9                    | Negative                                                   |
| 01-2191-03 | Cytogenic assay   | Human lymphocytes                                         | 0.05-8 µg/ml            | 3h: ± S9<br>24h:- S9    | Negative <sup>a</sup>                                      |
| 01-2191-01 | Micronucleus test | Mouse, bone marrow                                        | 60-2000<br>mg/kg/day    | n.a.                    | Positive<br>NOEL(m):<br>500 mg/kg<br>NOEL(f):<br>250 mg/kg |

a: Polyploidy was observed under all conditions, NOEL 0.22 µg/m

## Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

## Reproduction Toxicity

The reproductive and developmental toxicity studies performed with axitinib are presented in Table 5.

**Table 5. Reproductive and developmental toxicity studies**

| Study type/<br>Study ID / GLP                  | Species;<br>N / group | Dose<br>(mg / kg / day)                                           | Dosing<br>period                                   | Major findings<br>NOAEL (mg / kg / day)                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------|-----------------------|-------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Fertility / Early Embryonic Development</b> |                       |                                                                   |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| LIA00238 / GLP                                 | Mice<br>22/sex/gr     | M: 0, 10, 30,<br>100 (po, BID)<br>F: 0, 30, 100,<br>250 (po, BID) | M: 70 days <sup>a</sup><br>F: 30 days <sup>b</sup> | <p>≥30 mg/kg: ↓cauda epididymal sperm density. ↓gestation body weight. Dose related ↓mean number of viable embryos (treated females).</p> <p>≥100 mg/kg: ↓testes weigh. ↓gestational body weight, ↑abortions/total litter. ↓fertility index and ↑resorption (treated females).</p> <p>NOAEL<sub>male</sub>: 10 mg/kg/day<br/>NOAEL<sub>male fertility</sub>: 100 mg/kg/day<br/>NOAEL<sub>female</sub>: 250 mg/kg/day<br/>NOAEL<sub>embryo</sub>: &lt;30 mg/kg/day</p>      |
| <b>Embryo-fetal development</b>                |                       |                                                                   |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| LIA00236 / non-GLP<br>(Dose range)             | Mice<br>8F/gr         | 0, 3, 30, 60,<br>250, 500 (po,<br>BID)                            | GD6-17                                             | <p>≥3 mg/kg: ↑postimplantation loss; low incidences of medially rotated hindlimbs, dose related incidences of cleft palates.</p> <p>≥30 mg/kg: Maternal ↓body weight gain. Litters of complete resorptions. ↓fetal body weights, litter size and live fetuses. One fetus with cleft palate, depressed eye bulges, absent digits on forepaws, whole body edema and gastroschisis.</p> <p>NOAEL<sub>female</sub>: 3 mg/kg/day<br/>NOAEL<sub>fetus</sub>: &lt;3 mg/kg/day</p> |
| 06GR178 / GLP<br>(Dose range)                  | Rabbit<br>6F/gr       | 0, 10, 30, 100,<br>200 (po, BID)                                  | GD7-19                                             | <p>≥10 mg/kg: ↓Body weight gain, 1 late stage abortion, ↓ postimplantation loss, 1 fetus with short tail, 1 litter with edema</p>                                                                                                                                                                                                                                                                                                                                          |

of  
the hind limbs  
≥30 mg/kg: Not tolerated, clinical  
signs (red fluid in/under cage), ↓body  
weight and food consumption. 1 late  
stage abortion, complete  
postimplantation loss in all surviving  
animals  
≥100 mg/kg: All animals died or were  
euthanized due to poor tolerability  
NOAEL<sub>female</sub>: < 10 mg/kg/day  
NOAEL<sub>fetus</sub>: < 10 mg/kg/day

|                |                 |                           |        |                                                                                                                                                                                                                       |
|----------------|-----------------|---------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LIA00237 / GLP | Mice<br>22 F/gr | 0, 0.3, 1, 3<br>(po, BID) | GD6-17 | <u>3 mg/kg</u> : ↓fetal body weight. Cleft<br>palate (5.6% pr litter, 33.3% of litters).<br>Delayed and/or incomplete ossification<br>NOAEL <sub>female</sub> : 3 mg/kg/day<br>NOAEL <sub>fetus</sub> : 0.3 mg/kg/day |
|----------------|-----------------|---------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

a: Males were treated for 70 days prior to cohabitation and through cohabitation with the females  
b: Females were treated for 15 days prior to cohabitation and through to Day 7 of gestation

## Toxicokinetic data

An overview of the relationship between main findings in the repeat dose toxicity studies and plasma exposures for axitinib indicating LOAEL is presented in Figure 1.

**Figure 1 Key-response relationship to axitinib exposure in the repeat-dose toxicity studies**

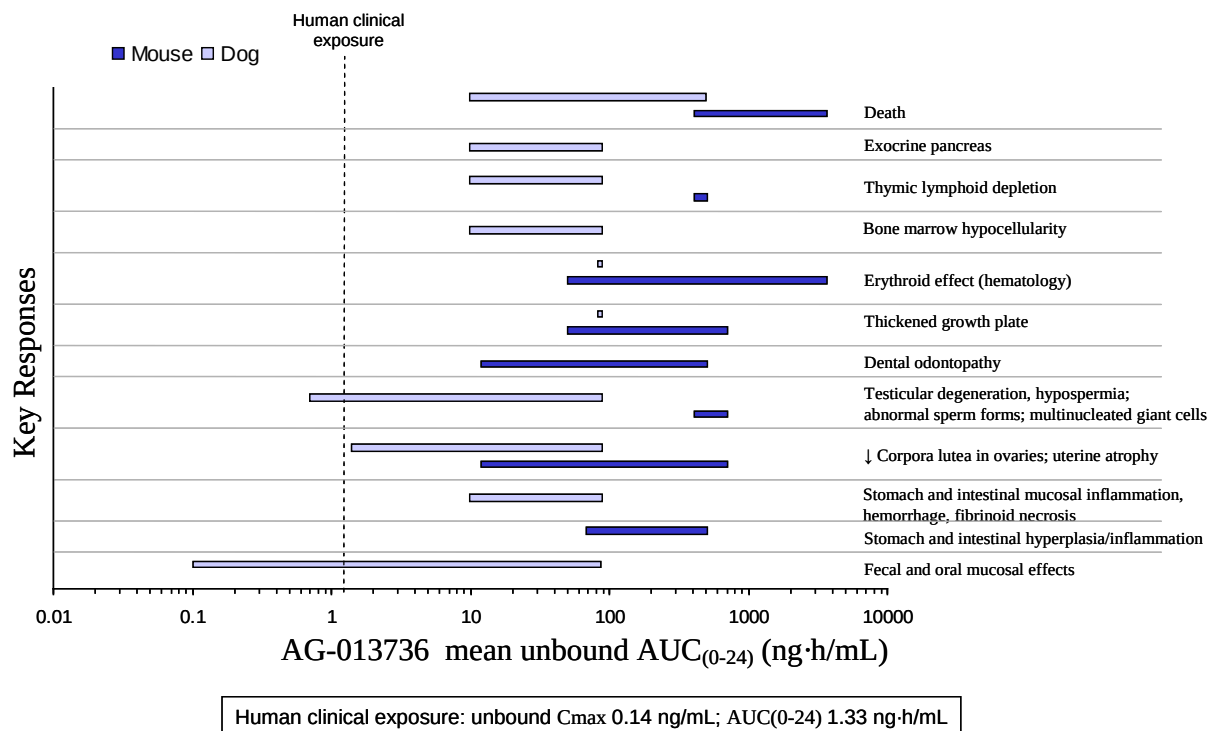


Table 6 presents the plasma exposure levels at NOAEL in the 26 week studies in mice and dogs, and in the 9 month study in dogs, and human plasma levels at the starting dose of 5 mg BID. Data are presented as total and unbound plasma levels.

**Table 6. Interspecies comparison in exposure based on exposure levels at NOAEL and human plasma levels at 5 mg axitinib (BID)**

| Species | Study ID / Study duration | NOAEL (mg / kg / day) | Fraction (total or unbound) | C <sub>max</sub> (ng / ml) | Ratio NOAEL / human exposure | AUC <sub>0-24</sub> (ng.h / ml) | Ratio NOAEL / human exposure |
|---------|---------------------------|-----------------------|-----------------------------|----------------------------|------------------------------|---------------------------------|------------------------------|
| Mouse   | 6750-148<br>26 weeks      | <10                   | Total                       | < 137.45                   | <4.94                        | < 401.07                        | <1.51                        |
|         |                           |                       | Unbound                     | < 4.12                     | <29.45                       | <12.03                          | <9.05                        |
| Dog     | 6750-150<br>26 weeks      | 6                     | Total                       | 43.03                      | 1.55                         | 136.97                          | 0.52                         |
|         |                           |                       | Unbound                     | 0.86                       | 6.14                         | 2.74                            | 2.06                         |
| Dog     | 6348-470<br>9 months      | 1 <sup>a</sup>        | Total                       | 1.72                       | 0.06                         | 5.12                            | 0.02                         |
|         |                           |                       | Unbound                     | 0.03                       | 0.21                         | 0.10                            | 0.08                         |
|         |                           | 6 <sup>b</sup>        | Total                       |                            |                              |                                 |                              |
|         |                           |                       | m                           | 19.9                       | 0.72                         | 66.2                            | 0.25                         |
|         |                           |                       | f                           | 43.7                       | 1.57                         | 162                             | 0.61                         |
|         |                           |                       | Unbound                     |                            |                              |                                 |                              |
|         |                           |                       | m                           | 0.40                       | 2.86                         | 1.32                            | 0.99                         |
|         |                           |                       | f                           | 0.87                       | 6.21                         | 3.24                            | 2.44                         |
| Human   | A40610469                 | 5 mg, BID             | Total                       | 27.8                       | -                            | 265                             | -                            |
|         |                           |                       | Unbound                     | 0.14                       | -                            | 1.33                            | -                            |

a: NOAEL for males (based on testis and epididymis findings)

b: NOAEL for other findings (both genders)

m: male; f: female

## Local Tolerance

Axitinib was evaluated for the potential to cause local irritation when administered IV or PV as a parenteral formulation in the ear of New Zealand white rabbits (data not shown).

## Other toxicity studies

The phototoxicity potential of axitinib was evaluated based on significant absorbance in the ultraviolet A range with a molar extinction coefficient of 32754 L/mol/cm at 333 nm when calculated at pH 7.4 and the potential to reach eye and skin tissue following systemic administration. Axitinib was studied for phototoxic potential in the 3T3 fibroblast Neutral Red Uptake assay and in hairless, albino mice. The studies are summarised in table 7.

**Table 7. The *in vitro* and *in vivo* phototoxicity studies conducted with axitinib**

| Assay / Study ID / GLP status / Test substance / Purity                                                                                              | Species / Sex / Number / Group                                                     | Dose / Route / duration or Concentration / Observation                                    | Major findings                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3T3 neutral red uptake phototoxicity assay / 05228 / GLP (however, there is no characterisation or stability data for the test substance) / Axitinib | <i>In vitro</i> / Balb/c 3T3, clone 31 mouse fibroblasts / 6 wells / concentration | 0.069-150 µg/mL for approximately one hour / Cell viability (measured as optical density) | <b>NEGATIVE</b><br>No significant differences between non-irradiated and irradiated cells. Limited reduction in viability at 150 µg/mL (83 and 78% for non- and irradiated cells) |

| Assay /<br>Study ID /<br>GLP status /<br>Test substance /<br>Purity                        | Species /<br>Sex / Number /<br>Group                          | Dose / Route /<br>duration or<br>Concentration /<br>Observation                                                                                                                                                                   | Major findings                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Single-dose oral<br>phototoxicity study/<br>RSA00087/<br>GLP/<br>Axitinib/<br>99.8% Purity | <i>In vivo</i> /<br>Crl:SKH1-hr<br>hairless mice/<br>6♀/group | 3, 30, 100 mg/kg PO<br>followed by<br>approximately 30-min<br>UV radiation one hour<br>post-dosing/<br>Clinical signs, skin<br>observation and body<br>weight<br>measurements on the<br>3 <sup>rd</sup> day after UV<br>radiation | <b>NEGATIVE</b><br>No skin reactions. No clinical observations.<br>Initial body weight loss in all groups including<br>control (ascribed to the anaesthesia and<br>restraint used for UV radiation exposure)<br><br>C <sub>max</sub> =382 ng/mL and AUC <sub>0-24</sub> = 1080<br>ng·hr/mL at 100 mg/kg |

### 2.3.5. Ecotoxicity / environmental risk assessment

Results of submitted studies to evaluate the environmental risk from axitinib are summarised in table 8.

**Table 8. Summary of main study results**

|                                                                                |                                |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                   |
|--------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Substance (INN/ Invented Name):</b> Intyta/Axitinib                         |                                |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                   |
| <b>CAS-number (if available):</b> 319460-85-0                                  |                                |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                   |
| <b>PBT screening</b>                                                           |                                | <b>Result</b>                                                                                                                                                                                                                                                                                                                                                                           | <b>Conclusion</b>                                                                 |
| Bioaccumulation potential- log K <sub>ow</sub>                                 | OECD107 (Flask-shaking method) | 2.19 (pH=4)<br>2.01 (pH=7)<br>1.94 (pH=9)                                                                                                                                                                                                                                                                                                                                               | Potential PBT (No)                                                                |
| <b>Phase I</b>                                                                 |                                |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                   |
| <b>Calculation</b>                                                             | <b>Value</b>                   | <b>Unit</b>                                                                                                                                                                                                                                                                                                                                                                             | <b>Conclusion</b>                                                                 |
| PEC <sub>surfacewater</sub> , default or refined (e.g. prevalence, literature) | 0.1                            | µg/L                                                                                                                                                                                                                                                                                                                                                                                    | > 0.01 threshold (YES)                                                            |
| Other concerns (e.g. chemical class)                                           |                                |                                                                                                                                                                                                                                                                                                                                                                                         | (N)                                                                               |
| <b>Phase II Physical-chemical properties and fate</b>                          |                                |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                   |
| <b>Study type</b>                                                              | <b>Test protocol</b>           | <b>Results</b>                                                                                                                                                                                                                                                                                                                                                                          | <b>Remarks</b>                                                                    |
| Adsorption-Desorption                                                          | OECD 106                       | Absorption 83%, K <sup>F</sup> <sub>oc</sub> = 3185 (activated sludge)<br>Absorption 95%, K <sup>F</sup> <sub>oc</sub> = 52196 (Don Ulgem soil)<br>Absorption 63%, K <sup>F</sup> <sub>oc</sub> = 751 (Speyer soil)<br>Absorption 97%, K <sup>F</sup> <sub>oc</sub> = 81593 (Taunton river sediment)<br>Absorption 60%, K <sup>F</sup> <sub>oc</sub> = 10376 (Weweantic river sediment) |                                                                                   |
| Ready Biodegradability Test                                                    | OECD 314B                      | Primary biodegradation T <sub>50</sub> =4.21 (after 28 days)<br>Ultimate biodegradation (CO <sub>2</sub> evolution) 3.4% in 28 days                                                                                                                                                                                                                                                     |                                                                                   |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems               | OECD 308                       | DT <sub>50, water</sub> = 3.7-6 days<br>DT <sub>50, sediment</sub> = ND<br>DT <sub>50, whole system</sub> = 100-112 days<br>% shifting to sediment >40%                                                                                                                                                                                                                                 | The individual metabolites represented less than 10% of the applied radioactivity |
| <b>Phase IIa Effect studies</b>                                                |                                |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                   |

| Study type                                                            | Test protocol | Endpoint                                                | value        | Unit | Remarks                                 |
|-----------------------------------------------------------------------|---------------|---------------------------------------------------------|--------------|------|-----------------------------------------|
| Algae, Growth Inhibition Test/ <i>Pseudokirchneriella subcapitata</i> | OECD 201      | NOEC (growth rate)                                      | 0.43         | mg/L | Freshwater green alga, 72 hour exposure |
| <i>Daphnia</i> sp. Reproduction Test                                  | OECD 211      | NOEC (reproduction and parental body length)            | 0.088        | mg/L | 21 day exposure                         |
| Fish, Early Life Stage Toxicity Test/ <i>Pimephales promelas</i>      | OECD 210      | NOEC (growth)                                           | 0.0035       | mg/L | Fathead Minnow, early lifecycle         |
| Activated Sludge, Respiration Inhibition Test                         | OECD 209      | EC <sub>50</sub><br>EC <sub>15</sub> (respiration rate) | >1000<br>737 | mg/L | Sewage microorganism                    |

The outcome of the ERA assessment is displayed in Table 9.

**Table 9. Risk characterisation**

| Environmental compartment | PEC                         | PNEC                        | PEC / PNEC             | Trigger value | Conclusion |
|---------------------------|-----------------------------|-----------------------------|------------------------|---------------|------------|
| Surfacewater              | 1x 10 <sup>-4</sup> mg/L    | 3.5 x 10 <sup>-4</sup> mg/L | 0.29                   | 1             | No risk    |
| Groundwater               | 2.5 x 10 <sup>-5</sup> mg/L | 0.0088 mg/L                 | 0.0028                 | 1             | No risk    |
| Sewage water              | 1 x 10 <sup>-4</sup> mg/L   | 73.7 mg/L                   | 1.4 x 10 <sup>-6</sup> | 0.1           | No risk    |
| Sediment organisms        | 0.16 mg/kg                  | 1 mg/kg                     | 0.16                   | 1             | No risk    |

### 2.3.6. Discussion and conclusion on the non-clinical aspects

*In vitro* data demonstrate that axitinib is a selective kinase inhibitor that appears to be more potent on VEGFR kinases and PDGFR kinases (including KIT) compared to other RTKs and intracellular kinases. Inhibition of VEGF-mediated intracellular signalling has been demonstrated in cells treated with axitinib in nM concentrations.

The lack of formal interaction studies is acceptable, considering that axitinib is intended used as monotherapy.

In safety pharmacology studies, elevated systolic, diastolic and mean arterial blood pressure were observed in mice and rats, and possibly in dogs. Hypertension has been observed in clinical studies with axitinib, and blood pressure is to be monitored before and during treatment with axitinib.

In studies of biotransformation, the major substances detected in mouse plasma were the parent drug and the sulfoxide metabolite M12, and the glucuronide conjugate M7. In humans, M7 was the major metabolite, together with M12. In dogs, only the sulfoxide metabolite M12 was detected in plasma. Qualitatively, the metabolism in mouse is sufficiently representative to humans. The major human metabolite M7 is however not formed in dog. In general, phase II conjugates are less pharmacological active than the parent substance and are not considered to pose safety concerns. Furthermore, adequate exposure in one species is considered sufficient in general toxicity evaluation. Taken together, it is acceptable that one of the main metabolites in humans (M7) appears to be formed by only one of the species chosen for non-clinical testing of axitinib. The use of mouse and dog for the toxicological evaluation of axitinib is therefore considered acceptable.

The desmethyl metabolite AG-013887 was found not to be present in human excreta, and was only identified *in vitro*. Therefore, it is agreed that testing of AG-013887 for CYP-related drug metabolism is not relevant. The rationale for not testing the two major circulating metabolites, M7 and M12, for CYP-related drug metabolism is accepted since the potential for interactions is deemed very low.

Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with NOAEL approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/ml, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with NOEL 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

The lack of carcinogenicity studies is acceptable considering the proposed patient population in accordance with the ICH S9 guideline.

Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Reversible physal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

In the nonclinical toxicology program, considerable variability in exposure was documented in the mouse and dog studies. Variability in clearance data after intravenous administration appears to be limited. Thus, plausible explanations for the high variability in exposure data after oral administration could be dissolution of the active substance, GI transit, absorption, and first pass extraction processes. Furthermore, statistical analyses have been performed to test for significant differences in C<sub>max</sub> and AUC between dose groups in the pivotal repeat-dose toxicity studies in mice and dogs. In mice, exposure levels were in general significantly different between groups. However, in the dog studies, statistical significant difference in exposure could not be demonstrated for all dose groups. Taken together, the cause of the high data variability is still unclear, and estimated safety margins must be interpreted cautiously. Nevertheless, dogs have been exposed to axitinib levels higher than what is expected in humans, and for the sought indication safety margins < 1 can be accepted. Further investigations are therefore not considered necessary.

Interspecies comparison for both total and unbound plasma levels of axitinib has been performed at NOAEL in the pivotal toxicity studies, and at expected human exposure at 5 mg BID, indicates no margins of safety for the toxic effects. With regards to potential for genotoxic effects, there are substantial safety margins to NOEL for the micronucleus formation (127 and 69 for C<sub>max</sub> and AUC, respectively, in female mice), indicating low clinical relevance. However, it should be noted that intended maximal human dosing is up to 10 mg BID, and higher human plasma levels would therefore

be expected. Further, the submitted pharmacokinetic and toxicokinetic data show a high variability, especially in dogs. The interspecies comparison should therefore be interpreted accordingly.

The clinical relevance of a negative phototoxicity study in albino mice could be questioned, considering low to non-existing margins of safety based on systemic exposure, that axitinib is distributed to pigmented skin and possibly retained in the uveal tract, and that no data has been presented showing that axitinib is sufficiently distributed to skin in non-pigmented mice. It is recognised, however, that distribution studies in pigmented mice shows that the axitinib-related radioactivity in pigmented skin was comparable with the levels in plasma and skeletal muscle (i.e. non-pigmented tissue) at 1, 4, 8, 24 and 48 hours after administration (below LoQ at time points > 4 hours), while the levels in the heavily pigmented uveal tract was substantially higher at all time points. It is therefore plausible that the axitinib-related radioactivity in pigmented skin would be comparable to the plasma concentration in both pigmented and non-pigmented mice, and the *in vivo* study is therefore considered valid. In view of the negative 3T3 assay *in vitro*, negative phototoxicity *in vivo* and the lack of photosensitive reactions in clinical safety data, axitinib is not considered to have a phototoxic potential.

With regard to the environmental risk assessment, axitinib is not expected to pose a risk to the environment.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

#### **GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

### **2.4.2. Pharmacokinetics**

A total of 23 phase I and phase II clinical studies with pharmacokinetic data were submitted, with 822 patients receiving axitinib, including 14 studies in healthy patients (A4061003, A4061004, A4061006, A4061007, A4061018, A4061021, A4061026, A 4061033, A4061037, A4061047, A4061050, A4061052, A4061053, A4061063), 4 studies in patients with advanced RCC (A4061012, A4061023, A4061035, A4061046), 4 studies in patients with various solid tumours (A4060010, A4061019, A4061022, A4061044), and 1 study in patients with hepatic impairment which included a control healthy volunteer group (A4061036).

Population pharmacokinetic analysis (PMAR-00075, PMAR-00079,) and PK/PD analysis (PMAR-00080, PMAR-00074 including supplementary analysis PMAR-00074S,) were made using data from most of the studies with PK data. In addition, PK data from 55 of the 361 patients from the phase III study (A4061032) were included in a separate population pharmacokinetics and PK/PD analyses (PMAR-000140).

Plasma concentrations versus time data were modelled using a population analysis approach to estimate the population pharmacokinetic parameters (mean and inter-subject variability) and to identify potential covariates (intrinsic and extrinsic factors) that impact axitinib pharmacokinetics. The population analysis full data set contained subject identification, dosing information, time of sample collection, plasma axitinib concentrations, demographics, and physiological data for healthy volunteers or patients.

The bioanalytical methods used to measure axitinib concentrations in human plasma and urine samples included a HPLC coupled with tandem mass spectrometric (MS/MS) detection.

## Absorption

After oral administration, maximal plasma concentrations occur within 4 hours (range of median  $T_{max}$  across studies 2.5-4.1 hours). Mean absolute bioavailability was found to be 58% in the fasted state and 54% in the fed state.

Different axitinib formulations have been used in the clinical studies, and several bioequivalence studies with different formulations, both in the fasted and fed state, are submitted. The commercial form is the crystal polymorph form XLI FCIR, while many studies have used form IV wet or dry granulation FCIR formulations. The axitinib form IV dry granulation 5-mg tablets were found bioequivalent to the form IV wet granulation 5-mg tablets in the fasted state. Axitinib form IV and form XLI 5-mg tablets were bioequivalent when administered in the fed state, but not in the fasted state.

Five 1-mg tablets and one 5-mg tablet of the commercial tablet (crystal polymorph Form XLI) in the fasted state were bioequivalent.

For the form IV FCIR tablet the average peak  $C_{max}$  concentration following oral-fed treatment was 39%-57% lower than the oral-fasted treatment in different studies. The  $AUC_{0-\infty}$  the average exposure for the oral-fed treatment was 7%-36% lower than the oral-fasted treatment. With this formulation, ventricle pH-reduction (by the proton pump inhibitor rabeprazole) reduced by 42% axitinib  $C_{max}$ , but AUC was only marginally affected.

For the commercial form XLI FCIR tablet, there were no clinically significant changes in axitinib plasma exposure or  $C_{max}$  in the presence of food. A high-fat, high-calorie meal with this formulation produced a mean 19% increase in axitinib exposure compared to an overnight fast (10 hours predose/4 hours post dose fast) regimen, while a moderate-fat, standard-calorie meal decreased axitinib exposure by 10% compared to axitinib fasted.

## Distribution

The plasma protein binding of axitinib at therapeutic concentrations was >99%. The average  $C_{max}$  and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg.

The summary of axitinib PK parameters following administration of multiple doses of axitinib (5 mg BID) is presented in table 10.

**Table 10. Summary of axitinib PK parameters following administration of multiple doses of axitinib (5 mg BID) in Patients with Advanced Renal Cell Carcinoma**

|              | Mean (%CV) [Median] <Geometric Mean> |                            |                     |                               |                             |                                |
|--------------|--------------------------------------|----------------------------|---------------------|-------------------------------|-----------------------------|--------------------------------|
|              | $C_{max}$<br>(ng/mL)                 | $AUC_{0-24}$<br>(ng hr/mL) | $T_{max}$<br>(hr)   | CL/F<br>(L/hr)                | $V_d/F$<br>(L)              | $t_{1/2}$<br>(hr)              |
| C1D15 (n=20) | 37.9 (79)<br>[28.5]<br><27.8>        | 367 (77)<br>[322]<br><265> | 2.00<br>(1.00-2.50) | 53.1 (80)<br>[31.4]<br><37.8> | 243 (105)<br>[140]<br><160> | 4.09 (144)<br>[2.57]<br><2.92> |

Source: A4061046 Interim Pharmacokinetic Report, In-Text Table 2

$C_{max}$  = maximal plasma concentration; %CV = percent coefficient of variation;  $AUC_{0-24}$  = area under the plasma concentration versus time curve from 0 to 24 hr; CL/F = apparent oral clearance;  $V_d/F$  = apparent oral volume of distribution of the drug during the elimination phase;  $T_{max}$  = time of maximal plasma concentration;  $t_{1/2}$  = plasma terminal elimination half-life.

\* median with range

## **Metabolism**

Following a single oral administration of  $^{14}\text{C}$ -labelled drug to healthy male volunteers, axitinib underwent extensive metabolism to a variety of primary and secondary metabolites. Metabolic pathways included depyridinylation followed by formation of a carboxylic acid (M5), glucuronidation (M7), methyl hydroxylation followed by glucuronidation (M8a), both sulfoxidation and N-oxidation (M9), sulfoxidation (M12), mono-oxygenation on the pyridine ring (M12a and M14), and sulfonation (M15). In plasma, the glucuronide M7 represented the predominant metabolite accounting for approximately 50% of the circulating radioactivity, while the sulfoxide M12 and unchanged parent drug exhibited comparable levels with each accounting for approximately 20% of the circulating radioactivity.

Several studies that included human biomaterials were conducted to investigate the metabolism of axitinib. These studies showed that axitinib is metabolized primarily in the liver by CYP3A4/5, and to a lesser extent (<10%) by CYP1A2, CYP2C19 and UGT1A1.

## **Elimination**

Hepatobiliary elimination is the major route of elimination for axitinib. About 20% of the administered dose is excreted renally as metabolites.

In urine, the carboxylic acid M5 represented the predominant metabolite (approximately 6% of the dose), followed by M12 (approximately 4% of the dose), M7 (approximately 3% of the dose), M9 (approximately 2% of the dose), and M8a (approximately 1 % of the dose). In faeces, the parent drug represented the predominant radioactive component accounting for 12% of the dose. All faecal metabolites together accounted for approximately 16% of the dose.

## **Dose proportionality and time dependencies**

Axitinib plasma pharmacokinetics was dose-proportional, linear pharmacokinetics was observed for the single dose 5 mg to 10 mg dose range. No conclusive data exists on doses higher than 10 mg. The plasma pharmacokinetics of axitinib at steady state was linear.

The mean observed accumulation ratio for axitinib plasma  $\text{AUC}_{0-12}$  with continuous BID dosing ranged from 1.35 to 1.48. The pharmacokinetic properties of axitinib remain constant during chronic dosing.

Inter-subject variability of axitinib PK parameters is about 80 CV% and intra-subject variability is about 20-22 CV%.

## **Special populations**

In the population pharmacokinetic analysis PMAR-00079, age over 60 years had statistically significant influences on axitinib CL. Age over 60 years was associated with a decrease in CL, resulting in correspondingly higher axitinib exposures. However, this effect did not substantially decrease the high variability associated with axitinib disposition and was not considered clinically significant. Therefore, no dose adjustment for axitinib is required in elderly patients.

Axitinib has not been tested in patients < 18 years of age.

In population analysis of axitinib pharmacokinetics in healthy volunteers increasing body weight was estimated to increase  $V_c$  of axitinib. However, this effect was within the range of estimated inter-individual variability and therefore not considered clinically relevant.

The pooled population pharmacokinetic dataset included 501 males and 89 females. Gender was not a significant covariate for CL and  $V_c$  for axitinib. No dose adjustments for axitinib are recommended based on gender.

The population pharmacokinetic analysis showed that Japanese ethnicity was associated with reduced axitinib clearance (~25%), resulting in correspondingly higher axitinib exposures. In addition, in a formal comparison of axitinib pharmacokinetics in 20 Caucasian and 20 Japanese healthy volunteers, the geometric mean ratios for axitinib AUC<sub>0-∞</sub> and C<sub>max</sub> in Japanese versus Caucasians were 103 % and 96.2 % respectively. The 25% reduction in axitinib CL in Japanese observed in the population pharmacokinetics analysis is less than the corresponding estimated typical inter-individual variance (~60%) in axitinib CL.

The pharmacokinetics, safety and tolerability of a single 5-mg dose of axitinib has been evaluated in 24 subjects including patients with mild (Child-Pugh A), patients with moderate (Child-Pugh B) impaired hepatic function and healthy volunteers with normal hepatic function. Mild hepatic impairment did not alter axitinib plasma exposure (AUC<sub>0-∞</sub> and C<sub>max</sub>) compared to normal hepatic function. There was a ~2-fold increase in axitinib AUC<sub>0-∞</sub> and a 1.3-fold increase in axitinib C<sub>max</sub> in patients with moderate hepatic impairment compared to healthy volunteers with normal hepatic function. Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh C).

Axitinib has not been studied in patients with renal impairment. Population PK analyses showed that axitinib clearance was not altered in patients with renal impairment and no dose adjustment of axitinib is required.

### **Pharmacokinetic interaction studies**

The applicant submitted the results of two *in vivo* drug-drug-interaction studies that were conducted to assess the potential for pharmacokinetic interactions of axitinib with a strong CYP3A4/5 inhibitor (ketoconazole) and CYP3A4/5 inducer (rifampin), respectively.

In study A4061004, ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days increased the mean AUC 2-fold and C<sub>max</sub> 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers.

In study A4061026, rifampicin, a strong inducer of CYP3A4/5 administered at a dose of 600 mg once daily for 9 days reduced the mean AUC by 79% and C<sub>max</sub> by 71% of a single 5 mg dose of axitinib in healthy volunteers.

The effect of the proton pump inhibitor rabeprazole on the steady-state plasma pharmacokinetics of 5 mg BID axitinib was assessed in 6 patients in study A4060010. In the presence of rabeprazole, the axitinib C<sub>max</sub> was decreased 42%, but the AUC was only marginally affected.

As smoking is known to induce CYP1A2, the effect of smoking on axitinib CL was evaluated in a population pharmacokinetic analysis included 434 non-smokers, 19 active smokers and 137 ex-smokers. The analysis indicated that active smokers had a higher axitinib CL (~102%), resulting in lower axitinib exposures, but the smoking effect was not well defined in the model (SE was estimated to be high, i.e. 44%).

The applicant submitted the results of the *in vitro* studies of CYP and UGT inhibition and induction.

*In vitro* studies (AG-013736-PDM-020) with human liver microsomes and specific P450 probe substrates were conducted to evaluate the ability of axitinib to inhibit cytochrome P450 isoforms (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). Axitinib competitively inhibited CYP1A2 and CYP3A4 with K<sub>i</sub> values of 0.7 and 8.3 μM, respectively. In addition, axitinib noncompetitively inhibited CYP2C8 and CYP2C9 with K<sub>i</sub> values of 0.5 and 52.2 μM, respectively. In the concentration range of 0.3-40 μM, axitinib moderately inhibited CYP2A6 but did not inhibit CYP2C19, CYP2D6, or CYP2E1.

The results of another *in vitro* study showed that axitinib is an inhibitor of digoxin efflux, with an inhibitory potency (IC<sub>50</sub>) of 3.0 µM indicating that axitinib is a potent inhibitor of P-glycoprotein.

In AG-013736-PDM-039 study the effect of axitinib on CYP1A2-dependent phenacetin O-deethylation in human liver microsomes was evaluated. Axitinib was shown to be a potent inhibitor of CYP1A2-dependent activity with IC<sub>50</sub> values ranging from 0.2-0.3 µM respectively.

In study 764-05388 axitinib at concentrations of 0.13, 0.65, and 1.29 µM was evaluated for the ability to induce cytochrome P450 enzymes (CYP1A1/2 and CYP3A4) in primary human hepatocyte cultures in comparison to prototypical inducers (rifampin, dexamethasone, 3-methylcholanthrene and β-naphthoflavone). Axitinib exhibited a 0.5- to 2.7-fold change in the levels of CYP1A1/2 activity in human hepatocytes, and caused a 0.1- to 1.1-fold change in CYP3A4-catalysed testosterone 6β-hydroxylation in human hepatocytes.

In a clinical study (A4061019) in which patients with advanced solid tumours were co-administrated axitinib and paclitaxel, a known CYP2C8 substrate, there was no increase in plasma exposures of paclitaxel.

### **2.4.3. Pharmacodynamics**

#### ***Mechanism of action***

Axitinib is an oral, potent and selective, small molecule ATP-competitive inhibitor of VEGFR-1, 2 and 3. VEGFR-1, 2 and 3 have been identified as important targets for tumour-associated angiogenesis and lymphangiogenesis, key processes that support tumour growth and metastasis (Holopainen et al. 2011). It has been demonstrated that angiogenesis in RCC is significantly dependent on VEGF and its receptors (Albiges et al. 2011).

#### ***Primary and Secondary pharmacology***

Soluble proteins that were assessed in the axitinib clinical development program included plasma VEGF, sVEGFR-2, sVEGFR-3 and sKIT. Plasma samples were collected in multiple Phase II studies including studies A4061011 (NSCLC), A4061014 (thyroid cancer), A4061015 (melanoma), 4061022 (advanced solid tumours), A4061035 (cytokine-refractory advanced RCC), and A4061044 (advanced solid tumours); in all studies a 5 mg BID starting dose of axitinib was used.

Significant decreases in sVEGFR-2 (mean % change from baseline ranging from -27% to -42%) and sVEGFR-3 (mean % change from baseline ranging from -26% to -55%) and increases in plasma VEGF (mean % change from baseline ranging 152% to 460%) concentrations were observed following axitinib 5 mg BID dosing in study A4061015. By contrast, axitinib had relatively little or no effect on plasma concentrations of sKIT at this clinical dose. Study A4061022 assessed changes in s-VEGFR-2 on Cycle 2 Day 1 following administration of axitinib 5 mg BID as a function of axitinib steady-state exposure (AUC<sub>0-12</sub> on Cycle 1 Day 15). The results showed rapid decreases in s-VEGFR-2 with increasing exposures up to ~200 ng.hr/mL after which further increases in plasma exposure were associated with marginal further decrease in s-VEGFR2. Following administration of a 5 mg BID dose of the intended commercial Form XLI axitinib tablets, the mean AUC<sub>0-24</sub> was 330-367 ng.hr/mL in the fed state (Studies A4061044 and A4061046).

VEGF promotes vasodilation by mechanisms involving NO and PGI<sub>2</sub> production, and VEGF plays an important role in maintaining baseline vascular tone by regulation of NO synthesis (Bhargava 2009). Increase in blood pressure is a frequent clinical observation associated with inhibition of the VEGF pathway (Robinson et al. 2010). The correlation between effects of axitinib on blood pressure and drug

exposure was studied in study A4061022. At the 5 mg axitinib dose, no discernible effects on dBP or sBP were observed.

The correlation of axitinib plasma exposures with elevation of dBP ( $\geq 90$  mmHg) was assessed in the population PK/PD report PMAR-00080. Since dBP is more stable than sBP, changes in dBP were used for the analysis. At baseline, approximately 10%, 3%, and 5% of RCC patients in studies A4061012, A4061023 and A4061035, respectively, had mild elevation of dBP (90-99 mmHg). By the end of the first treatment cycle, approximately 35%, 12%, and 75% of RCC patients in studies A4061012, A4061023 and A4061035, respectively, had experienced elevations of dBP.

To evaluate if the axitinib-related BP increase was simply a surrogate for axitinib plasma exposure (PMAR-00080), the relationship between AUC<sub>ss</sub> and BP (maximum absolute dBP, as well as change in dBP from baseline) at both the end of the first treatment cycle and any time during the study treatment) was explored using linear regression. Results showed a weak correlation between axitinib exposure and dBP for patients with cytokine-refractory (studies A4061012 and A4061035) and sorafenib-refractory (study A4061023) RCC patients ( $R^2$  values  $<0.10$ ). Also in the population PK/PD analysis PMAR-00140, using data from 55 patients from the Phase 3 study (A4061032) a weak correlation between axitinib exposure and dBP for all patients ( $R^2$  values  $<0.10$ ) was found.

PMAR-00074 and supplementary analysis PMAR-00074S are population PK/PD evaluations for the assessment of the effect of axitinib plasma concentration on the heart rate corrected QT interval length (QTc) prolongation. The analysis uses data from study A4061004, a randomised, 2-way crossover study in 35 healthy subjects. QT intervals were measured following a single dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole. Absolute QTcF and QTcB values were not greater than 450 msec for all males and not greater than 470 msec for all females in the study across all treatments. Similarly, the maximum QTcF and QTcB changes from baseline did not exceed the clinically significant category of 60 msec or greater for any of the subjects across all treatments.

#### **2.4.4. Discussion and conclusions on clinical pharmacology**

For the commercial form XLI FCIR tablet, there were no clinically significant changes in axitinib plasma exposure or  $C_{\max}$  in the presence of food. Axitinib may be administered with or without food.

The effect of increased pH has been investigated for the earlier polymorphic form IV of axitinib, yielding a 42% reduced  $C_{\max}$  and no significant effect on AUC. However, the final polymorphic form XLI has a 2-3 fold reduced aqueous solubility, and therefore, translation of the pH interaction results obtained from polymorphic form IV to the final polymorphic form XLI is uncertain. The CHMP recommended the applicant to assess the effect of increased pH in an ongoing study (A4061046, a double-blind, Phase II study in patients with metastatic RCC). Patients in this study are allowed the use of drugs that can increase gastric pH (proton pump inhibitors [PPI] as well as  $H_2$ -blockers), and it will be feasible to compare axitinib pharmacokinetics in patients taking PPIs and  $H_2$ -blockers versus those who are not.

In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population. No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A).

Virtually no data are available regarding patients with a creatinine clearance of  $<15$  ml/min. Therefore no dose adjustment is required for patients with renal impairment.

Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended.

CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended.

The effect of smoking-related CYP1A2 induction on axitinib pharmacokinetics has not been fully characterised. The risk of decreased axitinib plasma concentrations should be considered when administering axitinib to smokers. The CHMP recommended the applicant to submit a pooled PK/PoP-PK analysis with smoking as a covariate using data from ongoing trials in patients with non small-cell lung cancer and already available phase II data.

*In vitro studies* indicated that axitinib may have the potential to inhibit CYP2C8, CYP1A2 and P-glycoprotein. However, in a clinical study no effect of axitinib on the PK of paclitaxel (a CYP2C8-substrate) was found. Since no drug-drug interaction studies were performed to explore whether axitinib could inhibit CYP1A2 or P-glycoprotein a warning included in the section 4.5 of the SmPC, as follows: "*In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, CYP1A2 substrates should be used with caution since co-administration of axitinib may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline)*".

*In vitro* studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

PK/PD analyses indicated that axitinib-related increase in dBP in individual patients is an independent pharmacodynamic response that does not simply represent axitinib plasma exposure.

Axitinib at plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose did not produce clinically significant QTc prolongation.

## **2.5. Clinical efficacy**

The applicant conducted one pivotal phase III study A4061032 and three phase II single-arm studies A4061012, A4061035 and A4061023. The summary of efficacy studies conducted by the applicant is presented in table 11.

**Table 11. Clinical studies supporting the application for axitinib in the treatment of advanced RCC**

| Protocol                                                                                         | Title                                                                                                           | Study Design / Status                                                                                     | Study Initiation / Data Cut-off Date | Location(s)         | Treatment                                                                       | Planned / Actual No. of Subjects |
|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------|---------------------------------------------------------------------------------|----------------------------------|
| <b>Pivotal Phase 3 Study</b>                                                                     |                                                                                                                 |                                                                                                           |                                      |                     |                                                                                 |                                  |
| A4061032                                                                                         | Axitinib (AG-013736) as Second-Line Therapy for Metastatic Renal Cell Cancer: Axis Study                        | Phase 3, randomised, open-label, multi-center, multinational study/Completed <sup>a</sup>                 | 15 September 2008 / 31 August 2010   | Global              | <u>Starting dose:</u><br>Axitinib 5 mg PO BID<br>vs.<br>Sorafenib 400 mg PO BID | 650 <sup>b</sup> /723            |
| <b>Supportive Phase 2 Single-Agent Studies in Subjects with Cytokine-Refractory Advanced RCC</b> |                                                                                                                 |                                                                                                           |                                      |                     |                                                                                 |                                  |
| A4061012                                                                                         | Phase 2 Study of AG-013736 as Second-Line Treatment in Patients with Metastatic Renal Cell Cancer               | Phase 2, single-arm, 2-stage, open-label, multi-center study/ Completed <sup>a</sup>                      | 05 November 2002 / 01 February 2007  | US, France, Germany | <u>Starting dose:</u><br>Axitinib 5 mg PO BID                                   | 52/52                            |
| A4061035                                                                                         | Phase 2 Study of AG-013736 as Second-Line Treatment in Patients with Metastatic Renal Cell Cancer               | Phase 2, single-arm, single-stage, open-label, non-randomised, Multi-center study/ Completed <sup>a</sup> | 12 December 2007 / 26 February 2010  | Japan               | <u>Starting dose:</u><br>Axitinib 5 mg PO BID                                   | 63/64                            |
| <b>Supportive Phase 2 Single-Agent Study in Subjects with Sorafenib-Refractory Advanced RCC</b>  |                                                                                                                 |                                                                                                           |                                      |                     |                                                                                 |                                  |
| A4061023                                                                                         | Phase 2 Study of the Anti-Angiogenesis Agent AG-013736 in Patients with Refractory Metastatic Renal Cell Cancer | Phase 2, single-arm, open label, single-stage, multi-center, non-randomised/ Completed <sup>a</sup>       | 08 March 2006 / 16 January 2009      | US                  | <u>Starting dose:</u><br>Axitinib 5 mg PO BID                                   | 62/62                            |

<sup>a</sup> "Completed" signifies that the analysis for primary endpoint has been completed and a clinical study report (CSR) is available; however, subjects may still be receiving treatment under the same protocol and are being followed for overall survival and safety.

The cut-off date for the pivotal Phase 3 RCC study (A4061032) was 31 August 2010.

<sup>b</sup> Due to an underestimation of the dropout rate prior to progression, the planned enrollment was increased from the initial target enrollment of 540 subjects to 650 subjects (Protocol Amendment 4 dated 16 November 2009).

### 2.5.1. Dose response study

The axitinib starting dose of 5 mg BID was determined to be the MTD (using standard safety criteria) in the FIH study in subjects with advanced solid tumours (Study A4060010). The primary DLT was hypertension. Based on the results of the first 10 subjects, a dose of 20 mg BID exceeded the MTD. DLTs also occurred in subjects in the first 2 cohorts who received 10 mg BID (either as a starting dose or a dose reduction), and therefore this dose was also considered above the MTD.

The rationale for the 5 mg BID starting dose selection was further supported by the following data:

*Changes in vascular permeability/blood flow:* Clinical evaluation of drug-related changes in vascular permeability/blood flow in humans was assessed by dce-MRI at an axitinib starting dose of 5 mg BID. Axitinib exposures observed at the MTD (5 mg BID in the fasted state) in the FIH study (Study

A4060010) and those observed in clinical studies at the recommended starting dose (5 mg BID in the fed state; mean steady state AUC<sub>0-24</sub> 330-367 ng.hr/mL) were within the range of pharmacodynamic activity as determined by dce-MRI. This provided evidence that the starting dose in subjects that was selected based on safety considerations (5 mg BID) corroborates well with the optimal dose suggested by the pharmacodynamic assessment of drug-related changes in vascular permeability and flow.

*Changes in soluble proteins:* At the axitinib starting dose of 5 mg BID, drug-related changes in soluble proteins related to the antiangiogenesis pathway were measured. Overall, axitinib preferentially modulates sVEGFRs and sVEGF at the clinical starting dose of 5 mg BID.

*Population pharmacokinetic modelling of clinical response:* At the axitinib starting dose of 5 mg BID, population PK-PD modelling showed that the observed clinical response (tumour size reduction) in subjects with advanced RCC correlated closely with plasma exposures. In addition, clinical response was observed at 5 mg BID in subjects with advanced RCC.

## **2.5.2. Main study**

### **A4061032**

This 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 including sunitinib, bevacizumab + IFN- $\alpha$ , temsirolimus, or cytokine(s), or combination of these.

## **Methods**

### **Study Participants**

Eligible patients were male or female, 18 years or older, with histologically or cytologically confirmed diagnosis of RCC with a component of clear cell subtype, with evidence of metastatic disease. Subjects were to have at least one measurable target lesion documented radiographically (CT or MRI), and disease progression according to RECIST v1.0, after one prior systemic first-line regimen for advanced RCC. The prior regimen must have contained one or more of the following: sunitinib, bevacizumab + IFN- $\alpha$ , temsirolimus, or cytokine(s). Prior systemic treatment, radiotherapy, or surgical procedures should have ended at least 2 weeks prior to enrollment (4 weeks for bevacizumab + IFN- $\alpha$  treatment) with resolution of all treatment-related toxicity to NCI CTCAE Version 3.0 Grade  $\leq$  1 or back to baseline with the exception of alopecia or hypothyroidism. Subjects were to have adequate organ function, an ECOG PS of 0 or 1, and a life expectancy of  $\geq$ 12 weeks.

Subjects were excluded from the study if they had prior treatment of advanced RCC with more than one systemic first-line regimen, treatment with any neoadjuvant or adjuvant systemic therapy, major surgery <4 weeks or radiation therapy <2 weeks prior to starting the study treatment; prior palliative radiotherapy to metastatic lesion(s) was permitted, provided there was at least one measurable lesion that had not been irradiated.

### **Treatments**

Patients were randomised at a ratio of 1:1 to receive either axitinib (Arm A) or sorafenib (Arm B). Study treatment was required to begin within seven days of randomisation.

Treatment was administered continuously in 4-week cycles. In Arm A, the starting dose of axitinib was 5 mg BID administered orally with food. In Arm B, sorafenib was administered orally without food at a starting dose of 400 mg BID. In both arms, doses were to be taken as close to 12 hours apart as possible and at approximately the same times each day. Subjects who tolerated axitinib with no

related adverse events above CTCAE Grade 2 for a consecutive 2-week period were recommended to have their dose increased by one dose level to 7 mg BID and subsequently to a maximum of 10 mg BID (unless the subject's BP was >150/90 mm Hg or the subject was receiving antihypertensive medication). Except for hypertension and proteinuria, a dose reduction to one lower dose level to 3 mg BID and subsequently to a minimum of 2 mg BID was recommended in subjects experiencing axitinib-related Grade 3 non-hematologic toxicity. For treatment-related Grade 4 non-hematologic or hematologic toxicity, the axitinib dose was interrupted and restarted at one lower dose level as soon as improvement to CTCAE Grade  $\leq$  2 occurred.

In Arm B, when dose reduction was necessary to manage sorafenib-related adverse drug reactions, the sorafenib dose was reduced to 400 mg QD. If additional dose reduction was required, sorafenib was reduced to a single 400 mg dose every other day.

No other chemotherapy or experimental anticancer treatments were permitted during the study period. Palliative and supportive care for disease-related symptoms, including pain medications, was permitted. Palliative radiotherapy was permitted, but only for pain control to sites of bone disease present at baseline, and only following bone scan imaging demonstrating no new sites on bone metastasis.

Study treatment continued until subjects experienced PD, occurrence of unacceptable toxicity or death, or withdrawal of subject consent. However, subjects were eligible for continued treatment as assigned at randomisation beyond the time of PD, defined according to RECIST v1.0, at the discretion of the treating physician.

## **Objectives**

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

The secondary objectives included comparison of OS and ORR of patients in each arm, evaluation of safety and tolerability of axitinib, estimation of the DR of patients in each arm and comparison of the kidney-specific symptoms and health status of patients in each arm, as measured by the FKSI and EuroQol EQ-5D.

## **Outcomes/endpoints**

The primary endpoint was PFS defined as the time from randomisation to first documentation of objective tumour progression or to death due to any cause, whichever occurred first.

The key secondary endpoints were the following:

- Progression-Free Survival (investigator assessment).

- Overall Survival: OS was defined as the time from the date of randomisation to the date of death due to any cause. For patients still alive at the time of the analysis, the OS time was censored on the last date they were known to be alive. Patients lacking data beyond randomisation had their OS times censored at the date of randomisation.

- Objective Response Rate: ORR was defined as the percent of patients with confirmed complete CR or confirmed partial response (PR) according to RECIST criteria, relative to all randomised patients. Confirmed responses were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. Third-party blinded review and qualification were performed retrospectively by the IRC. Patients who did not have on-study radiographic tumour re-evaluation or

who died, progressed, or dropped out for any reason before reaching a CR or PR were counted as non-responders in the assessment of ORR. A patient who initially met the criteria for a PR and then subsequently became a confirmed CR was assigned a best response of CR.

- Duration of response: DR was defined as the time from the first documentation of objective tumour response (CR or PR), that was subsequently confirmed, to the first documentation of PD or to death due to any cause, whichever occurred first. If tumour progression data included more than one date, the first date was used.

Patients who achieved a PR and then a CR had times calculated using the date of the PR as the first day. DR was only calculated for the subgroup of patients with a confirmed objective tumour response.

Other secondary endpoints were the following:

-Functional Assessment of Cancer Therapy-Kidney Symptom Index: The FKSI contains 15 questions and includes a 9-question subscale known as the FKSI-DRS subscale that specifically measures symptoms related to advanced kidney cancer disease. This subscale includes the following items: lack of energy, pain, losing weight, bone pain, fatigue, short of breath, coughing, bothered by fevers, and haematuria. The total FKSI score is the sum of the 15 individual item scores. The total FKSI-DRS score is the sum of its 9 individual item scores.

-EuroQol Group's Self-Reported Health Status Measure: The EQ-5D is a self-administered generic health status instrument consisting of two parts. In the first part, respondents were asked to describe their current health state on five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having three levels of function (1=no problem, 2=some problem, and 3=extreme problem). The second part is a patient's self-rating of current health state on a visual analog scale (EQ-VAS) with endpoints labelled 'best imaginable health state' and 'worst imaginable health state'. The EQ-5D endpoints are the EQ-5D Index, which is derived by combining one level from each of the five dimensions and converting it to a single summary index or health utility value, and the EQ-VAS score, which ranges from 0 for worst imaginable health state to 100 for best imaginable health state. Overall, scores for the EQ-5D index range from -0.594 to 1, with low scores representing a higher level of dysfunction.

## **Sample size**

A total of 409 patients with PD or death were required for the log-rank test with an overall 1-sided significance level of 0.025 to have power of 0.90. This assumed a 40% improvement in median PFS from 5 months to 7 months in patients randomised to receive axitinib and non-uniform accrual (approximately 40% of patients enrolled at 9 months). Applying a 1:1 randomisation, a planned accrual period of 18 months, and a follow-up period of approximately 5 months, it was estimated that approximately 650 patients would need to be enrolled in order to observe 409 patients with PD or death by the end of the follow-up period. The initial target enrolment was 540 patients; however, due to an underestimation of the dropout rate in the original protocol, the protocol was amended and the planned enrolment was increased.

The sample size described above also allowed the assessment of differences in the secondary endpoint of OS with a high level of significance. A total of 417 events were required for a log-rank test with an overall 1-sided significance level of 0.025 to have power of 0.80. This assumed a 31.67 % improvement in median OS from 18 months to 23.7 months in patients randomised to receive axitinib, and a follow-up period of approximately 37 months.

The estimated sample size of 650 patients for PFS would also be sufficient to observe the 417 events needed for comparing median OS.

## Randomisation

Subjects were randomised in a 1:1 ratio to either the investigational treatment of single-agent axitinib (Arm A) or to the control treatment of single-agent sorafenib (Arm B). Randomisation was stratified according to ECOG performance status (0 vs. 1) and by prior regimen (sunitinib-containing regimen vs. bevacizumab-containing regimen vs. temsirolimus-containing regimen vs. cytokine-containing regimen).

## Blinding (masking)

The study was open-labelled. However, the independent assessment of the primary endpoint (PFS) was done in a blinded manner by the IRC.

## Statistical methods

A stratified (ECOG performance status and prior therapy) log-rank test with an overall 1-sided significance level of 0.025 was used to compare PFS between the two treatment arms.

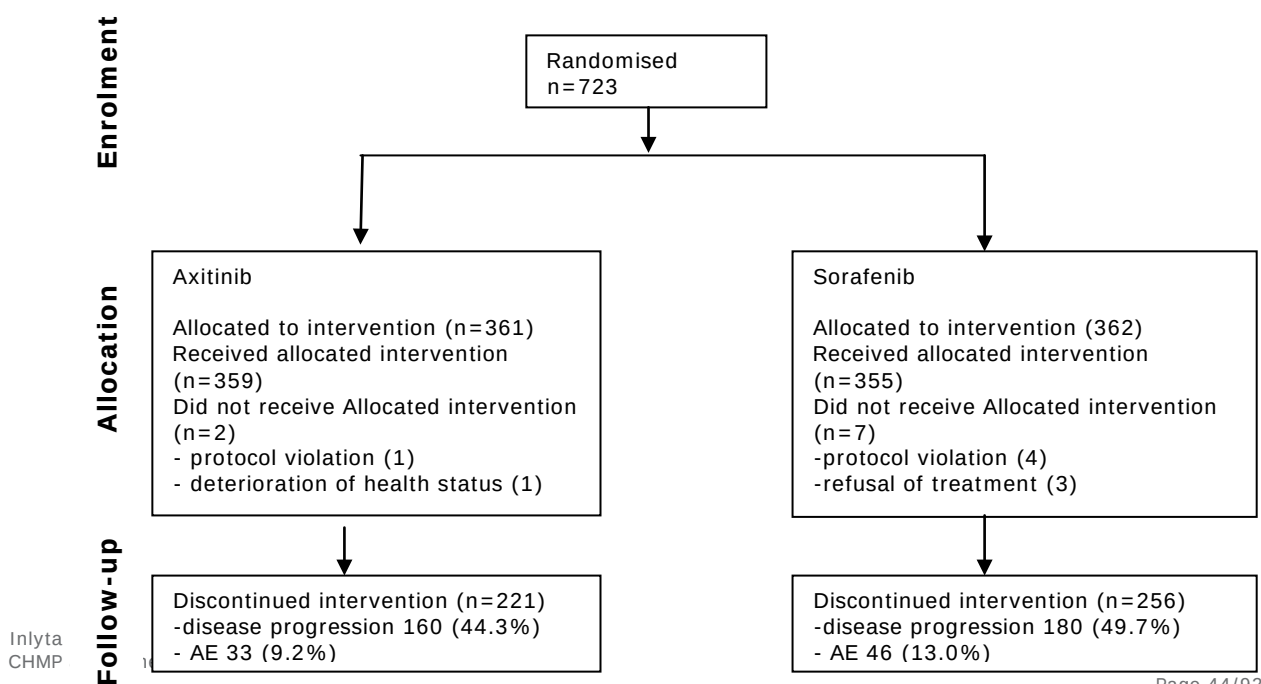
The study was designed to have one interim analysis and the final analysis. The interim analysis and the final analysis were based on the primary endpoint of PFS as assessed by the IRC.

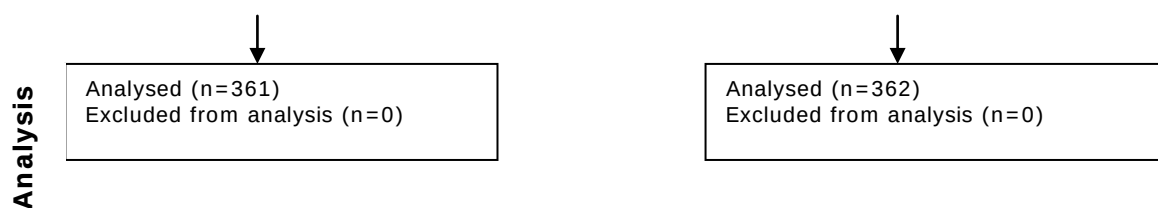
The interim analysis of efficacy and safety was planned to be performed after approximately 204 PFS events (approximately 50% of the total number of required events as assessed by the IRC. If exactly 204 expected events occurred at the time of the interim analysis, then the significance level for futility was 0.2293.

The final analysis was planned to take place when 409 patients had documented PD or death. The overall type I error rate was preserved at the nominal 0.025 level. However, due to the futility interim analysis occurring after 289 events instead of the originally targeted 204 events, the number of total events needed for the final analysis was needed to be increased from 409 to 423 to maintain the same power of 0.90.

## Results

### Participant flow





## Recruitment

First patient was randomised the 15th of September 2008 ; last treatment visit took place the 23rd of July 2010 and the cut-off date of the study was 31st of August 2010 ; last patient follow-up will probably take place in the first quarter of 2013.

## Conduct of the study

The clinical trial protocol was amended 4 times during the conduct of the study.

The major amendments 3 and 4 are briefly described below:

- Protocol Amendment 3 (dated 10 February 2009)

-Changed the wording of prior systemic first-line regimen strata to sunitinib-containing regimen, bevacizumab-containing regimen, temsirolimus-containing regimen, and cytokine-containing regimen to stratify prior systemic therapy according to similarity of mechanism of action.

-Revised inclusion criteria to include patients with RCC subtype of cytologically confirmed clear cell; to remove the requirement for documentation (using prestudy scans) of progressive disease and a 4-month window for progression; to allow enrollment of patients with hypothyroidism and to clarify that patients with uncontrolled angina were excluded.

-Revised the timing of the PK collection in Cycle 2 Day 1 and Cycle 3 Day 1 to allow collection of a predose sample up to 2 hours before the morning axitinib dose.

- Protocol Amendment 4 (dated 16 November 2009)

-Due to an underestimation of the dropout rate in the original protocol, the planned patient enrollment was increased from 540 to 650. The sample estimate was modelled without unblinding of the data and in consultation with the DMC. No change was made to the required number of PFS events.

-Revised population PK sample collection for patients randomised to the axitinib arm to allow collection of PK samples from patients who had already completed Cycle 3 without PK sampling; these patients could have had PK samples taken at any 1 cycle beyond Cycle 3.

-Allowed collection of UGT1A1 and other pharmacogenomic samples at any time during the study if they were not collected at Cycle 1 Day 1.

-Revised and allowed flexibility for the predose thyroid function tests to be performed within 7 days of Cycle 1 Day 1.

-Revised the "Analysis for Primary Endpoint" section of the protocol in line with Protocol Amendment 3 to remove the requirement for pre study scans confirming disease progression. The guidelines for analysis of the primary endpoint did not include sensitivity analysis for patients with confirmed prior progression compared to those who did not have confirmed prior progression based on pre study scan data.

-Updated the PRO analysis to include time to deterioration analysis.

The protocol deviations are summarised in table 12.

**Table 12. Protocol deviations**

| Protocol Deviation                                                                                                                                                    | Number of Patients | Patient Identification                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------------------------|
| Patient had previously received sorafenib as first-line therapy.                                                                                                      | 1                  | 11391005                                                                                      |
| Patient was stratified incorrectly as prior bevacizumab-containing therapy group. Patient should have been stratified as prior temsirolimus containing therapy group. | 4                  | 10981039, 10981006, 10211003, 11071011                                                        |
| Patient did not have a CT scan of the brain during screening.                                                                                                         | 2                  | 12481001, 12571001                                                                            |
| Missing baseline scans                                                                                                                                                | 2                  | 10511001, 12131015                                                                            |
| Patient had 2 prior lines of therapy.                                                                                                                                 | 4                  | 12441001 <sup>a</sup> , 11901004 <sup>b</sup> , 12471004 <sup>c</sup> , 11391005 <sup>d</sup> |
| Patient randomised despite lack of histologically confirmed component of clear cell subtype of renal cell carcinoma.                                                  | 1                  | 11711001 <sup>e</sup>                                                                         |
| Patient randomised despite violation of exclusion criterion number 10.                                                                                                | 3                  | 10481005, 10511002, 11191004                                                                  |
| Patient had presence of brain metastasis. <sup>f, g</sup>                                                                                                             | 8 <sup>f</sup>     | 10221001, 10551002, 10721004, 10981011, 11051003, 11751006, 11871006, 12481001                |
| Patient took axitinib 20 mg BID for 4 days (17-20 March 2010), rather than the protocol specified 10 mg BID                                                           | 1                  | 11561004                                                                                      |
| Patient admitted to study with elevated urine protein. <sup>f</sup>                                                                                                   | 1 <sup>f</sup>     | 11791007                                                                                      |

<sup>a</sup> Patient 12441001 received 2 prior regimens: IFN- $\alpha$  and IL-2 from 06 June 2005 to 05 December 2005; and sunitinib from 01 December 2007 to 25 July 2009. There is documentation of disease progression between the 2 regimens.

<sup>b</sup> Patient 11901004 received 2 prior regimens: sunitinib from 10 August 2009 to 21 October 2009; and bevacizumab + interferon from 10 November 2009 to 23 December 2009. There is documentation of disease progression between the 2 regimens.

<sup>c</sup> Patient 12471004 received 2 prior regimens: interferon from 09 May 2005 to 12 October 2005; and sunitinib from 31 January 2006 to 15 February 2010. There is documentation of disease progression between the 2 regimens.

<sup>d</sup> Patient 11391005 received 2 prior regimens: sorafenib from 10 September 2008 to 05 December 2008 and sunitinib from 05 December 2008 to 16 October 2009. There is documentation of disease progression between the 2 regimens.

<sup>e</sup> The patient was randomised with papillary cell histology.

<sup>f</sup> These patients were discontinued from treatment as a result of the protocol deviation.

<sup>g</sup> Exclusion criterion No. 8 precluded inclusion of patients with brain metastasis.

## Baseline data

Baseline demographic characteristics of the patients in the pivotal study are presented in table 13.

**Table 13. Demographic and baseline characteristics by treatment (FAS)**

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

Data cutoff date: 31 August 2010.

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

Abbreviations kg = kilogram, mg = milligram, MSKCC = Memorial Sloan-Kettering Cancer Center, N = number of patients, n = number of patients meeting specified criteria,

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

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

The disease characteristics at baseline were:

**Table 14. Pivotal Study A4061032: Summary of Disease Characteristics and Prior Tumour Treatment (FAS)**

| Variable                                                         | Axitinib<br>N=361   | Sorafenib<br>N=362  |
|------------------------------------------------------------------|---------------------|---------------------|
| <b>Disease Characteristics</b>                                   |                     |                     |
| Time since initial histopathological diagnosis (weeks)           |                     |                     |
| n                                                                | 361                 | 362                 |
| Mean (SD)                                                        | 183.6 (213.1)       | 179.1 (197.1)       |
| Median (min, max)                                                | 100.6 (0.1, 1219.6) | 102.2 (0.9, 1096.6) |
| Time since metastatic diagnosis (weeks)                          |                     |                     |
| n                                                                | 360                 | 362                 |
| Mean (SD)                                                        | 97.3 (108.8)        | 85.2 (87.0)         |
| Median (min, max)                                                | 58.6 (1.1, 752.7)   | 61.5 (1.1, 882.7)   |
| Histological classification, n (%)                               |                     |                     |
| Clear cell                                                       | 355 (98.3)          | 359 (99.2)          |
| Other                                                            | 1 (0.3)             | 0 (0.0)             |
| Not reported                                                     | 5 (1.4)             | 3 (0.8)             |
| Current stage, n (%)                                             |                     |                     |
| Stage III                                                        | 39 (10.8)           | 40 (11.0)           |
| Stage IV                                                         | 322 (89.2)          | 322 (89.0)          |
| Metastatic site                                                  |                     |                     |
| Lung                                                             | 274 (75.9)          | 292 (80.7)          |
| Lymph Node                                                       | 209 (57.9)          | 202 (55.8)          |
| Bone                                                             | 119 (33.0)          | 107 (29.6)          |
| Liver                                                            | 102 (28.3)          | 103 (28.5)          |
| Other                                                            | 139 (38.5)          | 130 (35.9)          |
| <b>Prior Tumour Treatment<sup>a</sup></b>                        |                     |                     |
| Prior treatment regimen, n (%)                                   |                     |                     |
| Sunitinib-containing regimen                                     | 192 (53.2)          | 195 (53.9)          |
| Cytokine-containing regimen                                      | 126 (34.9)          | 125 (34.5)          |
| Bevacizumab-containing regimen                                   | 31 (8.6)            | 29 (8.0)            |
| Temsirolimus-containing regimen                                  | 12 (3.3)            | 13 (3.6)            |
| Best response to pre-study systemic therapy <sup>b</sup> , n (%) |                     |                     |
| Complete Response                                                | 3 (0.8)             | 3 (0.8)             |
| Partial Response                                                 | 65 (18.0)           | 73 (20.2)           |
| Stable Disease                                                   | 153 (42.4)          | 132 (36.5)          |
| Progressive Disease                                              | 120 (33.2)          | 134 (37.0)          |
| Unknown                                                          | 20 (5.5)            | 18 (5.0)            |
| Prior surgery for primary diagnosis, n (%)                       |                     |                     |
| None                                                             | 154 (42.7)          | 149 (41.2)          |
| Resected                                                         | 145 (40.2)          | 136 (37.6)          |
| Biopsy                                                           | 74 (20.5)           | 85 (23.5)           |
| Partially resected                                               | 18 (5.0)            | 29 (8.0)            |
| Unresected                                                       | 4 (1.1)             | 7 (1.9)             |
| Not found                                                        | 4 (1.1)             | 5 (1.4)             |
| Not reported                                                     | 8 (2.2)             | 10 (2.8)            |
| Prior surgery for nephrectomy, n (%)                             |                     |                     |
| Yes                                                              | 327 (90.6)          | 331 (91.4)          |
| No                                                               | 34 (9.4)            | 31 (8.6)            |
| Previous radiotherapy, n (%)                                     |                     |                     |
| Yes                                                              | 75 (20.8)           | 73 (20.2)           |
| No                                                               | 286 (79.2)          | 289 (79.8)          |

% = (n/N) x 100

Abbreviations: Max=maximum; Min=minimum; N=number of subjects; n=number of subjects meeting specified criteria; SD=standard deviation

<sup>a</sup> Prior tumour treatment is based on CRF data.

<sup>b</sup> Two subjects (12531009 and 12571009) on the sorafenib treatment arm were missing responses on the CRF.

## Numbers analysed

The study incorporated 723 patients, with 361 patients in the axitinib arm. Of those, 361 (100.0%) patients were included in the FAS population (all patients who were randomised), and 359 (99.4%) patients were included in the SA set (all patients who received at least one dose of study medication). Of the 362 patients in the sorafenib arm, 362 (100.0%) patients were included in the FAS and 355 (98.1%) patients were included in the SA set.

Efficacy analyses were performed on the FAS (ITT); safety analyses were performed on the SA set.

## Outcomes and estimation

### Primary endpoint

The efficacy results in terms of the primary endpoint of PFS and for the primary analysis of 31 August 2010 are summarised in table 15.

**Table 15. Study A4061032: Summary of PFS by treatment and stratification factor, stratified analysis, ICR assessment (FAS)**

| Progression-Free Survival Parameter                                          | Axitinib<br>(N = 361) | Sorafenib<br>(N = 362) |
|------------------------------------------------------------------------------|-----------------------|------------------------|
| <b>Overall stratified analysis (N)</b>                                       | 361                   | 362                    |
| Progression Status [n (%)]                                                   |                       |                        |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 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 <sup>a</sup> | 169 (46.8)            | 152 (42.0)             |
| Progression-free survival (months)                                           |                       |                        |
| Quartiles (95% CI) <sup>b</sup>                                              |                       |                        |
| 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 <sup>c</sup> (95% CI)                                           | 0.665 (0.544, 0.812)  | NA                     |
| p-value <sup>d</sup>                                                         | <0.0001               | NA                     |
| <b>Prior sunitinib-containing regimen (N)</b>                                | 194                   | 195                    |
| Progression Status [n (%)]                                                   |                       |                        |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 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 <sup>a</sup> | 77 (39.7)             | 75 (38.5)              |
| Progression-free survival (months)                                           |                       |                        |
| Quartiles (95% CI) <sup>b</sup>                                              |                       |                        |
| 25%                                                                          | 1.7 (1.5, 2.8)        | 1.5 (1.5, 2.0)         |
| 50% (median)                                                                 | 4.8 (4.5, 6.4)        | 3.4 (2.8, 4.7)         |
| 75%                                                                          | 12.0 (8.3, 17.7)      | 6.7 (5.2, 15.7)        |
| Axitinib vs. sorafenib                                                       |                       |                        |
| Hazard ratio <sup>c</sup> (95% CI)                                           | 0.741 (0.573, 0.958)  | NA                     |
| p-value <sup>e</sup>                                                         | 0.0107                | NA                     |
| <b>Prior cytokine-containing regimen (N)</b>                                 | 126                   | 125                    |
| Progression Status [n (%)]                                                   |                       |                        |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 50 (39.7)             | 69 (55.2)              |
| Objective progression observed                                               | 47 (94.0)             | 65 (94.2)              |
| Death without objective progression                                          | 3 (6.0)               | 4 (5.8)                |
| Subject did not progress or die due to any cause while on study <sup>a</sup> | 76 (60.3)             | 56 (44.8)              |

|                                    |                      |                  |
|------------------------------------|----------------------|------------------|
| Progression-free survival (months) |                      |                  |
| Quartiles (95% CI) <sup>b</sup>    |                      |                  |
| 25%                                | 6.4 (3.3, 8.6)       | 2.8 (2.7, 4.6)   |
| 50% (median)                       | 12.1 (10.1, 13.9)    | 6.5 (6.3, 8.3)   |
| 75%                                | NE (13.9, NE)        | 10.1 (8.3, 12.8) |
| Axitinib vs. sorafenib             |                      |                  |
| Hazard ratio <sup>c</sup> (95% CI) | 0.464 (0.318, 0.676) | NA               |
| p-value <sup>e</sup>               | <0.0001              | NA               |

Source: A4061032 CSR Table 13.4.1.2

% = n/N x 100

Abbreviations: CI=confidence interval; IRC=independent review committee; N=number of subjects; n=number of subjects meeting specified criteria; NA=not applicable; NE=not estimable

<sup>a</sup> On study includes treatment plus 28-day follow-up period.

<sup>b</sup> Based on the Brookmeyer and Crowley method

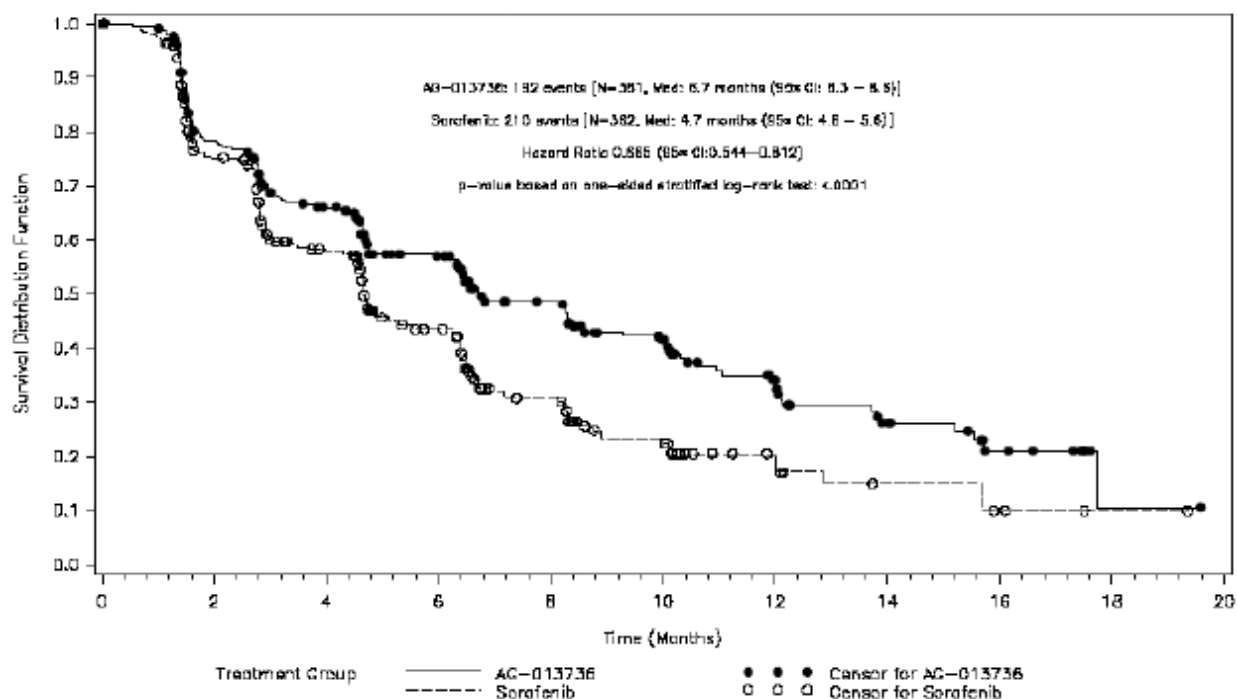
<sup>c</sup> Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test.

<sup>d</sup> For the Overall Stratified Analysis, the p-value was from a 1-sided log-rank test stratified by ECOG performance status and prior treatment regimen.

<sup>e</sup> P-value was from a 1-sided log-rank test stratified by ECOG performance status.

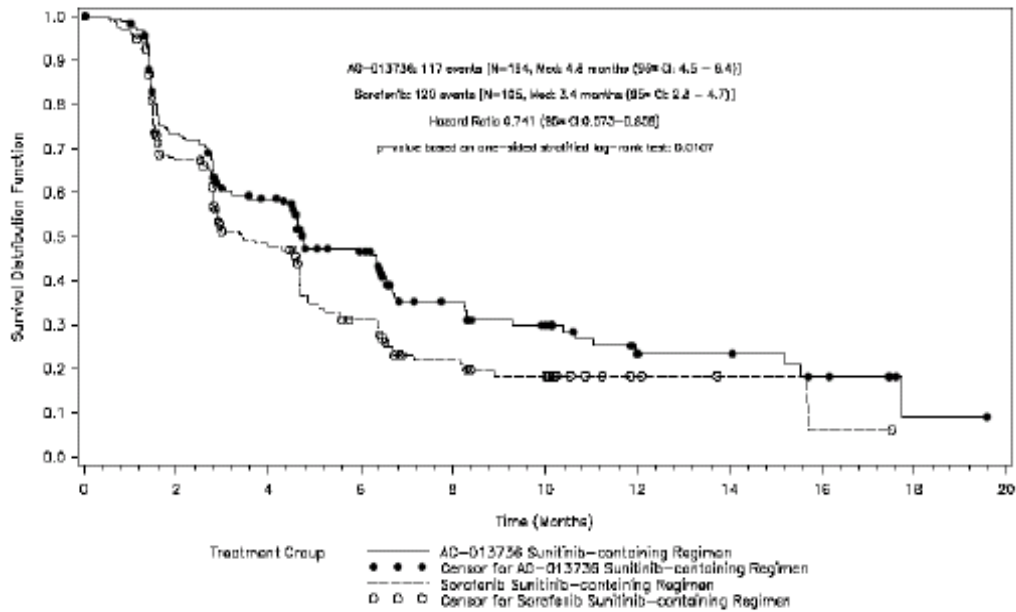
The Kaplan-Meier curve of PFS based on overall stratified analysis is displayed in Figure 2.

**Figure 2. Study A4061032: Kaplan-Meier Curves of PFS, by Treatment, IRC Assessment (FAS)**

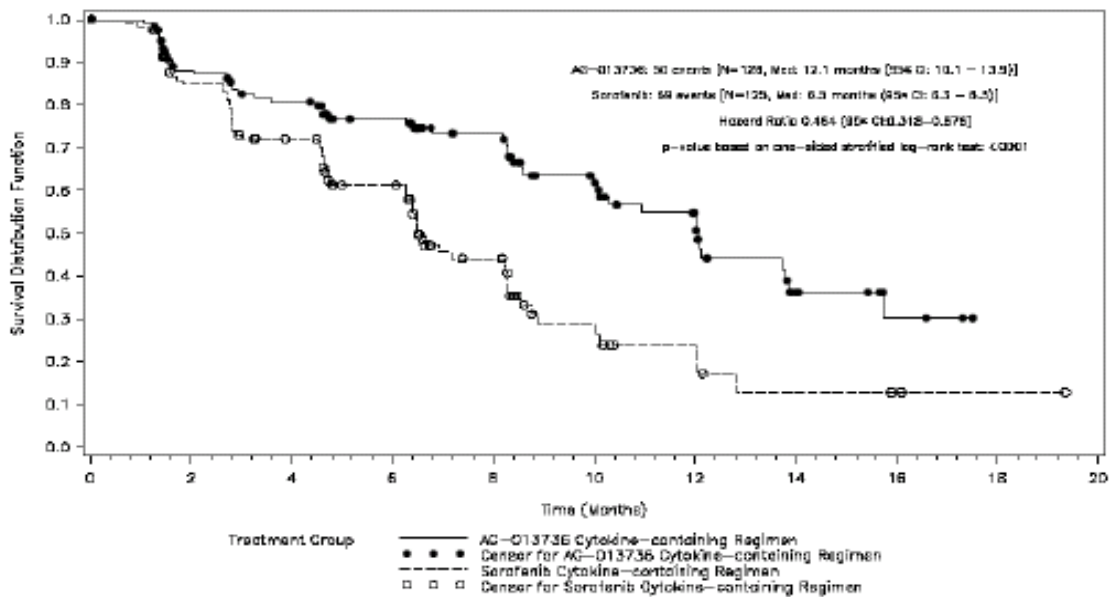


The Kaplan-Meier curve of PFS based on prior sunitinib-containing regimen and prior cytokine-containing regimen (stratified by ECOG-PS) are displayed in Figures 3 and 4

**Figure 3. Study A4061032: Kaplan-Meier Curves of PFS, by Treatment and Prior Sunitinib-Containing Regimen, IRC Assessment (FAS)**



**Figure 4. Study A4061032: Kaplan-Meier Curves of PFS, by Treatment and Prior Cytokine-Containing Regimen, IRC Assessment (FAS)**



The applicant also submitted the results of an updated PFS analysis with a cut-off date of 3 June 2011, which are summarised in table 16.

**Table 16. Pivotal Study A4061032: Summary of PFS by Treatment and Stratification Factor, Stratified Analysis, IRC Assessment (FAS); (Cut-off Date 03 June 2011)**

| <b>Progression-Free Survival Parameter</b>                                   | <b>Axitinib<br/>(N = 361)</b> | <b>Sorafenib<br/>(N = 362)</b> |
|------------------------------------------------------------------------------|-------------------------------|--------------------------------|
| <b>Overall stratified analysis (N)</b>                                       | 361                           | 362                            |
| Progression Status [n (%)]                                                   |                               |                                |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 239 (66.2)                    | 241 (66.6)                     |
| Objective progression observed                                               | 226 (94.6)                    | 231 (95.9)                     |
| Death without objective progression                                          | 13 (5.4)                      | 10 (4.1)                       |
| Subject did not progress or die due to any cause while on study <sup>a</sup> | 122 (33.8)                    | 121 (33.4)                     |
| Progression-free survival (months)                                           |                               |                                |
| Quartiles (95% CI) <sup>b</sup>                                              |                               |                                |
| 25%                                                                          | 2.7 (1.7, 2.9)                | 2.5 (1.6, 2.8)                 |
| 50% (median)                                                                 | 6.8 (6.4, 8.3)                | 4.7 (4.6, 6.3)                 |
| 75%                                                                          | 15.7 (13.2, 18.0)             | 8.9 (8.2, 10.4)                |
| Axitinib vs. sorafenib                                                       |                               |                                |
| Hazard ratio <sup>c</sup> (95% CI)                                           | 0.670 (0.558, 0.805)          | NA                             |
| p-value <sup>d</sup>                                                         | <0.0001                       | NA                             |
| <b>Prior sunitinib-containing regimen (N)</b>                                | 194                           | 195                            |
| Progression Status [n (%)]                                                   |                               |                                |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 137 (70.6)                    | 133 (68.2)                     |
| Objective progression observed                                               | 128 (93.4)                    | 127 (95.5)                     |
| Death without objective progression                                          | 9 (6.6)                       | 6 (4.5)                        |
| Subject did not progress or die due to any cause while on study <sup>a</sup> | 57 (29.4)                     | 62 (31.8)                      |
| Progression-free survival (months)                                           |                               |                                |
| Quartiles (95% CI) <sup>b</sup>                                              |                               |                                |
| 25%                                                                          | 1.7 (1.5, 2.8)                | 1.5 (1.5, 2.0)                 |
| 50% (median)                                                                 | 4.8 (4.5, 6.5)                | 3.4 (2.8, 4.7)                 |
| 75%                                                                          | 12.0 (8.3, 15.5)              | 6.5 (5.6, 8.5)                 |
| Axitinib vs. sorafenib                                                       |                               |                                |
| Hazard ratio <sup>c</sup> (95% CI)                                           | 0.736 (0.578, 0.937)          | NA                             |
| p-value <sup>e</sup>                                                         | 0.0063                        | NA                             |
| <b>Prior cytokine-containing regimen (N)</b>                                 | 126                           | 125                            |
| Progression Status [n (%)]                                                   |                               |                                |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 72 (57.1)                     | 84 (67.2)                      |
| Objective progression observed                                               | 69 (95.8)                     | 80 (95.2)                      |
| Death without objective progression                                          | 3 (4.2)                       | 4 (4.8)                        |
| Subject did not progress or die due to any cause while on study <sup>a</sup> | 54 (42.9)                     | 41 (32.8)                      |
| Progression-free survival (months)                                           |                               |                                |
| Quartiles (95% CI) <sup>b</sup>                                              |                               |                                |
| 25%                                                                          | 4.7 (2.9, 8.3)                | 2.8 (2.7, 4.7)                 |
| 50% (median)                                                                 | 12.0 (10.1, 13.9)             | 6.6 (6.4, 8.3)                 |
| 75%                                                                          | 21.5 (15.9, 24.8)             | 11.5 (9.6, 12.9)               |
| Axitinib vs. sorafenib                                                       |                               |                                |
| Hazard ratio <sup>c</sup> (95% CI)                                           | 0.519 (0.375, 0.720)          | NA                             |
| p-value <sup>e</sup>                                                         | <0.0001                       | NA                             |
| <b>Prior bevacizumab-containing regimen (N)</b>                              | 29                            | 30                             |
| Progression Status [n (%)]                                                   |                               |                                |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 23 (79.3)                     | 17 (56.7)                      |
| Objective progression observed                                               | 23 (100.0)                    | 17 (100.0)                     |
| Death without objective progression                                          | 0                             | 0                              |
| Subject did not progress or die due to any cause while on study <sup>a</sup> | 6 (20.7)                      | 13 (43.3)                      |
| Progression-free survival (months)                                           |                               |                                |
| Quartiles (95% CI) <sup>b</sup>                                              |                               |                                |
| 25%                                                                          | 1.7 (1.4, 3.8)                | 2.8 (2.5, 4.5)                 |
| 50% (median)                                                                 | 4.2 (2.8, 6.6)                | 4.5 (2.8, 6.5)                 |
| 75%                                                                          | 6.8 (4.8, 15.7)               | 6.7 (4.5, NE)                  |
| Axitinib vs. sorafenib                                                       |                               |                                |
| Hazard ratio <sup>c</sup> (95% CI)                                           | 1.047 (0.550, 1.993)          | NA                             |
| p-value <sup>e</sup>                                                         | 0.5340                        | NA                             |
| <b>Prior temsirolimus-containing regimen (N)</b>                             | 12                            | 12                             |

| Progression-Free Survival Parameter                                          | Axitinib<br>(N = 361) | Sorafenib<br>(N = 362) |
|------------------------------------------------------------------------------|-----------------------|------------------------|
| Progression Status [n (%)]                                                   |                       |                        |
| Subject progressed or died due to any cause while on study <sup>a</sup>      | 7 (58.3)              | 7 (58.3)               |
| Objective progression observed                                               | 6 (85.7)              | 7 (100.0)              |
| Death without objective progression                                          | 1 (14.3)              | 0                      |
| Subject did not progress or die due to any cause while on study <sup>a</sup> | 5 (41.7)              | 5 (41.7)               |
| Progression-free survival (months)                                           |                       |                        |
| Quartiles (95% CI) <sup>b</sup>                                              |                       |                        |
| 25%                                                                          | 1.5 (1.5, 10.2)       | 1.5 (1.3, 5.3)         |
| 50% (median)                                                                 | 10.1 (1.5, 19.0)      | 5.3 (1.5, 10.1)        |
| 75%                                                                          | 10.2 (10.1, 19.0)     | 10.1 (2.8, 10.1)       |
| Axitinib vs. sorafenib                                                       |                       |                        |
| Hazard ratio <sup>c</sup> (95% CI)                                           | 0.446 (0.127, 1.565)  | NA                     |
| p-value <sup>e</sup>                                                         | 0.0922                | NA                     |

Data cutoff date: 03 June 2011

Abbreviations: CI=confidence interval; IRC=independent review committee; N=number of subjects; n=number of subjects meeting specified criteria; NA=not applicable; NE=not estimable

<sup>a</sup> On study includes treatment plus 28-day follow-up period.

<sup>b</sup> Based on the Brookmeyer and Crowley method

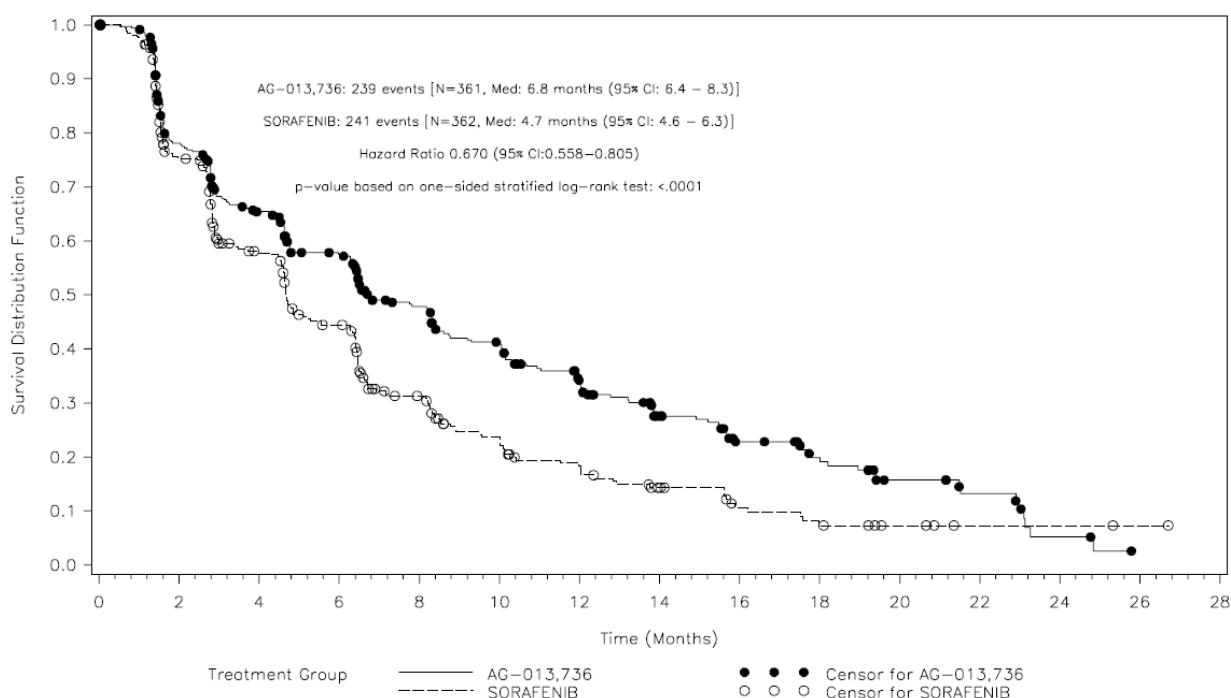
<sup>c</sup> Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test.

<sup>d</sup> For the Overall Stratified Analysis, the p-value was from a 1-sided log-rank test stratified by ECOG performance status and prior treatment regimen. Note, p-value is for descriptive purposes only as the final analysis of PFS has already occurred.

<sup>e</sup> P-value was from a 1-sided log-rank test stratified by ECOG performance status. Note, p-value is for descriptive purposes only as the final analysis of PFS has already occurred.

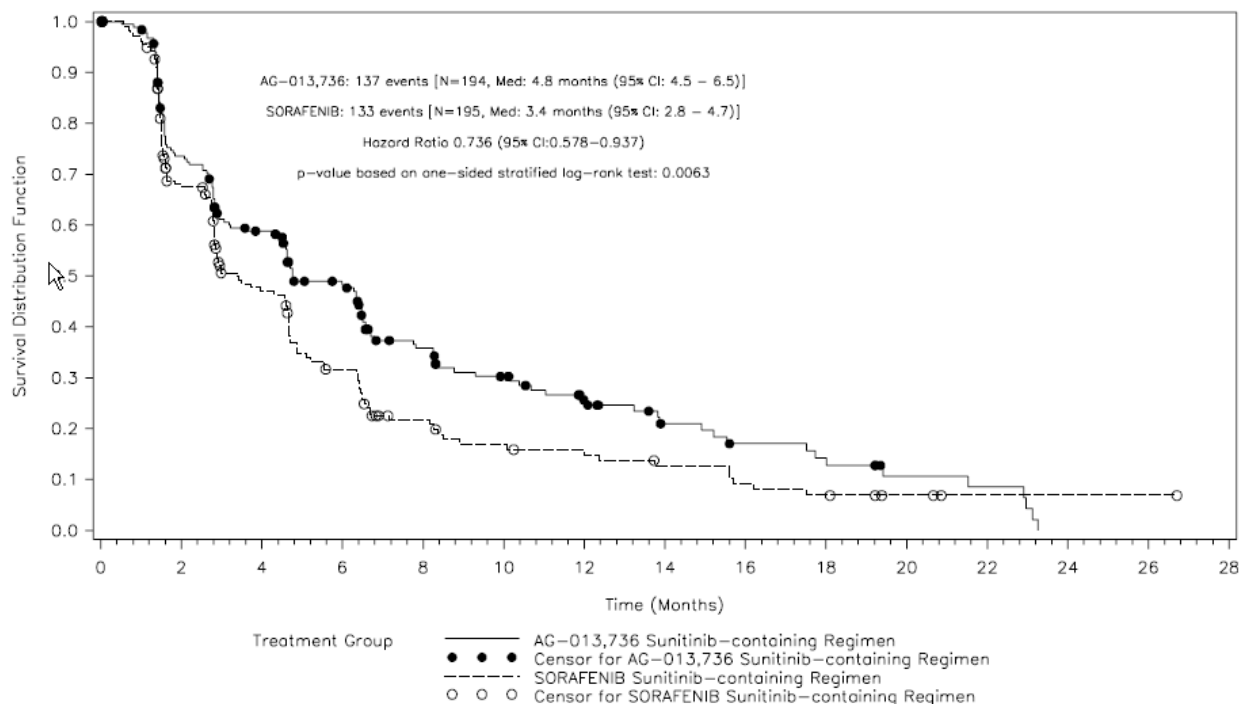
The Kaplan-Meier curve of PFS based on overall stratified analysis is displayed in Figure 5.

**Figure 5. Study A4061032: Kaplan-Meier Curves of PFS, by Treatment, IRC Assessment (FAS) (Cut-off Date 03 June 2011)**



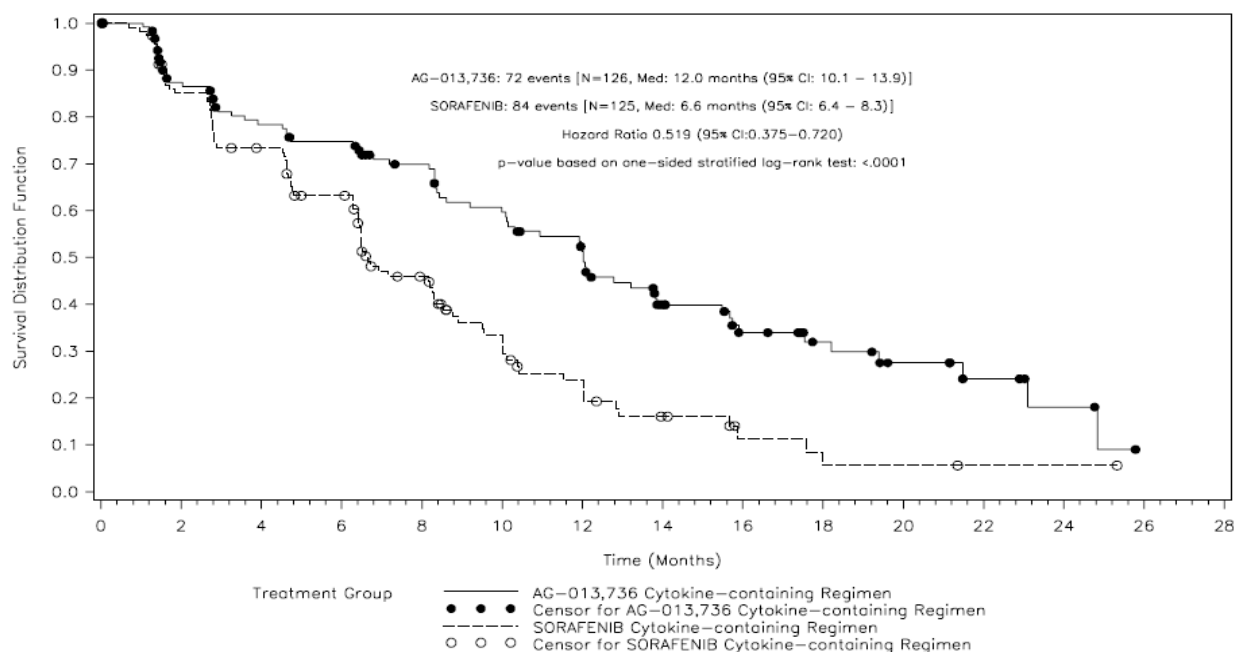
The Kaplan-Meier curve of PFS based on prior sunitinib-containing regimen (stratified by ECOG-PS) is displayed in Figure 6.

**Figure 6. Study A4061032: Kaplan-Meier Curves of PFS, by Treatment and Prior Sunitinib-Containing Regimen, IRC Assessment (FAS) (Cut-off Date 03 June 2011)**



The Kaplan-Meier curve of PFS based on prior cytokine-containing regimen (stratified by ECOG-PS) is displayed in Figure 7.

**Figure 7. Study A4061032: Kaplan-Meier Curves of PFS, by Treatment and Prior cytokine-Containing Regimen, IRC Assessment (FAS) (Cut-off Date 03 June 2011)**



### Key secondary endpoints

- **Overall survival**

The efficacy results of OS for the updated analysis of 1 November 2011 are summarised in table 17 and figure 8.

**Table 17. Pivotal Phase 3 RCC Study A4061032: Summary of Final Analysis of OS by Treatment and Stratification Factor; Stratified Analysis – FAS (Cut-off date 01 November 2011)**

| <b>Overall Survival Parameter</b>                                      | <b>Axitinib<br/>N=361<br/>n (%)</b> | <b>Sorafenib<br/>N=362<br/>n (%)</b> |
|------------------------------------------------------------------------|-------------------------------------|--------------------------------------|
| <b>Overall stratified analysis (n)</b>                                 | <b>361</b>                          | <b>362</b>                           |
| Dead                                                                   | 211 (58.4)                          | 214 (59.1)                           |
| Cause of death                                                         |                                     |                                      |
| Disease under study                                                    | 179 (84.8)                          | 175 (81.8)                           |
| Study treatment toxicity                                               | 0                                   | 2 (<1.0)                             |
| Unknown                                                                | 16 (7.6)                            | 25 (11.7)                            |
| Other                                                                  | 16 (7.6)                            | 12 (5.6)                             |
| Alive <sup>a</sup>                                                     | 150 (41.6)                          | 148 (40.9)                           |
| Reason for censorship                                                  |                                     |                                      |
| Alive                                                                  | 136 (90.7)                          | 134 (90.5)                           |
| Patients no longer willing to participate                              | 3 (2.0)                             | 7 (4.7)                              |
| Lost to follow-up                                                      | 11 (7.3)                            | 7 (4.7)                              |
| Survival probability at Month 12 (95% CI) <sup>b</sup>                 | 67.1% (62.0%, 71.7%)                | 68.2% (63.1%, 72.7%)                 |
| Kaplan-Meier estimates of time to event (months)                       |                                     |                                      |
| Quartile (95% CI) <sup>c</sup>                                         |                                     |                                      |
| 25%                                                                    | 8.9 (7.2, 10.6)                     | 9.3 (7.9, 10.8)                      |
| 50%                                                                    | 20.1 (16.7, 23.4)                   | 19.2 (17.5, 22.3)                    |
| 75%                                                                    | 34.6 (31.6, NE)                     | 34.5 (31.9, 35.0)                    |
| Axitinib vs sorafenib                                                  |                                     |                                      |
| Hazard ratio <sup>d</sup>                                              | 0.969                               |                                      |
| 95% CI of hazard ratio                                                 | 0.800-1.174                         |                                      |
| P-value <sup>e</sup>                                                   | 0.3744                              |                                      |
| <b>Stratification category: prior sunitinib-containing regimen (n)</b> | <b>194</b>                          | <b>195</b>                           |
| Dead                                                                   | 131 (67.5)                          | 131 (67.2)                           |
| Cause of death                                                         |                                     |                                      |
| Disease under study                                                    | 115 (87.8)                          | 111 (84.7)                           |
| Study treatment toxicity                                               | 0                                   | 1 (<1.0)                             |
| Unknown                                                                | 6 (4.6)                             | 12 (9.2)                             |
| Other                                                                  | 10 (7.6)                            | 7 (5.3)                              |
| Alive <sup>a</sup>                                                     | 63 (32.5)                           | 64 (32.8)                            |
| Reason for censorship                                                  |                                     |                                      |
| Alive                                                                  | 56 (88.9)                           | 59 (92.2)                            |
| Patients no longer willing to participate                              | 3 (4.8)                             | 3 (4.7)                              |
| Lost to follow-up                                                      | 4 (6.3)                             | 2 (3.1)                              |
| Survival probability at Month 12 (95% CI) <sup>b</sup>                 | 59.8% (52.5%, 66.3%)                | 61.8% (54.5%, 68.2%)                 |
| Kaplan-Meier estimates of time to event (months)                       |                                     |                                      |
| Quartile (95% CI) <sup>c</sup>                                         |                                     |                                      |
| 25%                                                                    | 7.0 (6.4, 9.1)                      | 7.5 (6.0, 10.0)                      |
| 50%                                                                    | 15.2 (12.8, 18.3)                   | 16.5 (13.7, 19.2)                    |
| 75%                                                                    | 32.4 (24.4, NE)                     | 35.0 (24.0, 35.0)                    |
| Axitinib vs sorafenib                                                  |                                     |                                      |
| Hazard ratio <sup>d</sup>                                              | 0.997                               |                                      |
| 95% CI of hazard ratio                                                 | 0.782-1.270                         |                                      |
| P-value <sup>e</sup>                                                   | 0.4902                              |                                      |
| <b>Stratification category: prior cytokine-containing regimen (n)</b>  | <b>126</b>                          | <b>125</b>                           |
| Dead                                                                   | 51 (40.5)                           | 57 (45.6)                            |
| Cause of death                                                         |                                     |                                      |
| Disease under study                                                    | 37 (72.5)                           | 42 (73.7)                            |
| Study treatment toxicity                                               | 0                                   | 1 (1.8)                              |
| Unknown                                                                | 9 (17.6)                            | 10 (17.5)                            |
| Other                                                                  | 5 (9.8)                             | 4 (7.0)                              |
| Alive <sup>a</sup>                                                     | 75 (59.5)                           | 68 (54.4)                            |
| Reason for censorship                                                  |                                     |                                      |
| Alive                                                                  | 69 (92.0)                           | 61 (89.7)                            |
| Patients no longer willing to participate                              | 0                                   | 3 (4.4)                              |

| Overall Survival Parameter                             | Axitinib<br>N=361<br>n (%) | Sorafenib<br>N=362<br>n (%) |
|--------------------------------------------------------|----------------------------|-----------------------------|
| Lost to follow-up                                      | 6 (8.0)                    | 4 (5.9)                     |
| Survival probability at Month 12 (95% CI) <sup>b</sup> | 82.3% (74.4%, 87.9%)       | 80.5% (72.4%, 86.5%)        |
| Kaplan-Meier estimates of time to event (months)       |                            |                             |
| Quartile (95% CI) <sup>c</sup>                         |                            |                             |
| 25%                                                    | 15.9 (13.1, 22.5)          | 13.8 (11.7, 18.0)           |
| 50%                                                    | 29.4 (24.5, NE)            | 27.8 (23.1, 34.5)           |
| 75%                                                    | NE (31.6, NE)              | 34.5 (31.9, 34.5)           |
| Axitinib vs sorafenib                                  |                            |                             |
| Hazard ratio <sup>d</sup>                              | 0.813                      |                             |
| 95% CI of hazard ratio                                 | 0.555-1.191                |                             |
| P-value <sup>e</sup>                                   | 0.1435                     |                             |

Data cutoff date: 01 November 2011

Abbreviations: CI = confidence interval; N = number of patients; n = number of patients meeting specified criteria; NE = not estimable

<sup>a</sup> Patients who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

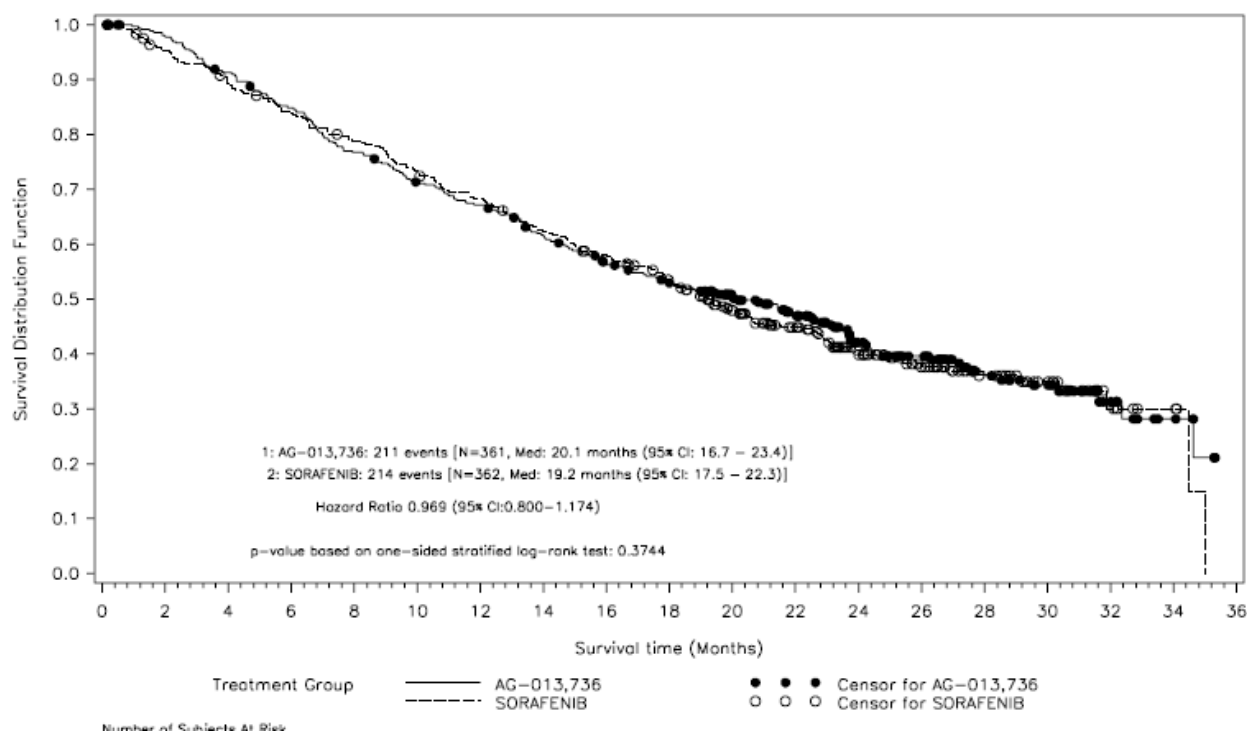
<sup>b</sup> Calculated from the log(-log[12-month survival probability]) using a normal approximation and back transformation.

<sup>c</sup> Based on the Brookmeyer and Crowley method.

<sup>d</sup> Assuming proportional hazards model, 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.

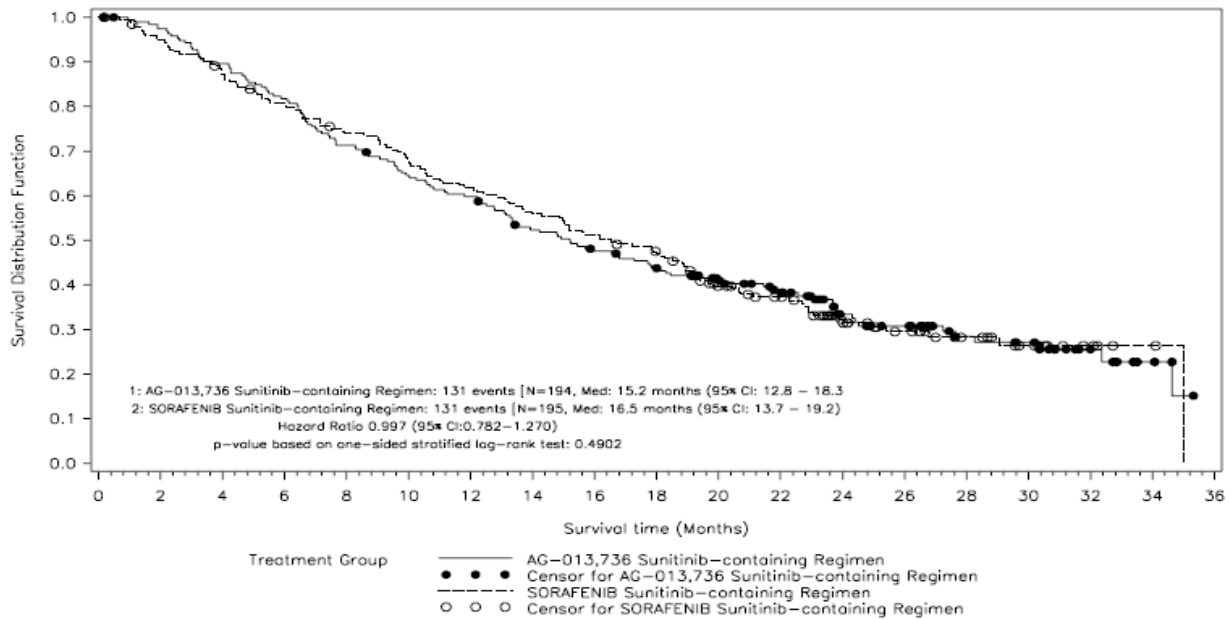
<sup>e</sup> For overall stratified analysis, p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status and prior treatment. For the population with prior treatment, the p-value was from a 1-sided log-rank test stratified by ECOG performance status.

**Figure 8. Pivotal Phase 3 RCC Study A4061032: Kaplan-Meier Curves of OS by Treatment (FAS); (Cut-off Date 01 November 2011)**

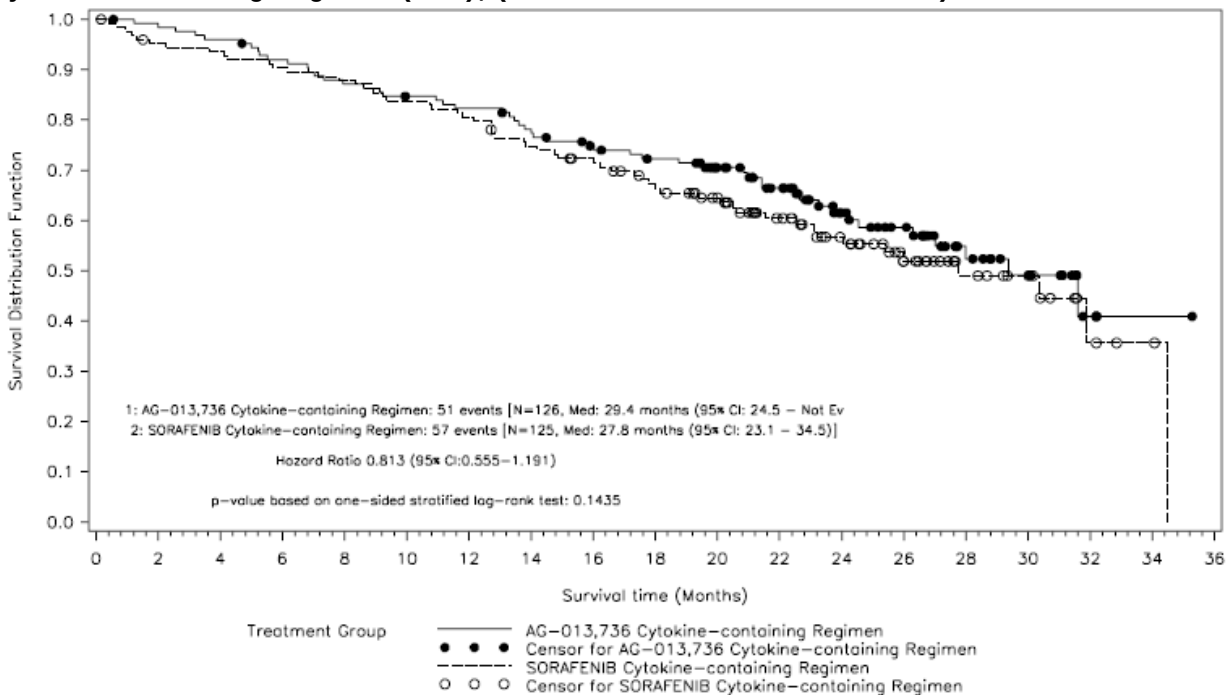


The Kaplan-Meier plots of OS based on prior sunitinib- and cytokine-containing regimen are displayed in Figures 9 and 10 respectively.

**Figure 9. Pivotal Phase 3 RCC Study A4061032: Kaplan-Meier Curves of OS by Treatment and Prior Sunitinib-Containing Regimen (FAS); (Cut-off Date 01 November 2011)**



**Figure 10. Pivotal Study A4061032: Kaplan-Meier Curves of OS by Treatment and Prior Cytokine-Containing Regimen (FAS); (Cut-off Date 01 November 2011)**



- **Objective Response Rate**

The ORR results are presented in Table 18.

**Table 18. Pivotal Study A4061032: Summary of Best Overall Tumour Response by Treatment (FAS) (Cut-off Date 31 August 2010)**

| <b>Best Overall Response Parameter</b>              | <b>Axitinib<br/>(N = 361)</b> | <b>Sorafenib<br/>(N = 362)</b> |
|-----------------------------------------------------|-------------------------------|--------------------------------|
| <b>IRC Assessment</b>                               |                               |                                |
| <b>Overall stratified analysis (n)</b>              | <b>361</b>                    | <b>362</b>                     |
| Subjects with baseline assessment, n (%)            | 360 (99.7)                    | 359 (99.2)                     |
| Subjects with measurable disease at baseline, n (%) | 350 (97.0)                    | 349 (96.4)                     |
| Best overall response, n (%)                        |                               |                                |
| Complete response                                   | 0 (0.0)                       | 0 (0.0)                        |
| Partial response                                    | 70 (19.4)                     | 34 (9.4)                       |
| Stable disease (≥20 weeks)                          | 96 (26.6)                     | 77 (21.3)                      |
| Stable disease (<20 weeks)                          | 84 (23.3)                     | 120 (33.1)                     |
| Progressive disease                                 | 78 (21.6)                     | 76 (21.0)                      |
| Not assessed / Indeterminate                        | 22 (6.1)                      | 42 (11.6)                      |
| Overall confirmed objective response rate (CR+PR)   | 70 (19.4)                     | 34 (9.4)                       |
| 95% exact CI <sup>a</sup>                           | 15.4%, 23.9%                  | 6.6%, 12.9%                    |
| Treatment comparison (axitinib vs. sorafenib)       |                               |                                |
| Risk ratio <sup>b</sup>                             | 2.056                         |                                |
| 95% CI of risk ratio <sup>b</sup>                   | 1.408, 3.003                  |                                |
| P-value <sup>c</sup>                                | 0.0001                        |                                |
| <b>Prior sunitinib-containing regimen (n)</b>       | <b>194</b>                    | <b>195</b>                     |
| Subjects with baseline assessment, n (%)            | 194 (100.0)                   | 194 (99.5)                     |
| Subjects with measurable disease at baseline, n (%) | 194 (100.0)                   | 193 (99.0)                     |
| Best overall response, n (%)                        |                               |                                |
| Complete response                                   | 0 (0.0)                       | 1 (0.5)                        |
| Partial response                                    | 25 (12.9)                     | 16 (8.2)                       |
| Stable disease (≥20 weeks)                          | 66 (34.0)                     | 38 (19.5)                      |
| Stable disease (<20 weeks)                          | 52 (26.8)                     | 62 (31.8)                      |
| Progressive disease                                 | 37 (19.1)                     | 50 (25.6)                      |
| Not assessed / Indeterminate                        | 14 (7.2)                      | 26 (13.3)                      |
| Overall confirmed objective response rate % (CR+PR) | 25 (12.9)                     | 17 (8.7)                       |
| 95% exact CI <sup>a</sup>                           | 8.5%, 18.4%                   | 5.2%, 13.6%                    |
| Treatment comparison (axitinib vs. sorafenib)       |                               |                                |
| Risk ratio <sup>b</sup>                             | 1.48                          |                                |
| 95% CI of risk ratio <sup>b</sup>                   | 0.827, 2.649                  |                                |
| P-value <sup>d</sup>                                | 0.0921                        |                                |
| <b>Prior cytokine-containing regimen (n)</b>        | <b>126</b>                    | <b>125</b>                     |
| Subjects with baseline assessment, n (%)            | 126 (100.0)                   | 124 (99.2)                     |
| Subjects with measurable disease at baseline, n (%) | 126 (100.0)                   | 124 (99.2)                     |
| Best overall response, n (%)                        |                               |                                |
| Complete response                                   | 0 (0.0)                       | 0 (0.0)                        |
| Partial response                                    | 45 (35.7)                     | 21 (16.8)                      |
| Stable disease (≥20 weeks)                          | 39 (31.0)                     | 51 (40.8)                      |
| Stable disease (<20 weeks)                          | 25 (19.8)                     | 34 (27.2)                      |
| Progressive disease                                 | 10 (7.9)                      | 9 (7.2)                        |
| Not assessed / Indeterminate                        | 7 (5.6)                       | 9 (7.2)                        |
| Overall confirmed objective response rate % (CR+PR) | 45 (35.7)                     | 21 (16.8)                      |
| 95% exact CI <sup>a</sup>                           | 27.4%, 44.7%                  | 10.7%, 24.5%                   |
| Treatment comparison (axitinib vs. sorafenib)       |                               |                                |
| Risk ratio <sup>b</sup>                             | 2.127                         |                                |
| 95% CI of risk ratio <sup>b</sup>                   | 1.35, 3.352                   |                                |
| P-value <sup>d</sup>                                | 0.0003                        |                                |

<sup>a</sup> Using exact method based on F-distribution

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

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

<sup>d</sup> P-value is from a 1-sided Cochran-Mantel-Haenszel test stratified by ECOG performance status.

## • Duration of response

Based on blinded IRC assessment, the median DR in the axitinib arm was 11 months (95% CI;7.4, not estimable) compared with 10.6 months in the sorafenib arm (95% CI ; 8.8, 11.5) (data not shown).

### Other secondary endpoints

There were no statistically significant differences in the results of the analysis of the FKSI-15 or the EQ-5D self reported health status measure between the two treatment arms (data not shown).

### Ancillary analyses

No ancillary analyses were submitted.

### Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 19. Summary of Efficacy for trial A4061032**

|                                                                                                                                                                                                                                                                                                          |                                            |                                 |                                                                                                                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><u>Title:</u></b> A Phase III, Randomised, open-label, 2-arm, multicenter study of axitinib vs sorafenib in patients with mRCC following failure of 1 prior systemic first-line regimen containing 1 or more of the following: sunitinib, bevacizumab + IFN- $\alpha$ , temsirolimus, or cytokine(s). |                                            |                                 |                                                                                                                                                                                                                                                       |
| Study identifier                                                                                                                                                                                                                                                                                         | A 406 1032, NCT00678392                    |                                 |                                                                                                                                                                                                                                                       |
| Design                                                                                                                                                                                                                                                                                                   | multicenter, randomised, open-label, 2-arm |                                 |                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                          | Duration of main phase:                    |                                 | Until disease progression, unacceptable toxicity or withdrawal of consent                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                          | Duration of Run-in phase:                  |                                 | not applicable                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                          | Duration of Extension phase:               |                                 | not applicable                                                                                                                                                                                                                                        |
| Hypothesis                                                                                                                                                                                                                                                                                               | Superiority                                |                                 |                                                                                                                                                                                                                                                       |
| Treatments groups                                                                                                                                                                                                                                                                                        | Axitinib                                   |                                 | 5 mg twice daily taken orally with food, doses taken 12 hours apart as continuous dosing at the same times each day. If well tolerated for 2 week period, dose could have been increased to 10 mg BID, at investigating physician discretion (N=359 ) |
|                                                                                                                                                                                                                                                                                                          | Sorafenib                                  |                                 | 400 mg twice daily continuously without food (at least 1 h before or 2 hours after eating); doses taken 12 hours apart as continuous dosing at the same times each day (N=355 )                                                                       |
| Endpoints and definitions                                                                                                                                                                                                                                                                                | Primary endpoint                           | Progression-free survival (PFS) | Time from randomisation to first progression to first documentation of objective tumour progression or to death due to any cause, whichever occurred first based on IRC assessment                                                                    |
|                                                                                                                                                                                                                                                                                                          | Secondary endpoint                         | Overall response rate (ORR)     | Percent of patients with confirmed complete response (CR) or partial response (PR) according to RECIST                                                                                                                                                |
| Database lock                                                                                                                                                                                                                                                                                            | 11/11/2010                                 |                                 |                                                                                                                                                                                                                                                       |
| <b><u>Results and Analysis</u></b>                                                                                                                                                                                                                                                                       |                                            |                                 |                                                                                                                                                                                                                                                       |
| Analysis description                                                                                                                                                                                                                                                                                     | Primary Analysis                           |                                 |                                                                                                                                                                                                                                                       |

|                                                 |                                                                                                                                                                                                                                                                                                                    |                             |                       |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-----------------------|
| Analysis population and time point description  | Full Analysis Set (the FA set included all subjects who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether subjects received study drug or received a different drug from that to which they were randomised) , 11/11/2010 (402 PFS events observed) |                             |                       |
| Descriptive statistics and estimate variability | Treatment group                                                                                                                                                                                                                                                                                                    | Axitinib                    | Sorafenib             |
|                                                 | Number of subject                                                                                                                                                                                                                                                                                                  | 361                         | 362                   |
|                                                 | PFS (median, in months)                                                                                                                                                                                                                                                                                            | 6.7                         | 4.7                   |
|                                                 | 95% CI                                                                                                                                                                                                                                                                                                             | (6.3, 8.6)                  | (4.6, 5.6)            |
|                                                 | ORR [No. (%)]                                                                                                                                                                                                                                                                                                      | 70 (19.4)                   | 34 (9.4)              |
|                                                 | 95% CI                                                                                                                                                                                                                                                                                                             | (15.4, 23.9)                | (6.6, 12.9)           |
|                                                 | Median duration of response (months)                                                                                                                                                                                                                                                                               | 11.0                        | 10.6                  |
|                                                 | 95% CI                                                                                                                                                                                                                                                                                                             | (7.4, not estimable)        | (8.8, 11.5)           |
| Effect estimate per comparison                  | Primary endpoint PFS                                                                                                                                                                                                                                                                                               | Comparison groups           | Axitinib vs Sorafenib |
|                                                 |                                                                                                                                                                                                                                                                                                                    | HR                          | 0.665                 |
|                                                 |                                                                                                                                                                                                                                                                                                                    | 95% CI                      | (0.544, 0.812)        |
|                                                 |                                                                                                                                                                                                                                                                                                                    | Stratified log-rank p-value | <0.0001               |
| Notes                                           | Stratification factors for the primary analysis (logrank): ECOG performance status and prior treatment                                                                                                                                                                                                             |                             |                       |

## Analysis performed across trials (pooled analyses and meta-analysis)

No analyses across trials were submitted.

## Clinical studies in special populations

No studies have been conducted in special populations.

## Supportive studies

The applicant has submitted three supportive Phase II studies (studies A406012, A4061023, and A4061035).

The Phase II studies were open-label, single-arm, multi-centre, clinical studies of single-agent axitinib in patients with advanced RCC. In study A4061012, a Simon's Minimax 2-stage design was used to test the alternative hypothesis that the true response rate was  $\geq 15\%$  versus the null hypothesis that the true ORR was  $\leq 5\%$ . In study A4061035, a single stage design was used to test the alternative hypothesis that the true response rate was  $\geq 25\%$  versus the null hypothesis that the true ORR was  $\leq 10\%$ . A single stage design was used in study A4061023 to test the alternative hypothesis that the true response rate was  $\geq 20\%$  versus the null hypothesis that the true ORR was  $\leq 8\%$ .

Subjects were to have a histologically- or cytologically proven diagnosis of advanced RCC. Study A4061035 (N=64) required that these tumours had a component of clear cell subtype. Studies A4061012 (N=52) and A4061035 enrolled subjects whose disease had progressed on or after treatment with cytokine-based therapy, while study A4061023 (N=62) enrolled subjects whose disease had progressed on or after treatment with sorafenib-based therapy. The majority of subjects were male in all 3 studies, and the majority of subjects had clear cell RCC. In Studies A4061012 and A4061023, most subjects were white, while in Study A4061035, all subjects were Japanese. A majority (>50%) of subjects had an ECOG-PS of 0 except in the sorafenib-refractory study A4061023 where the majority of subjects were ECOG performance status 1. Subjects were to have adequate organ functions and no evidence of uncontrolled hypertension.

All subjects received axitinib administered at a starting dose of 5 mg BID under fasting conditions in Study A4061012 and with food in Studies A4061023 and A4061035.

In Study A4061023 and A4061035, intra-subject dose escalations (up to a maximum of 10 mg BID) were permitted based on tolerability. Subjects who tolerated axitinib (no treatment related adverse events above Grade 2 for 2 consecutive weeks) could have their dose increased up to 7 mg BID and then to a maximum of 10 mg BID (unless the subject's BP was >150 mm Hg [systolic BP] or >90 mm Hg [diastolic BP] or the subject was receiving antihypertensive medication). Axitinib could be decreased due to toxicity to as low as 2 mg BID. In Study A4061012, a less aggressive form of dose escalation was implemented: patients who tolerated axitinib could have their dose increased by 20% after at least 8 weeks of treatment unless the subject was responding to therapy.

The primary endpoint for the studies was ORR according to RECIST based on tumour assessments performed every 8 weeks. Evaluation by a blinded IRC (independent review committee) was performed in Study A4061035. Secondary endpoints included PFS (analyzed post-hoc in Study A4061012); TTP (except in Study A4061023); DR; OS and PROs (patient reported outcomes) (except in Study A4061035).

## Results

An overall summary of efficacy results (except PROs) for the Phase II studies is provided in Table 20, and a comparison of the median PFS across the phase II and phase III studies is presented in Figure 11.

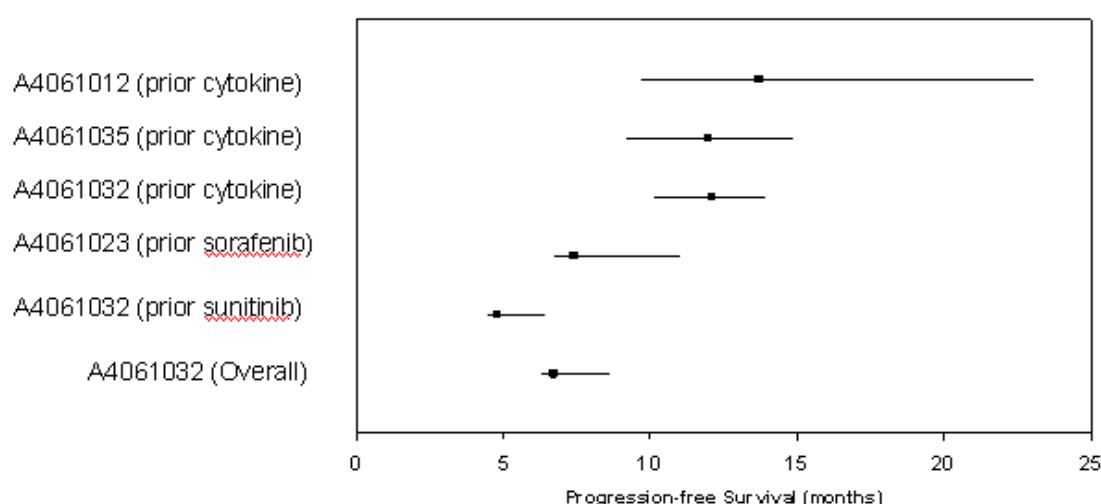
**Table 20: Summary of efficacy results for the Phase II studies**

| Parameter                       | A4061012 <sup>b</sup><br>N=52 | A4061035 <sup>b</sup><br>N=64 | A4061023 <sup>c</sup><br>N=62 |
|---------------------------------|-------------------------------|-------------------------------|-------------------------------|
| <b>ORR % (95 % CI)</b>          | 44.2 (30.5, 58.7)             | 54.7 (41.7, 67.2)             | 22.6 (12.9, 35.0)             |
| <b>Best overall response %:</b> |                               |                               |                               |
| Complete response (CR)          | 3.8                           | 0                             | 0                             |
| Partial response (PR)           | 40.4                          | 54.7                          | 22.6                          |
| Stable disease (SD)             | 25.0                          | 40.6                          | 17.7                          |
| Progressive disease (PD)        | 21.2                          | 1.6                           | 24.2                          |
| Indeterminate (INT)             | 3.8                           | 3.1                           | 12.9                          |
| Missing                         | 5.8                           | -                             | 22.6                          |
| <b>Progression status %</b>     |                               |                               |                               |
| Subject progressed or died      | 69.2                          | 59.4                          | 58.1                          |
| Subject did not progress or die | 30.8                          | 40.6                          | 41.9                          |
| <b>PFS (months)<sup>a</sup></b> |                               |                               |                               |
| Median (95% CI)                 | 13.7 (9.7, 23.0)              | 12.0 (9.2, 14.8)              | 7.4 (6.7, 11.0)               |
| <b>TTP (months)</b>             |                               |                               | -                             |

|                          |                  |                  |                  |
|--------------------------|------------------|------------------|------------------|
| Median (95% CI)          | 15.7 (8.4, 23.4) | 12.0 (9.2, 14.8) |                  |
| <b>DR (months)</b>       |                  |                  |                  |
| Median (95% CI)          | 23.0 (20.9, NE)  | 12.8 (7.7, 15.5) | 17.4 (7.4, NE)   |
| <b>Survival Status %</b> |                  |                  |                  |
| Died                     | 53.8             | -                | 72.6             |
| Still alive <sup>d</sup> | 46.2             | -                | 27.4             |
| <b>OS (months)</b>       |                  |                  |                  |
| Median (95% CI)          | 29.9 (20.3, NE)  | -                | 13.6 (8.4, 18.7) |

<sup>a</sup>Investigator assessments. <sup>b</sup>Cytokine refractory advanced RCC. <sup>c</sup>Sorafenib-refractory advanced RCC. <sup>d</sup> Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

**Figure 11: Comparison of Median PFS in Pivotal Study A4061032 with Supportive Studies A4061012, A4061035, and A4061023**



Patient reported outcomes were assessed in supportive Studies A4061012 and A4061023. In Study A4061012, there was little change from baseline in mean scores on the EORTC-QLQ C30 HRQoL results for up to 40 weeks of treatment. In study A4061023, axitinib had little effect on individual disease-related symptoms. In summary, the patients treated with axitinib generally maintain their HRQoL.

### 2.5.3. Discussion on clinical efficacy

#### Design and conduct of clinical studies

Dose-response studies have not been submitted by the applicant. The starting dose of axitinib of 5 mg BID was well justified based on determinations of tolerability in patients in early studies and on pharmacodynamic effects in clinical studies.

The open label design of the pivotal study was chosen due to known toxicity differences between axitinib and sorafenib, and also due to differences in dosing regimens between the axitinib and the sorafenib arm. The open design leads to an increased risk of bias. However, the primary analysis of PFS was based on a blinded IRC assessment.

The relevance of sorafenib as comparator has been questioned. Sorafenib has only been studied in patients who are cytokine refractory and should thus be considered an experimental treatment in patients previously treated with a TKI. In order to assess the efficacy of axitinib, inclusion of a placebo arm would have been informative to assess the efficacy of both sorafenib and axitinib in these

patients. However, many clinicians would have considered it unethical to use a placebo control at that point in time. Furthermore, it is recognized that sorafenib was the only available active comparator on the market at the time that the pivotal study was designed and initiated.

The overall design of the pivotal study, including the inclusion and exclusion criteria, is adequate. The distribution of demographics and baseline characteristics and also other important factors like previous malignancy and disease history were well balanced between arms. A predominance of men contra women, and white contra other races, characterised the study.

## **Efficacy data and additional analyses**

Results from the study revealed a median PFS of 6.7 months for the axitinib group and 4.7 months for the sorafenib group (HR: 0.665; 95% CI: 0.544, 0.812;  $p < 0.0001$ ). The benefit in PFS was confirmed in an updated analysis (cut-off of 3 June 2011), showing a median PFS of 6.8 months for the axitinib group versus 4.7 months for the sorafenib group (HR=0.670; 95% CI: 0.558, 0.805;  $p < 0.0001$ ).

The updated analysis of PFS according to subgroups of prior treatment based on blinded IRC, revealed a much lesser effect in the group with prior sunitinib regimen than in the prior cytokine group of patients. The difference in median PFS between the two arms in the prior sunitinib treated patients was 1.4 months (HR=0.74; 95% CI: 0.58, 0.94;  $p = 0.0063$ ), while in the prior cytokine treated patients the difference was much more pronounced with 5.4 months (HR= 0.52; 95% CI: 0.38, 0.72;  $p < 0.0001$ ).

The analysis of OS in the pivotal study gave no indication of any survival benefit of axitinib over sorafenib in the prior sunitinib group (HR=0.997; 95% CI: 0.78, 1.27) but a positive trend for OS was observed for axitinib over sorafenib in the prior cytokine group (HR= 0.813; 95% CI: 0.56, 1.19) with median OS of 29.4 months in the axitinib arm and 27.8 months in the sorafenib arm.

The analysis of ORR showed a statistically significant improvement of 13.9% for axitinib compared to sorafenib in patients pre-treated with cytokines. In the prior-sunitinib group, the difference in ORR between axitinib and sorafenib was 3.6%.

Duration of response and patient reported outcomes were only analysed for the overall study population. There were no differences in these endpoints between the axitinib and sorafenib study arms.

The group of patients previously treated with temsirolimus and bevacizumab+IFN- $\alpha$  are very small ( $n=25$  and  $n=59$ , respectively), and therefore no firm conclusions can be made regarding the efficacy in these subgroups.

However, the inconsistencies in the efficacy results of axitinib across the subpopulations based on prior therapy underscores that there is a need for a more precise definition of the patient populations benefiting from therapy with axitinib. Multiple agents for mRCC with overlapping mechanisms of action are presently being developed, but the rationale for selection of a second TKI is weak, and whether to select an mTOR instead of a TKI in second line treatment of RCC has not been thoroughly addressed. This further underlines the need of further research on predictive biomarkers. Therefore, the CHMP recommended that the applicant should investigate suitable biomarkers in metastatic RCC to allow identification and selection of a more targeted population of patients most likely to benefit from treatment with axitinib second line. This research is not expected to change the observed benefits but will provide further guidance on the treatment choice and will define better the therapeutic regimens. A report on the extended research program should be submitted within 3 months of the Commission Decision. Progress reports should be submitted on a yearly basis.

## **Additional expert consultation**

Following the CHMP request, a Scientific Advisory Group meeting was convened on 2 March 2012 to provide advice on the following list of questions:

### **1. Is sorafenib acceptable as comparator in the pivotal trial for axitinib?**

At the time that the pivotal trial was designed and initiated and based on the available knowledge at the time, sorafenib must be considered as a reasonable comparator. Although sorafenib was given in the trial in a non-approved indication (as second line treatment after first line sunitinib), it was also given in its approved indication (as second line treatment in patients who have failed prior interferon-alpha or interleukin-2 based therapy).

### **2. Is there a place for treatment with another VEGF-targeting TKI in the treatment of mRCC patients previously treated with sunitinib, e.g. in patients not suited for treatment with everolimus?**

It is indeed welcome to have an additional option in the treatment armamentarium of second line mRCC therapy, particularly since axitinib has a distinct toxicity profile compared to available medicines. Although the development of agents with overlapping mechanisms of action and hence activities gives more choices to the physician and the patient, there is still uncertainty about the therapeutic value of second line TKIs in mRCC after failure of first line sunitinib and important questions, such as whether TKIs or mTOR inhibitors should be the preferred choice for second line mRCC therapy, have not been answered. It is a major shortcoming of the concurrent development of multiple agents for mRCC in recent years that biomarkers have not been identified to help define target patient populations for each compound, or that comparative or combination trials have not been conducted to guide treatment choice and better define therapeutic regimens. This further underlines the need of further research, e.g. biomarker driven, as firmly underlined by the present, approved in 2006, and publicly available proposed-upcoming guidelines.

### **3. Is the observed PFS benefit of axitinib compared to sorafenib (+1.4 months in mPFS) in patients pre-treated with sunitinib considered clinically relevant given that no positive trend was observed for OS in this subpopulation?**

It is important to note that the comparison of axitinib in the pivotal trial was against an active comparator and that the median PFS in the axitinib arm was 4.8 months, which is considered clinically relevant. With regard to the 1.4 month difference in PFS compared to sorafenib, it is noted that, although small and clinically questionable, the difference was formally statistically significant, that the Hazard Ratio for the comparison was 0.74 and that the toxicity profile of axitinib was better than that of sorafenib. In absolute terms, the benefit-risk of axitinib in second line RCC treatment is therefore considered positive.

### **4. What is the relevance of an indication for axitinib restricted to patients previously treated with cytokines, considering the newer therapies now recommended for first line treatment of mRCC?**

Although the use of cytokines as first line RCC treatment may currently be more of a health economic issue, an indication for axitinib as second line treatment after failure of such cytokine therapy would still be of clinical use and it would serve clinical reality. However, there is no reason not to administer axitinib after first line sunitinib, as well, as the pivotal study was positive even in the subgroup of patients with prior sunitinib treatment. Overall, an indication in second line RCC after failure of prior sunitinib or cytokine treatment could be supported. There is not adequate information on the use of axitinib after first line bevacizumab or temsirolimus treatment.

#### **2.5.4. Conclusions on the clinical efficacy**

In conclusion, a clinically relevant effect of axitinib has been shown in the patients previously treated with sunitinib or a cytokine. Regarding the primary endpoint PFS, the magnitude of the observed effect (HR=0.736 in the prior-sunitinib group; HR=0.519 in the prior-cytokine group) is considered clinically significant. The robustness of the primary endpoint was supported by a positive trend on OS in the prior-cytokine group. In the prior-sunitinib group there was no indication of any survival benefit of axitinib over sorafenib, however, the PFS results were very consistent and robust in all pre-specified and exploratory sensitivity and subgroup analyses to support on overall favourable conclusion.

#### **2.6. Clinical safety**

The clinical program for axitinib included 31 completed studies and 10 ongoing studies at the time of the safety data cut-off date, 31 August 2010. The safety analyses presented are based on healthy volunteers and subjects with malignant disease who received axitinib in the completed clinical studies (including 2617 subjects). Separate analyses of critical safety data (demography, discontinuations, and SAEs including deaths) are available from ongoing clinical studies in subjects with solid tumours including a continued access study. In addition, SAEs, including deaths, are included from 4 IIR studies. There were 1067 subjects in ongoing studies at the date of cut-off.

A total of 3655 subjects (Phases I-III studies), were evaluated for safety, including 2507 (68.6%) who received at least one dose of axitinib, 994 (27.2%) who received a comparator and 154 (4.2%) reported as "blinded therapy". The studies included healthy volunteers (14 studies), subjects with hepatic impairment (1 study), subjects with haematological malignancies (1 study) and subjects with various solid tumours (15 completed and 10 ongoing studies).

Of the 2507 subjects who received at least one dose of axitinib, 885 subjects (35.3%) with various solid tumours received axitinib as a single agent (699 subjects in completed studies; 186 subjects in ongoing studies), and 1059 subjects (42.2%) received axitinib as a component of combination therapy. Of the remaining 563 axitinib-treated subjects, 16 subjects with advanced solid tumours received axitinib in a dose escalation study (A4060010), 12 subjects in a haematological malignancy study (A4061036), 24 received axitinib in the hepatic impairment study (A4061036), and 511 were healthy volunteers. As of the safety cut-off date, 154 subjects were being treated in an ongoing single-agent pivotal phase III RCC study in treatment-naïve subjects (A4061051), for which the data are provided under the heading "blinded therapy". A total of 699 subjects received single-agent axitinib in completed studies, including 537 (76.8%) subjects who received single-agent axitinib in the 4 completed advanced RCC studies (pivotal phase III Study A4061032, and supportive phase II Studies A4061012, A4061023, and A4061035). In addition, 24 subjects received axitinib in IIR studies.

All subjects receiving at least one dose of study medication with treatment assignments designated according to the actual study treatment received were included in the analysis of safety. The pooled safety analyses for completed single-agent studies included subjects who received a 5 mg BID starting doses of axitinib.

An updated cumulative safety analysis was provided by the applicant with a cut-off date 1 February 2011. The new analysis included safety data from 3944 subjects treated in 42 clinical trials. This analysis included only the information on the SAEs including deaths; no analysis of all causality AEs or treatment-related AEs was performed as of 01-Feb-2011.

## Patient exposure

The majority of the safety data presented is summarized according to the study cohorts shown in Table 21.

**Table 21. Overall number of subjects in the axitinib clinical program (cut-off date 1 February 2011)**

| Study Type                                              | Axitinib <sup>a</sup> | Comparator | Blinded Therapy |
|---------------------------------------------------------|-----------------------|------------|-----------------|
| Healthy Volunteer Studies                               | 511 <sup>L</sup>      |            |                 |
| Single-Agent Studies:                                   |                       |            |                 |
| Completed Single-Agent Studies in RC                    | 537                   | 355        | -               |
| Completed Single-Agent Studies                          | 699                   | 355        | -               |
| Ongoing Single-Agent Studies                            | 256                   | -          | 364             |
| Combination Studies:                                    |                       |            |                 |
| Completed Pancreatic Cancer Studies                     | 372                   | 340        | -               |
| Other Completed Combination Studies                     | 224                   | 56         | -               |
| Ongoing Combination Studies                             | 464                   | 243        | -               |
| Other Studies:                                          |                       |            |                 |
| Haematological Malignancy Study                         | 12                    | -          | -               |
| <i>Ongoing Continued Access Study</i>                   | 31                    | -          | -               |
| Hepatic Impairment Study                                | 24                    | -          | -               |
| Study A4060010 – Doses above 5 mg BID                   | 16                    |            |                 |
| Phase 1 portion of Completed Combination Study A4061016 | 8                     |            |                 |
| <b>TOTAL</b>                                            | <b>2586</b>           | <b>994</b> | <b>364</b>      |

## Adverse events

In the pivotal study, 95.3% of the patients in the axitinib arm and 97.7% of the patients in the sorafenib arm) in both treatment groups reported treatment-emergent AEs; most AEs were of Grade 1/2 severity, and AEs of Grade  $\geq 3$  were reported with lower but at similar rates for the axitinib (65.7%) and sorafenib (68.2%) treatment groups. Table 22 summarizes the most commonly reported AEs (all causality) in  $\geq 5\%$  (all grades) of subjects in either treatment group.

**Table 22. Treatment-Emergent, All-Causality Adverse Events Summarized by Maximum Severity Grade for  $\geq 5\%$  (All Grades; Decreasing Frequency) of Subjects in Either Treatment Group in Study A4061032 (cut-off date, 31 August 2010)**

| Preferred Term <sup>a</sup>                | Axitinib (N = 359)             |                                  | Sorafenib (N = 355)            |                                  |
|--------------------------------------------|--------------------------------|----------------------------------|--------------------------------|----------------------------------|
|                                            | Grade 3+ <sup>b</sup><br>n (%) | All Grades <sup>c</sup><br>n (%) | Grade 3+ <sup>b</sup><br>n (%) | All Grades <sup>c</sup><br>n (%) |
| <b>Any AEs</b>                             | 236 (65.7)                     | 342 (95.3)                       | 242 (68.2)                     | 347 (97.7)                       |
| Diarrhea                                   | 38 (10.6)                      | 197 (54.9)                       | 26 (7.3)                       | 189 (53.2)                       |
| Hypertension                               | 56 (15.6)                      | 145 (40.4)                       | 39 (11.0)                      | 103 (29.0)                       |
| Fatigue                                    | 41 (11.4)                      | 140 (39.0)                       | 18 (5.1)                       | 112 (31.5)                       |
| Decreased appetite                         | 18 (5.0)                       | 122 (34.0) <sup>d</sup>          | 13 (3.7)                       | 101 (28.5)                       |
| Nausea                                     | 9 (2.5)                        | 116 (32.3)                       | 4 (1.1)                        | 77 (21.7)                        |
| Dysphonia                                  | 0                              | 111 (30.9)                       | 0                              | 48 (13.5)                        |
| Palmar-plantar erythrodysesthesia syndrome | 18 (5.0)                       | 98 (27.3)                        | 57 (16.1)                      | 181 (51.0)                       |
| Weight decreased                           | 8 (2.2)                        | 89 (24.8)                        | 5 (1.4)                        | 74 (20.8)                        |
| Vomiting                                   | 12 (3.3)                       | 85 (23.7)                        | 3 (0.8)                        | 61 (17.2)                        |
| Asthenia                                   | 19 (5.3)                       | 74 (20.6)                        | 9 (2.5)                        | 50 (14.1)                        |
| Constipation                               | 4 (1.1)                        | 73 (20.3)                        | 3 (0.8)                        | 72 (20.3)                        |
| Hypothyroidism                             | 1 (0.3)                        | 69 (19.2)                        | 0                              | 29 (8.2)                         |
| Cough                                      | 3 (0.8)                        | 55 (15.3)                        | 2 (0.6)                        | 59 (16.6)                        |
| Mucosal inflammation                       | 5 (1.4)                        | 55 (15.3)                        | 2 (0.6)                        | 44 (12.4)                        |
| Arthralgia                                 | 7 (1.9)                        | 54 (15.0)                        | 5 (1.4)                        | 39 (11.0)                        |
| Stomatitis                                 | 5 (1.4)                        | 54 (15.0)                        | 1 (0.3)                        | 44 (12.4)                        |
| Dyspnea                                    | 9 (2.5)                        | 53 (14.8)                        | 10 (2.8)                       | 43 (12.1)                        |
| Abdominal pain                             | 8 (2.2)                        | 51 (14.2)                        | 3 (0.8)                        | 38 (10.7)                        |

|                                   | <b>Axitinib (N = 359)</b>   |                               | <b>Sorafenib (N= 355)</b>   |                               |
|-----------------------------------|-----------------------------|-------------------------------|-----------------------------|-------------------------------|
| Back pain                         | 9 (2.5)                     | 50 (13.9)                     | 6 (1.7)                     | 46 (13.0)                     |
| Headache                          | 2 (0.6)                     | 49 (13.6) <sup>d</sup>        | 0                           | 40 (11.3)                     |
| Pain in extremity                 | 2 (0.6)                     | 45 (12.5)                     | 2 (0.6)                     | 48 (13.5)                     |
| Rash                              | 1 (0.3)                     | 45 (12.5)                     | 14 (3.9)                    | 112 (31.5)                    |
| Proteinuria                       | 11 (3.1)                    | 39 (10.9)                     | 6 (1.7)                     | 26 (7.3)                      |
| Dysgeusia                         | 0                           | 38 (10.6)                     | 0                           | 29 (8.2)                      |
| Dry skin                          | 0                           | 36 (10.0)                     | 0                           | 38 (10.7)                     |
| Dyspepsia                         | 0                           | 36 (10.0)                     | 0                           | 8 (2.3)                       |
| Dizziness                         | 2 (0.6)                     | 33 (9.2)                      | 0                           | 15 (4.2)                      |
| Abdominal pain upper              | 3 (0.8)                     | 29 (8.1)                      | 1 (0.3)                     | 14 (3.9)                      |
| Insomnia                          | 0                           | 29 (8.1)                      | 0                           | 18 (5.1)                      |
| Myalgia                           | 3 (0.8)                     | 25 (7.0)                      | 0                           | 10 (2.8)                      |
| Pyrexia                           | 3 (0.8)                     | 25 (7.0)                      | 1 (0.3)                     | 37 (10.4)                     |
| Pruritus                          | 0                           | 24 (6.7)                      | 0                           | 44 (12.4)                     |
| Dehydration                       | 13 (3.6)                    | 23 (6.4)                      | 4 (1.1)                     | 9 (2.5)                       |
| Disease progression               | 23 (6.4)                    | 23 (6.4)                      | 14 (3.9)                    | 14 (3.9)                      |
| Epistaxis                         | 0                           | 22 (6.1)                      | 0                           | 15 (4.2)                      |
| Oropharyngeal pain                | 0                           | 20 (5.6)                      | 0                           | 19 (5.4)                      |
| Chest pain                        | 1 (0.3)                     | 19 (5.3)                      | 4 (1.1)                     | 16 (4.5)                      |
| Flatulence                        | 0                           | 19 (5.3)                      | 0                           | 8 (2.3)                       |
| Hypotension                       | 3 (0.8)                     | 19 (5.3)                      | 4 (1.1)                     | 10 (2.8)                      |
| Musculoskeletal pain              | 2 (0.6)                     | 19 (5.3)                      | 1 (0.3)                     | 21 (5.9)                      |
| Pain                              | 2 (0.6)                     | 18 (5.0) <sup>d</sup>         | 6 (1.7)                     | 15 (4.2)                      |
| Edema peripheral                  | 1 (0.3)                     | 17 (4.7)                      | 3 (0.8)                     | 20 (5.6)                      |
| <b>Preferred Term<sup>a</sup></b> | <b>Grade 3+<sup>b</sup></b> | <b>All Grades<sup>c</sup></b> | <b>Grade 3+<sup>b</sup></b> | <b>All Grades<sup>c</sup></b> |
|                                   | <b>n (%)</b>                | <b>n (%)</b>                  | <b>n (%)</b>                | <b>n (%)</b>                  |
| Alopecia                          | 0                           | 14 (3.9)                      | 0                           | 115 (32.4)                    |
| Anemia                            | 2 (0.6)                     | 13 (3.6)                      | 14 (3.9)                    | 41 (11.5)                     |
| Lipase increased                  | 2 (0.6)                     | 9 (2.5)                       | 12 (3.4)                    | 19 (5.4)                      |
| Erythema                          | 0                           | 8 (2.2)                       | 1 (0.3)                     | 36 (10.1)                     |

a MedDRA (version 13.1) coding dictionary applied.

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

c All Grades includes Grades 1-5.

d An additional event of decreased appetite, headache and pain did not have a grade assigned and a result did not contribute to the table summarizing AEs by grade; therefore the overall incidences of these AEs were 34.3%, 13.9% and 5.3%, respectively.

The most commonly reported treatment-related AEs in  $\geq 5\%$  (based on all grades) of subjects in either treatment group are presented in Table 23.

**Table 23. Treatment-Emergent, Treatment-Related Adverse Events Summarized by Maximum Severity Grade for  $\geq 5\%$  (All Grades; Decreasing Frequency) of Subjects in Either Treatment Group in Pivotal Study A4061032 (cut-off date, 31 August 2010)**

| Preferred Term                             | Axitinib (N=359)  |                     | Sorafenib (N=355) |                     |
|--------------------------------------------|-------------------|---------------------|-------------------|---------------------|
|                                            | Grade 3+<br>n (%) | All Grades<br>n (%) | Grade 3+<br>n (%) | All Grades<br>n (%) |
| <b>Any AE</b>                              | 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)            |

Table 24 displays adverse reactions reported in patients who received axitinib in the pivotal study for the treatment of patients with RCC.

**Table 24. Adverse reactions reported in the RCC study in patients who received axitinib**

| System Organ Class                   | Frequency Category | Adverse Reactions            | All Grades <sup>a</sup><br>% | Grade 3 <sup>a</sup><br>% | Grade 4 <sup>a</sup><br>% |
|--------------------------------------|--------------------|------------------------------|------------------------------|---------------------------|---------------------------|
| Blood and lymphatic system disorders | Common             | Anaemia                      | 2.8                          | 0.3                       | 0                         |
|                                      | Uncommon           | Polycythaemia <sup>b</sup>   | 0.3                          | 0                         | 0                         |
| Endocrine disorders                  | Very Common        | Hypothyroidism <sup>b</sup>  | 18.4                         | 0.3                       | 0                         |
|                                      | Uncommon           | Hyperthyroidism <sup>b</sup> | 0.6                          | 0                         | 0                         |
| Metabolism and nutrition disorders   | Very Common        | Decreased appetite           | 28.4                         | 3.3                       | 0.3                       |
|                                      | Common             | Dehydration                  | 4.7                          | 2.5                       | 0                         |
|                                      | Uncommon           | Hyperkalaemia                | 0.8                          | 0.6                       | 0                         |
|                                      |                    | Hypercalcaemia               | 0.6                          | 0                         | 0                         |
| Nervous system disorders             | Very Common        | Headache                     | 10.3                         | 0.6                       | 0                         |
|                                      |                    | Dysgeusia                    | 10.3                         | 0                         | 0                         |
|                                      | Common             | Dizziness                    | 5.6                          | 0                         | 0                         |

| System Organ Class                                   | Frequency Category | Adverse Reactions                                      | All Grades <sup>a</sup><br>% | Grade 3 <sup>a</sup><br>% | Grade 4 <sup>a</sup><br>% |
|------------------------------------------------------|--------------------|--------------------------------------------------------|------------------------------|---------------------------|---------------------------|
|                                                      | Uncommon           | Posterior reversible encephalopathy syndrome           | 0.3                          | 0.3                       | 0                         |
| Ear and labyrinth disorders                          | Common             | Tinnitus                                               | 2.2                          | 0                         | 0                         |
| Vascular disorders                                   | Very Common        | Hypertension                                           | 39.3                         | 15.3                      | 0.3                       |
|                                                      |                    | Haemorrhage <sup>b, c</sup>                            | 10.6                         | 0.3                       | 0.3                       |
|                                                      | Common             | Venous thromboembolic events <sup>b, c</sup>           | 1.9                          | 0.8                       | 0.8                       |
|                                                      |                    | Arterial thromboembolic events <sup>b, c</sup>         | 1.1                          | 1.1                       | 0                         |
|                                                      | Uncommon           | Hypertensive crisis                                    | 0.6                          | 0.3                       | 0.3                       |
| Respiratory, thoracic and mediastinal disorders      | Very Common        | Dysphonia                                              | 28.1                         | 0                         | 0                         |
|                                                      | Common             | Dyspnoea                                               | 7.0                          | 0.3                       | 0                         |
|                                                      |                    | Cough                                                  | 5.3                          | 0                         | 0                         |
|                                                      |                    | Oropharyngeal pain                                     | 3.3                          | 0                         | 0                         |
| Gastrointestinal disorders                           | Very Common        | Diarrhoea                                              | 51.3                         | 9.7                       | 0.3                       |
|                                                      |                    | Vomiting                                               | 16.7                         | 1.4                       | 0                         |
|                                                      |                    | Nausea                                                 | 28.7                         | 1.4                       | 0                         |
|                                                      |                    | Stomatitis                                             | 14.5                         | 1.4                       | 0                         |
|                                                      |                    | Constipation                                           | 12.3                         | 0                         | 0                         |
|                                                      | Common             | Abdominal pain                                         | 8.4                          | 0.6                       | 0.3                       |
|                                                      |                    | Upper abdominal pain                                   | 6.1                          | 0.3                       | 0                         |
|                                                      |                    | Dyspepsia                                              | 7.8                          | 0                         | 0                         |
|                                                      |                    | Flatulence                                             | 4.5                          | 0                         | 0                         |
|                                                      |                    | Haemorrhoids                                           | 2.2                          | 0                         | 0                         |
|                                                      | Uncommon           | Gastrointestinal perforation <sup>b, d</sup>           | 0.3                          | 0                         | 0.3                       |
|                                                      |                    | Anal fistula <sup>b</sup>                              | 0.3                          | 0                         | 0                         |
| Skin and subcutaneous tissue disorders               | Very Common        | Palmar-plantar erythrodysesthesia (hand-foot syndrome) | 27.3                         | 5.0                       | 0                         |
|                                                      |                    | Rash                                                   | 11.7                         | 0.3                       | 0                         |
|                                                      |                    | Dry skin                                               | 10.0                         | 0                         | 0                         |
|                                                      | Common             | Pruritus                                               | 5.8                          | 0                         | 0                         |
|                                                      |                    | Erythema                                               | 2.2                          | 0                         | 0                         |
| Musculoskeletal and connective tissue disorders      | Common             | Alopecia                                               | 3.3                          | 0                         | 0                         |
|                                                      |                    | Myalgia                                                | 5.3                          | 0.6                       | 0.3                       |
|                                                      |                    | Arthralgia                                             | 8.6                          | 0.6                       | 0                         |
|                                                      |                    | Pain in extremity                                      | 8.9                          | 0.3                       | 0                         |
| Renal and urinary disorders                          | Very Common        | Proteinuria                                            | 10.3                         | 3.1                       | 0                         |
| General disorders and administration site conditions | Very Common        | Fatigue                                                | 34.8                         | 9.5                       | 0.3                       |
|                                                      |                    | Asthenia <sup>c</sup>                                  | 17.5                         | 3.6                       | 0.3                       |
|                                                      |                    | Mucosal inflammation                                   | 15.0                         | 1.4                       | 0                         |
| Investigations                                       | Very Common        | Weight decreased                                       | 16.4                         | 1.4                       | 0                         |
|                                                      | Common             | Thyroid stimulating hormone increased                  | 4.5                          | 0                         | 0                         |
|                                                      |                    | Lipase increased                                       | 2.2                          | 0.6                       | 0                         |
|                                                      |                    | Alanine aminotransferase increased                     | 1.9                          | 0.3                       | 0                         |

| System Organ Class | Frequency Category | Adverse Reactions                    | All Grades <sup>a</sup><br>% | Grade 3 <sup>a</sup><br>% | Grade 4 <sup>a</sup><br>% |
|--------------------|--------------------|--------------------------------------|------------------------------|---------------------------|---------------------------|
|                    |                    | Aspartate aminotransferase increased | 1.1                          | 0.3                       | 0                         |
|                    |                    | Alkaline phosphatase increased       | 1.4                          | 0                         | 0                         |
|                    |                    | Amylase increased                    | 1.7                          | 0                         | 0                         |
|                    | Uncommon           | Blood bilirubin increased            | 0.6                          | 0                         | 0                         |
|                    |                    | Creatinine increased                 | 0.6                          | 0                         | 0                         |

<sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

<sup>b</sup> See Description of selected adverse reactions section

<sup>c</sup> Fatal (Grade 5) cases were reported

<sup>d</sup> Adverse reaction is all-causality incidence

Safety events of special interest to axitinib included hypertension, thyroid dysfunction, ATEs, VTEs, elevation of haemoglobin/haematocrit, haemorrhage, gastrointestinal perforation, wound healing complications, PRES, proteinuria, hepatic effects, liver-related AEs, asthenic conditions, rash, PPES and diarrhoea.

### *Hypertension*

Hypertension was reported in 40.4% of patients receiving axitinib and 29.0% of subjects receiving sorafenib. Grade 3 or greater hypertension was reported in 15.6% of subjects receiving axitinib and 11.0% of subjects receiving sorafenib. The median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Although hypertension was one of the most commonly reported AEs in the pivotal study, hypertensive crisis was reported in <1% of patients receiving axitinib and permanent discontinuation of axitinib treatment due to hypertension was infrequent (0.3%).

Prior to the first dose of study drug, the use of antihypertensive medication was similar for the axitinib group (167 patients [46.5%]) and the sorafenib group (171 patients [48.2%]). After the first dose of study drug, the initiation of a new antihypertensive medication or the increase in dose of an existing antihypertensive medication was more common in the axitinib group (196 patients [54.6%]) than in the sorafenib group (141 patients [39.7%]).

### *Thyroid Dysfunction*

Hypothyroidism was reported at baseline for 18.4% and 17.1% of patients in the axitinib and sorafenib treatment groups, respectively in the pivotal study; similar proportions of patients in each treatment group were receiving thyroid medication. Hypothyroidism was reported in 19.2 % of the patients in the axitinib arm and in 8.2 % of the patients in the sorafenib arm whereas; the incidence of hyperthyroidism was 0.6% in axitinib group and 1.1 in the sorafenib group. There were no events of Grade 5 severity or discontinuations due to thyroid dysfunction in either treatment group. Increased TSH was reported as an adverse reaction in 4.5% of patients receiving axitinib. Among the patients who had a normal TSH level (defined as <5 µU/mL before treatment), elevations of TSH to ≥10 µU/mL occurred in 32.2% of patients receiving axitinib, and 10.8% of patients receiving sorafenib.

### *Arterial Thromboembolic Events (ATEs)*

In the pivotal study, Grade 3/4 ATEs were reported in 1.1% of patients receiving axitinib (including 3 patients with transient ischemic attack [TIA] and 1 patient with retinal artery occlusion, all were grade 3/4) and 0.8% of patients receiving sorafenib (including 2 patients with myocardial infarction and 1 subject with ischemic stroke; 2 of these events were Grade 3/4). A fatal cerebrovascular accident was reported in one patient (0.3%) receiving axitinib.

In monotherapy studies of axitinib, ATEs were reported in 1.0% of patients receiving axitinib (including transient ischemic attack, myocardial infarction, and cerebrovascular accident), 7 of these patients were patients in the completed RCC studies (7/537, 1.3%).

### *Venous Thromboembolic Events (VTEs)*

In the pivotal study, venous thromboembolic adverse reactions were reported in 1.9% of patients receiving axitinib and 0.6% of patients receiving sorafenib. The most common VTEs in patients treated with axitinib were pulmonary embolism (PE): 7 patients (1.9%) and deep vein thrombosis (DVT): 2 patients (0.6%). All other VTEs were reported by 1 subject. Grade 3/4 VTEs were reported by in 1.7% of patients receiving axitinib (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis). One axitinib-treated subject (0.3%) experienced a Grade 5 AE (pulmonary embolism), three weeks after the last axitinib dose and while receiving subsequent everolimus.

In the pooled data from Phase II and III RCC studies, VTEs were reported in 2.8% of patients who received axitinib. Across all the completed single-agent axitinib (including RCC) studies, 3.0% experienced VTEs and there were two fatal PEs in patients who received axitinib, both pulmonary embolisms, and deemed not related to treatment by the investigator.

### *Elevation in Haemoglobin/Haematocrit*

Polycythemia as an AE was reported in 0.3% of the patients receiving axitinib and in no patients receiving sorafenib in the pivotal study. One of the three patients had Grade 3 polycythemia; the other two patients had Grade 1 or 2 polycythemia, one of which was considered related to treatment. The polycythemia reported in these three patients was not SAE.

Routine laboratory assessments detected elevated haemoglobin above the upper limit of normal (ULN) in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N=537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

### *Haemorrhage*

In the pivotal study (patients who had evidence of untreated brain metastasis or recent active gastrointestinal bleeding were excluded), haemorrhagic events were reported in 10.6% of patients receiving axitinib and 18.0% of patients receiving sorafenib. The most common haemorrhagic adverse reactions in patients treated with axitinib were epistaxis (5.3%), haematuria (1.4%), rectal haemorrhage (1.1%) and gingival bleeding (1.1%).

Most events were Grade 1 or 2. Grade 3 or 4 haemorrhagic events was reported in 0.8% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage and lower gastrointestinal haemorrhage) and 3.1% of patients receiving sorafenib.

There was 1 Grade 5 event (gastric haemorrhage) in axitinib-treated patients (0.3%) and 3 Grade 5 events (duodenal ulcer haemorrhage, GI haemorrhage and retroperitoneal haemorrhage) in sorafenib-treated patients (0.8%) in the pivotal study. The gastric haemorrhage in the axitinib group, and the GI haemorrhage and retroperitoneal haemorrhage in the sorafenib group were treatment related.

In completed RCC studies, 22.9% experienced haemorrhages. Ten patients (1.9%) experienced Grade 3/4 haemorrhages. In completed single-agent studies, 26.0% experienced haemorrhages. Haemoptysis was reported as an adverse reaction in 1.6% of patients, including one case (0.1%) of Grade >3 event. In study A4060010, 2 patients with adenocarcinoma of the lung died with haemoptysis; one of these deaths was considered related to axitinib.

#### *Gastrointestinal Perforation*

In the pivotal study, based on PTs, gastrointestinal perforation was reported in 1 (0.3%) axitinib-treated patient (severity grade not reported) and no sorafenib-treated patient. There were 3 GI perforations (0.6% [including the PTs GI perforation and large intestine perforation]) in the completed RCC studies and totally 5 GI perforations (0.7% [including the PTs GI perforation, intestinal perforation and large intestine perforation]) in completed single-agent studies.

In monotherapy studies with axitinib (N=699), fistulas were reported in 0.7% of patients (all-causality incidence) and fatal gastrointestinal perforation was reported in one patient (0.1%).

In the pancreatic cancer studies (A4061016 and A4061028), based on PTs, 3 patients treated with axitinib + gemcitabine had GI perforations, two of which were considered related to treatment.

#### *Diarrhoea*

In the pivotal study, diarrhoea was reported in 54.9% of patients receiving axitinib and 53.2% of patients receiving sorafenib. Grade 3 or greater diarrhoea was reported in 10.6% of patients receiving axitinib and 7.3% of patients receiving sorafenib. Although diarrhoea was frequently reported, it was generally mild to moderate and did not lead to permanent discontinuation of axitinib. There were somewhat higher incidences of diarrhoea in all supportive RCC studies; the reported frequencies of diarrhoea as AE (all-causality) were; for study A4061012: all grades: 63.5%; grade 3+: 15.4%, for study A4061023 all grades 61.3%; grade 3+: 14.5% and in study A4061035: all grades 67.2%; grade 3+: 4.7%.

#### *Wound Healing Complications*

In the pivotal study, 4 patients (1.1%), all of whom were treated with axitinib, experienced AEs involving wounds, 1 case was Grade 3/4 (Wound decomposition). All patients recovered; no cases were considered serious. The frequency for all completed RCC studies pooled were 2.0% (11/537), and from all completed (including RCC) single-agent axitinib studies 1.9% (13/699). There were no grade 5 wound healing complications.

#### *Posterior Reversible Encephalopathy Syndrome (PRES)*

Three (0.4%) of the 699 axitinib-treated patients experienced PRES in the completed single-agent studies (2 of these were reported in the completed RCC studies, 2/537 [0.4%]; one in the pivotal study (0.3%), one in the supportive studies); in 2 (0.3%) of the patients the PRES was Grade 3/4. In the pancreatic studies, PRES was reported in 1 patient (1/372, 0.3%) in the axitinib+gemcitabine arm, this event was of grade 4. There were no Grade 5 events.

#### *Proteinuria*

In the pivotal study, 10.9% of axitinib-treated patients and 7.3% of sorafenib-treated patients reported proteinuria as an AE. Proteinuria of severity of Grade 3 was reported in 3.1% of patients receiving axitinib and 1.7% of patients receiving sorafenib. There were no reports of Grade 4 or Grade 5 proteinuria. There were no discontinuations from axitinib or sorafenib due to proteinuria as an AE in Study A4061032. Based on urinalysis results, the incidence of proteinuria was 52.9% in patients receiving axitinib and 50.0% for those receiving sorafenib. The majority of the urine protein

abnormalities were Grade 1 or 2. Proteinuria as an AE was reported for 15.3% of axitinib-treated patients in completed RCC studies.

#### *Hepatic Effects*

An assessment of the impact of axitinib on the liver was undertaken based on a review of nonclinical data and data from completed clinical trials. This evaluation consisted of a review of 1) liver function test abnormalities, 2) potential Hy's Law cases identified through eDISH plot, 3) AEs possibly related to the liver, 4) subject withdrawals possibly related to the liver, and 5) deaths possibly related to the liver.

The clinical assessment is based on 2409 patients from all completed clinical studies, including 1838 patients receiving axitinib. In the dose-finding study A4060010, concurrent elevations of ALT (12 x ULN) and bilirubin (2.3 x ULN), considered to be drug-related hepatotoxicity (adjudicated to be "probably" related to axitinib and met the criteria for being a Hy's Law case), was observed in one patient with colorectal cancer who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose), for 37 days. No severe case of DILI attributable to axitinib at the starting dose of 5 mg BID, with selected patients receiving subsequent stepwise titrated doses to a maximum of 10 mg BID, were revealed. In the pivotal study, no concurrent elevations of ALT (>3 x ULN) and bilirubin (>2 x ULN) were observed for either axitinib or sorafenib.

There were 25 potential Hy's Law cases (ie, in Hy's law quadrant) in patients receiving axitinib and 1 was adjudicated to be a true probable Hy's law case (discussed above). The majority of potential Hy's law cases came from pancreatic studies and none from the pivotal study.

#### *Liver-related Adverse Events*

In the pivotal study there were 24 patients (6.7%) with a total of 31 liver-related AEs (all Grades) in the axitinib-treatment. The most frequent AEs (>1%) were ALT increased, AST increased, ascites, and hyperbilirubinemia. Most AEs were Grades 1/2. There were 6 patients (1.7%) with 7 Grades 3/4 AEs. There were no Grade 5 liver-related AEs. In addition, there were no liver-related SAEs in the axitinib arm and 6 in the sorafenib arm. All six required hospitalization. Of the 178 patients with advanced RCC in the 3 Phase II RCC supportive studies there were 4 potential liver-related SAEs; 2 cases of hepatorenal syndrome, 1 case of hyperbilirubinemia, and 1 case of jaundice. All cases required hospitalization. The 2 hepatorenal syndrome events were associated with fatal outcomes; the other 2 events had not resolved at the time of the report. Hepatorenal syndrome for 1 subject was listed as an SAE with a fatal outcome on the safety database; however, this AE was not listed on the clinical database.

In completed RCC-studies, liver-related AEs were observed in 59/537 patients (11.0%). The most frequent AEs (>1%) were ALT increased, AST increased, hyperbilirubinemia, and ascites. Most AEs were mild (Grade 1/2). There were 13 patients (2.4%) with 17 Grades 3/4 AEs and 1 subject with hepatorenal syndrome associated with a fatal outcome. In addition, hepatorenal syndrome for 1 subject was listed as an SAE with a fatal outcome on the safety database.

#### *Asthenic Conditions*

Asthenic conditions were reported in 57.1% of patients in the axitinib group and in 46.2% of patients in the sorafenib group in the pivotal study, but did not lead to discontinuation from treatment. Asthenia and fatigue were reported in 20.6% and 39.0 % of patients in the axitinib group and in 14.1% and 31.5 % of patients in the sorafenib group respectively. One Grade 5 event, asthenia, occurred in the pivotal study and one Grade 5 event (asthenia) in the axitinib+gemcitabine group in a study in pancreatic cancer patients, both events were considered related to treatment.

## Rash

Events coding to epidermal and dermal conditions were reported in 60.3% of patients in the sorafenib arm and 33.4% of patients in the axitinib arm in the pivotal study. There were more Grade 3/4 events in sorafenib-treated patients (8.5%) than in axitinib-treated patients (1.4%). There were no Grade 5 events in either treatment group. The most common events (all-causality) were rash, dry skin, and pruritus in both treatment groups.

In completed RCC studies, 197/537 (36.7%) and in completed single-agent studies, 267/699 (38.2%) reported events (all-causality) coding to epidermal and dermal conditions. The majority of the events were Grade 1 or 2. The most common events (all-causality) in the completed single-agent studies were rash (14.4%), dry skin (12.2%), pruritus (6.3%), erythema (4.0%), and skin exfoliation (2.4%).

## Palmar-plantar erythrodysesthesia syndrome (PPES, or hand-foot syndrome)

The incidence of PPES was 51.0% in sorafenib-treated patients and 27.3% in axitinib-treated patients in the pivotal study. The majority of the cases in axitinib-treated patients were Grade 1 or 2. There was more Grade 3 or greater PPES in sorafenib-treated patients (16.1%) than in axitinib-treated patients (5.0%). Only few discontinued treatment due to this AE (1 on axitinib, 4 on sorafenib).

The incidence of PPES varied widely across the completed RCC studies from 5.8% in study A4061012 to 75.0% in study A4061035. The incidences in studies A4061032 (27.3%) and A4061023 (35.5%) were intermediate. PPES was reported by 28.9% of axitinib-treated subjects in the completed single-agent studies. The majority were Grade 1 or 2. Grade 3 PPES was reported for 6.6% of subjects.

## Serious adverse event / deaths / other significant events

### Deaths

Based on the results from the update safety analysis (cut-off date 01 February 2011) there were 61 deaths in the pivotal RCC study; 36 (10%) in the axitinib arm and 25 (7%) in the sorafenib arm. Of these fatal outcomes, 5 cases in each arm were considered due to study drug and 2 cases of subjects who died of unknown causes (one in each arm). In one of the supportive studies in RCC there was one additional fatal event which was not considered related to treatment.

All fatal SAEs that occurred with axitinib or sorafenib treatment are summarized in table 25.

**Table 25. Summary of Deaths–(cut-off date 01 February 2011)**

|                            | Pivotal<br>Phase 3<br>Study A4061032 |           | Supportive<br>Phase 2<br>Study A4061035 |
|----------------------------|--------------------------------------|-----------|-----------------------------------------|
|                            | Axitinib                             | Sorafenib | Axitinib                                |
| Number of Subjects Treated | 359                                  | 355       | 64                                      |
| <b>All Deaths</b>          | <b>36</b>                            | <b>25</b> | <b>1</b>                                |
| Death Due to Study Drug    | 5                                    | 5         | 0                                       |
| Death Due to Disease       | 27                                   | 17        | 1                                       |
| Under Study                |                                      |           |                                         |
| Death Due to Other Cause   | 4                                    | 4         | 0                                       |

### Serious adverse events

The SAEs for which there were at least 4 events in either treatment group are summarized in table 26.

**Table 26. Serious Adverse Events (All-Causality) Summarized for  $\geq 4$  Events (Either Treatment Group) in Pivotal Study A4061032 (cut-off date 01 February 2011)**

| Preferred Term <sup>a</sup>           | Axitinib (N=359)<br>Number of Events | Sorafenib (N=355)<br>Number of Events |
|---------------------------------------|--------------------------------------|---------------------------------------|
| Disease progression                   | 30                                   | 17                                    |
| Metastatic renal cell carcinoma       | 26                                   | 14                                    |
| Dehydration                           | 10                                   | 1                                     |
| Diarrhea                              | 8                                    | 5                                     |
| Pyrexia                               | 7                                    | 4                                     |
| Pneumonia                             | 6                                    | 5                                     |
| Dyspnea                               | 5                                    | 5                                     |
| Pulmonary embolism                    | 5                                    | 1                                     |
| Vomiting                              | 4                                    | 1                                     |
| Pneumothorax                          | 4                                    | 1                                     |
| Infection                             | 4                                    | 0                                     |
| Fatigue                               | 4                                    | 0                                     |
| Pleural effusion                      | 3                                    | 5                                     |
| Pain                                  | 2                                    | 5                                     |
| General physical health deterioration | 2                                    | 4                                     |
| Myocardial infarction                 | 1                                    | 5                                     |
| Gastrointestinal haemorrhage          | 1                                    | 4                                     |
| Hypotension                           | 1                                    | 4                                     |
| Anemia                                | 0                                    | 7                                     |
| Lower respiratory tract infection     | 0                                    | 4                                     |

<sup>a</sup> MedDRA (version 13.1) coding dictionary applied.

As shown in Table 26, the most common SAEs (all-causality) in both treatment arms were disease progression, and metastatic RCC. The SAEs that were reported during the safety update follow-up period and now meet criteria ( $\geq 4$  events each) for inclusion include vomiting, pneumothorax, myocardial infarction, gastrointestinal (GI) hemorrhage, and lower respiratory tract infection. More common ( $\geq 2$  fold) events included dehydration, pulmonary embolism, vomiting, pneumothorax, infection, and fatigue in the axitinib arm, and pain, general physical health deterioration, myocardial infarction, GI hemorrhage, hypotension, anaemia, and lower respiratory tract infection in the sorafenib arm.

## Laboratory findings

Laboratory findings revealed that 52.5% of patients in the sorafenib arm had haemoglobin decreases (and anaemia reported as AE) and 34.9% of patients in the axitinib arm whereas elevated haemoglobin above the ULN was reported in 8.6% of patients in the axitinib arm and only in 0.8% of patients in the sorafenib arm. Furthermore, creatinine increased (55.1%) and hypercalcaemia (30.1%) were more common in the axitinib arm whereas hypophosphataemia (49.5%), lipase increased (46.0%), amylase increased (32.6%) and hypocalcaemia (28.0%) were more frequent in the sorafenib arm. Very similar changes in the liver function tests were observed.

In general, most laboratory abnormalities were mild in severity apart from grade 3/4 lipase increased that occurred in 14.6% of patients in both treatment arms and grade 3/4 hypophosphataemia that was reported in 16.2% of sorafenib-treated patients. Proteinuria was very commonly reported in 52.9% of patients in the axitinib arm and in 50.0% of patients in the sorafenib arm.

The results of the updated analysis (cut-off date 1 February 2011) was overall very similar to previous findings. The majority of the laboratory test abnormalities were Grade 1 or 2.

## ECGs

Based on the evaluation of ECG recordings in 152 patients in completed single agent studies, 4 patients (all from the pivotal study) had a postbaseline absolute value  $>500$  msec and/or a change from baseline  $>60$  msec. In all 4 patients, confounding factors were present and 3 out of 4 patients

had abnormal ECGs at baseline. None of these patients had clinically relevant symptoms. The applicant has also reviewed all AEs that potentially could be associated with effects on the QTc interval in the completed single agent studies. There were no reports of sudden deaths, ventricular arrhythmia or Torsade de pointes. In addition, in study A4061004 (in healthy volunteers) the largest axitinib-related mean, placebo-corrected time-matched change for axitinib with Bazett's correction [QTcB]) was 4.4 msec (90% CI; 1.9, 6.9) which is lower than the level of regulatory concern. Similarly, the PK-PD analysis from the same study did not find a correlation between QTc prolongation and axitinib plasma concentration.

## **Safety in special populations**

In the pivotal study, 34% of patients treated with axitinib were  $\geq 65$  years of age. The majority of patients were White (77%) or Asian (24%).

In the axitinib group, 93.6% of subjects  $< 65$  years and 98.4% of subjects  $\geq 65$  years experienced AEs (all-causality). Higher incidences of diarrhoea (64.2% vs. 50.0%), fatigue (47.2% vs. 34.7%), weight decreased (30.1% vs. 22.0%), dysphonia (36.6% vs 28.0%), and decreased appetite (43.9% vs. 29.2%) were observed in axitinib-treated subjects  $\geq 65$  years compared with subjects  $< 65$  years. Hypertension was more frequently reported in subjects  $< 65$  years than in subjects  $\geq 65$  years (44.9% vs 31.7%).

Grade 3 or greater AEs were more frequent in axitinib-treated subjects  $\geq 65$  years. Grade 3 or greater asthenia (9.8% vs 3.0%) and decreased appetite (7.3% vs 3.8%) were more frequent in the older age group. Based on the centralized AEM database, the incidence of SAEs (all-causality) was higher for axitinib-treated subjects  $\geq 65$  years (36.6% [45/123]) than for subjects  $< 65$  years (25.8% [61/236]). The incidence of discontinuation due to AEs was higher in subjects  $\geq 65$  years than in subjects  $< 65$  years.

The majority of patients in the pivotal study were White (77%) or Asian (24%). The incidence of treatment-related grade  $> 3$  AEs was 59.7 % in Asians vs. 45.7 % in Caucasians. The incidence of treatment-related SAEs was 15.6 % in Asians vs. 9.8 % in White patients.

## **Safety related to drug-drug interactions and other interactions**

The results from the drug-drug interactions study were submitted and discussed under Clinical Pharmacology section. No deaths, serious adverse events or adverse events leading to treatment discontinuation were reported in these studies.

## **Discontinuation due to adverse events**

In the pivotal study, 9.2% of patients in the axitinib arm and 13% of patients in the sorafenib arm discontinued treatment permanently due to adverse events.

According to the updated analysis (cut-off date 1 February 2011) treatment-related AEs led to discontinuations in 4.7% of axitinib-treated patients compared to 9.3% in the sorafenib arm. These numbers and the most common events that led to discontinuations are in line with previous findings.

## **Post marketing experience**

N/A

### 2.6.1. Discussion on clinical safety

The applicant has given a detailed overview of the study populations included in the safety evaluation. The methods used in the safety evaluation are considered adequate. Overall, the size of the safety database is considered as satisfactory

Almost all subjects (95.3% of the patients in the axitinib arm and 97.7% of the patients in the sorafenib arm) in the pivotal RCC study experienced at least one adverse event during the study period. The most common AEs reported in the axitinib group (in  $\geq 20\%$  subjects) were diarrhoea, hypertension, fatigue, dysphonia, nausea, decreased appetite, and palmar-plantar erythrodysesthesia (hand-foot) syndrome. Most of these events occurred with Grade 1 or 2 severities.

The incidences of many of the most common AEs were higher in axitinib-treated subjects who had received prior sunitinib than in axitinib-treated subjects who had received prior cytokines, whereas especially the frequency of hypertension was higher for both groups who had received prior cytokines than for those who had received prior sunitinib.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The most important serious adverse reactions reported in patients receiving axitinib were arterial thromboembolic events (1.1%), venous thromboembolic events (1.9%), haemorrhage (10.6% [including gastrointestinal haemorrhage, cerebral haemorrhage and haemoptysis]), gastrointestinal perforation and fistula formation (0.3%), hypertensive crisis ( $<1\%$ ), and posterior reversible encephalopathy syndrome (0.4%).

In total, 36 deaths occurred in the axitinib arm vs. 25 in the sorafenib arm. The majority of these events were due to progressive disease (27 and 17 in the two arms, respectively). Five events in each arm were considered treatment-related. This is one additional event in both arms compared to the previous analysis. There is no indication that axitinib promotes disease progression/the development of new lesions.

Other safety events of special interest and concern with regard to axitinib include hypertension, thyroid dysfunction, ATEs, VTEs, elevation of haemoglobin/haematocrit, haemorrhage, gastrointestinal perforation, wound healing complications, PRES, proteinuria, hepatic effects, asthenic conditions, rash and PPES.

Axitinib affects the incidence of hypertension and thyroid dysfunction, and sometimes aggravates these conditions if pre-existing, however, these AEs are largely manageable. Both blood pressure and thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Sections 4.4 and 4.8 of the SmPC include this information.

Axitinib should be used with caution in patients who are at risk for, or who have a history of ATEs and VTEs.

Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib. An increase in red blood cell mass may increase the risk of thromboembolic events. Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment.

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. In patients with signs or symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Asthenia and fatigue were frequently reported in axitinib-treated subjects (20.6% and 39.0%, respectively), and fatigue was the only grade 3 or greater AE that was reported more frequently ( $\geq 5\%$  difference) in the axitinib treatment group than in the sorafenib treatment group. The incidence of skin reactions including epidermal and dermal conditions, and PPES was lower in the axitinib-treated subjects than in sorafenib-treated subjects.

There does not seem to be any clear signals of a clinically meaningful prolongation of the QT interval observed with axitinib, however, two patients had grade  $\geq 3$  QTc prolongation (absolute QTc  $> 500$  msec) at Cycle 1 day 15, and two additional patients had on-treatment increase in QTc greater than 60 msec in the pivotal study. Therefore QTc prolongation has been identified as an important potential risk. However in order to get most optimal information about new suspected cases, the applicant should include enhanced pharmacovigilance activities with use of a questionnaire to systematically collect follow-up data of ICSRs that can be associated with QT prolongation.

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose. Inlyta is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product. Women of childbearing potential must use effective contraception during and up to 1 week after treatment. It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Since Inlyta contains lactose patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take it.

There is no specific treatment for axitinib overdose. In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1). In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis. In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

There are some differences in safety parameters based on age, race, gender or region. Since the axitinib dose is individually titrated as clinically indicated (ie. according to safety and tolerability), none of these differences in itself leads to a recommendation of a definitive dose reduction. The applicant has updated the SmPC with regards to observed differences of certain AEs and race/genetics.

## 2.6.2. Conclusions on the clinical safety

The safety profile of axitinib is consistent with the expected profile for a tyrosine kinase inhibitor selectively targets the VEGFR-1, VEGFR-2 and VEGFR-3 signalling. Severe, serious and even fatal events occur, but the incidences are low. Most common AEs are well-known and largely manageable with dose reductions and temporary interruptions. Despite dosage optimisation based on tolerability, the majority of adverse events were mild or modest in severity and relatively few patients discontinued therapy due to AEs. There does not seem to be more AEs in subjects treated with axitinib compared to sorafenib, although the incidences of the individual AEs differ. Compared to sorafenib, treatment with axitinib was associated with some distinct features (more hypertension, but less skin toxicity, less hand-foot syndrome, less anaemia, less alopecia).

Overall, axitinib seems to be acceptably tolerated as monotherapy in patients with advanced RCC that have failed prior cytokine and sunitinib therapy.

## 2.7. Pharmacovigilance

### Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### Risk Management Plan

The applicant submitted a risk management plan.

**Table 27. Summary of the risk management plan**

| Safety Concern                           | Proposed Pharmacovigilance Activities (PV) | Proposed Risk Minimisation Activities                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Identified Risks</b>                  |                                            |                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Arterial embolic and thrombotic events   | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic and thrombotic event within the previous 12 months."                                                                                              |
| Elevation of hemoglobin or hematocrit    | Routine PV                                 | Polycythaemia Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Monitor haemoglobin or haematocrit before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level." |
| Gastrointestinal perforation and fistula | Routine PV                                 | See SmPC, Section 4.4. "Monitor for symptoms of gastrointestinal perforation periodically throughout treatment with axitinib."                                                                                                                                                                                                                                                                                     |

| Safety Concern                                      | Proposed Pharmacovigilance Activities (PV) | Proposed Risk Minimisation Activities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hemorrhage (including tumour hemorrhage)            | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If bleeding requires medical intervention, temporarily interrupt the axitinib dose."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Hypertension                                        | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In case of persistent hypertension despite use of anti-hypertensive medications, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension." In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome, a diagnostic brain magnetic resonance image (MRI) should be considered." |
| Proteinuria                                         | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Posterior reversible encephalopathy syndrome (PRES) | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "In patients with signs/symptoms of PRES, temporarily interrupt or permanently discontinue axitinib. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Thyroid dysfunction                                 | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Monitor thyroid function before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Venous thrombotic and embolic events                | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects).<br>See SmPC, Section 4.4. "Axitinib should be used with caution in patients who are at risk for, or who have had a history of these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| Safety Concern                                                                | Proposed Pharmacovigilance Activities (PV) | Proposed Risk Minimisation Activities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Overexposure in patients with a history of hepatic or hepatobiliary disorders | Routine PV                                 | <p>See SmPC, Section 4.4. "Monitor liver function tests before initiation of, and periodically throughout, treatment with axitinib."</p> <p>See SmPC, Section 4.2. "Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population."</p> <p>See SmPC, Section 5.2. "Hepatic impairment <i>In vitro</i> and <i>in vivo</i> data indicate that axitinib is primarily metabolised by the liver. Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population."</p> |
| Palmar-plantar erythrodysesthesia                                             | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Fatigue and asthenic conditions                                               | Routine PV                                 | Listed in SmPC Section 4.8 (undesirable effects)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Overexposure with CYP3A inhibitors                                            | Routine PV                                 | <p>See SmPC, Section 4.2 and 4.5. "Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of an alternate concomitant medicine with no or minimal CYP3A4/5 inhibition potential is recommended.</p> <p>Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g., from a starting dose of 5 mg twice daily to a reduced dose of 2 mg twice daily) is recommended.</p> <p>Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy. If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered."</p>                                                                                                                                                                                                                                                                                                      |

| <b>Safety Concern</b>                       | <b>Proposed Pharmacovigilance Activities (PV)</b>                                          | <b>Proposed Risk Minimisation Activities</b>                                                                                                                                                                                           |
|---------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hepatic disorders                           | Routine PV                                                                                 | ALT, AST, ALP and blood bilirubin increased, are listed in SmPC Section 4.8 (undesirable effects). See SmPC, Section 4.4. "Monitor liver function tests before initiation of, and periodically throughout, treatment with axitinib."   |
| Effects on the exocrine pancreas            | Routine PV                                                                                 | Blood amylase increased and Lipase increased are listed in SmPC Section 4.8 (undesirable effects). No additional minimization activities are currently required for this potential risk.                                               |
| Renal failure                               | Routine PV                                                                                 | Renal failure and Proteinuria are listed in SmPC Section 4.8 (undesirable effects). See SmPC, Sections 4.2 & 5.2. No dose adjustment is required.                                                                                      |
| Neutropenia/cytopenia                       | Routine PV                                                                                 | Thrombocytopenia, Neutropenia and Leucopenia are listed in SmPC Section 4.8 (undesirable effects). No additional minimization activities are required for this potential risk.                                                         |
| <b>Potential Risks</b>                      |                                                                                            |                                                                                                                                                                                                                                        |
| Wound healing complications                 | Routine PV                                                                                 | See SmPC, Section 4.4. "Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing." |
| Congestive heart failure/<br>Cardiomyopathy | Routine PV                                                                                 | No minimization activities are required for this potential risk.                                                                                                                                                                       |
| QT prolongation                             | Routine PV including enhanced pharmacovigilance activities with use of a QTc questionnaire | No minimization activities are required for this potential risk.                                                                                                                                                                       |
| Reproductive and developmental toxicity     | Routine PV                                                                                 | See SmPC, sections 4.6 and 5.3.                                                                                                                                                                                                        |
| Thrombotic microangiopathy                  | Routine PV                                                                                 | No minimization activities are required for this potential risk.                                                                                                                                                                       |
| Carcinogenicity                             | Routine PV                                                                                 | See SmPC, Section 5.3. "Carcinogenicity studies have not been performed with axitinib." No additional minimization activities are required for this potential risk.                                                                    |
| Osteonecrosis of the jaw                    | Routine PV                                                                                 | No minimization activities are required for this potential risk.                                                                                                                                                                       |

| Safety Concern                                                                                                                                  | Proposed Pharmacovigilance Activities (PV) | Proposed Risk Minimisation Activities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug interactions with CYP1A2, 2C8 and P-glycoprotein substrates                                                                                | Routine PV                                 | <p>See SmPC, Section 4.5. “<i>In vitro</i> studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).</p> <p><i>In vitro</i> studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.</p> <p><i>In vitro</i> studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, <i>in vivo</i>.”</p> |
| <b>Missing Information</b>                                                                                                                      |                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Risks in pregnant and lactating women                                                                                                           | Routine PV                                 | See SmPC, Section 4.6. “There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations. Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicine.”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Risks in paediatric subjects                                                                                                                    | Routine PV                                 | See SmPC, Section 4.2. “The safety and efficacy of axitinib in children (<18 years) have not been established. No data are available.”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Risks in patients with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) | Routine PV                                 | See SmPC, Sections 4.2 & 5.2. No dose adjustment is required. Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Risks in subjects with severe hepatic impairment (>Child-Pugh Class B)                                                                          | Routine PV                                 | See SmPC, Section 4.4. “Monitor liver function tests before initiation of, and periodically throughout, treatment with axitinib.”<br>See SmPC, Sections 4.2 and 5.2. “Hepatic impairment: Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Safety Concern                                                                                                                                                                                                                                                 | Proposed Pharmacovigilance Activities (PV) | Proposed Risk Minimisation Activities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risks in patients with brain metastasis, spinal cord compression, or carcinomatous meningitis                                                                                                                                                                  | Routine PV                                 | <p>SmPC, Section 4.4 contains the following warning:<br/> <u>Haemorrhage</u><br/> In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).</p> <p>Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Risks in patients with recent myocardial infarction, severe/unstable angina, coronary/ peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, deep vein thrombosis or pulmonary embolism | Routine PV                                 | <p>SmPC, Section 4.4 contains the following warning:<br/> <u>Arterial embolic and thrombotic events</u><br/> In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).</p> <p>Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic and thrombotic event within the previous 12 months.</p> <p><u>Venous embolic and thrombotic events</u><br/> In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).</p> <p>Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic and thrombotic event within the previous 6 months.</p> <p>SmPC, Section 4.8, lists ATEs and VTEs as adverse drug reactions.</p> |

| Safety Concern                                                                                       | Proposed Pharmacovigilance Activities (PV) | Proposed Risk Minimisation Activities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------------------------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risks in patients with active peptic ulcer disease                                                   | Routine PV                                 | <p>Although the SmPC does not contain any specific wording related to peptic ulcer disease, SmPC, Section 4.4 includes the warnings about GI perforation and Haemorrhage.</p> <p><u>Haemorrhage</u><br/>In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).</p> <p>Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.</p> <p><u>Gastrointestinal perforation and fistula formation</u><br/>In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).</p> <p>Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.</p> |
| Risks in patients with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks) | Routine PV                                 | <p>SmPC, Section 4.4 contains the following warning in section 4.4:</p> <p>Wound healing complications<br/>No formal studies of the effect of axitinib on wound healing have been conducted.</p> <p>Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

**Table 28: Additional pharmacovigilance activities**

| Description                                                                                                                                                                                   | Due date   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| The applicant should include enhanced pharmacovigilance activities with use of a questionnaire to systematically collect follow-up data of ICSRs that can be associated with QT prolongation. | 4 Oct 2012 |

No additional risk minimisation activities were required beyond those included in the product information.

## 2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

### **3. Benefit-Risk Balance**

#### ***Benefits***

##### **Beneficial effects**

The applicant submitted one pivotal trial in support of the efficacy of axitinib in patients with advanced RCC after failure of treatment with one prior systemic therapy including sunitinib, bevacizumab + IFN- $\alpha$ , temsirolimus, or cytokine(s), or combination of these.

In the overall population of the pivotal phase III study a median PFS of 6.8 months for the axitinib group and 4.7 months for the sorafenib group has been observed. Median PFS in the subgroup of patients previously treated with cytokines as 1<sup>st</sup> line therapy was 12.0 months for axitinib and 6.6 months for sorafenib (HR=0.519; 95% CI: 0.375, 0.720;  $p < 0.0001$ ). In patients previously treated with sunitinib median PFS for axitinib was 4.8 months vs. 3.4 months for sorafenib (HR =0.736; 95% CI: 0.578, 0.937;  $p=0.0063$ ).

This effect was further substantiated by results in the secondary efficacy endpoints: A positive trend for OS was observed in the prior-cytokine group (HR= 0.813; 95% CI: 0.555, 1.191;  $p=0.1435$ ,) with median OS of 29.4 months in the axitinib arm and 27.8 months in the sorafenib arm. The analysis of ORR showed a statistically significant improvement of 13.9% for axitinib compared to sorafenib in patients pre-treated with cytokines (HR=2.392; 95% CI: 1.434, 3.993;  $p=0.0002$ ). In the prior-sunitinib group, the difference in ORR between axitinib and sorafenib was 3.6% (HR=1.477; 95% CI: 0.792, 2.754;  $p=0.1085$ ).

Duration of response and patient reported outcomes were only analysed for the overall study population. There were no differences in these endpoints between the axitinib and sorafenib study arms.

##### **Uncertainty in the knowledge about the beneficial effects**

The group of patients previously treated with temsirolimus and bevacizumab+IFN- $\alpha$  are very small ( $n=25$  and  $n=59$ , respectively), and therefore no firm conclusions can be made regarding the efficacy in these subgroups. Therefore the indication has been restricted to the patients previously treated with sunitinib or cytokine.

Based on the analysis of OS in the pivotal study there is no indication of any survival benefit of axitinib over sorafenib in the prior sunitinib group (HR=0.997).

##### ***Risks***

The most common AEs reported in the axitinib group (in  $\geq 20\%$  subjects) were diarrhoea, hypertension, fatigue, dysphonia, nausea, decreased appetite, and palmar-plantar erythrodysesthesia (hand-foot) syndrome. Most of these events occurred with Grade 1 or 2 severities.

The most common ( $>3\%$ ) severe events (grade 3-5 events pooled) in the axitinib arm were hypertension (15.6%), diarrhoea (10%), fatigue (9.7%), palmar-plantar erythrodysesthesia syndrome (5.0%), asthenia (4.2%), decreased appetite (3.6%) and proteinuria (3.1%). In comparison, the most common severe events in the sorafenib arm were palmar-plantar erythrodysesthesia syndrome (16.1%), hypertension (11.0%), diarrhoea (7.0%), fatigue (3.7%), rash (3.7%) and lipase increased (3.1%).

Axitinib affects the incidence of hypertension and of thyroid dysfunction, and sometimes aggravates these conditions if pre-existing. The hypertension reported during the study was largely manageable, but hypertension is still considered an unfavourable effect of axitinib.

## **Uncertainty in the knowledge about the unfavourable effects**

Overall, the safety profile of axitinib is consistent with the expected profile for a tyrosine kinase inhibitor selectively targets the VEGFR-1, VEGFR-2 and VEGFR-3 signalling.

There does not seem to be any clear signals of a clinically meaningful prolongation of the QT interval observed with axitinib, however, two patients had grade  $\geq 3$  QTc prolongation (absolute QTc >500 msec) at Cycle 1 day 15, and two additional patients had on-treatment increase in QTc greater than 60 msec in the pivotal study. Therefore QTc prolongation has been identified as an important potential risk. However in order to get most optimal information about new suspected cases, the applicant will include enhanced pharmacovigilance activities with use of a questionnaire to systematically collect follow-up data of ICSRs that can be associated with QT prolongation.

## **Importance of favourable and unfavourable effects**

Treatment with axitinib showed an improvement in the median progression free survival. Results in ORR supported the observed improvement in PFS. Axitinib showed a clear antitumour effect in patients with advanced RCC that have failed prior cytokine and sunitinib therapy. The results are considered to be mature, robust and of clinical relevance.

Based on the safety data from the submitted studies, axitinib seems to be acceptably tolerated as monotherapy in patients with advanced RCC. There does not seem to be more AEs in subjects treated with axitinib compared to sorafenib, although the incidences of some of the individual AEs varies between the two treatment arms. The majority of adverse events were mild or modest in severity and relatively few patients discontinued therapy due to AEs.

## **Benefit-risk balance**

Overall, the efficacy of axitinib has been demonstrated. The adverse event profile of axitinib in second-line therapy of mRCC seems acceptable and generally manageable. The benefit-risk balance for axitinib for the treatment of adult patients, with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine, is considered positive. The favourable effects outweigh the negative effects of Inlyta.

## ***Discussion on the benefit-risk balance***

The indication has been restricted to the patients previously treated with sunitinib or cytokine. The group of patients previously treated with temsirolimus and bevacizumab+IFN- $\alpha$  are very small (n=25 and n=59, respectively) and no firm conclusions can be made regarding the efficacy in these subgroups.

In the opinion of the divergent CHMP members the benefit-risk balance in the subpopulation of patients previously treated with sunitinib is considered negative.

## 4. Recommendations

### ***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Inlyta is not similar to Nexavar and Torisel within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

### ***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Inlyta in the treatment of adult patients, with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine, is favourable and therefore recommends the granting of the marketing authorisation under subject to the following conditions:

### ***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription

### ***Conditions and requirements of the Marketing Authorisation***

#### ***Risk Management System***

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

### ***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

Not applicable

### ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.

Divergent position to the majority recommendation is appended to this report.

### ***New Active Substance Status***

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that axitinib is qualified as a new active substance.

## REFERENCES

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## **APPENDIX 1**

### **DIVERGENT POSITION**

### **DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS**

A clinically relevant effect of axitinib has convincingly been demonstrated in the patients previously treated with cytokines. Uncertainty about the effects of axitinib specifically concerns its use in the subgroup of patients previously treated with sunitinib and are related to the issues described below.

The magnitude of the PFS benefit for axitinib over sorafenib is uncertain since the PFS estimate for sorafenib in the pivotal study lacks external validation from a registrational phase III study. At present, everolimus is the only drug approved for use in a second line treatment of mRCC after prior sunitinib. Sorafenib is only approved for use after prior cytokines in this setting. The lack of external validation of the effect of the comparator on PFS in the AXIS study is of particular importance since median PFS of axitinib in the prior sunitinib group is rather modest and the analysis of OS in the pivotal study gave no indication of any survival benefit of axitinib over sorafenib in this subgroup (HR=0.997).

In terms of effect on PFS axitinib is much less active in the prior sunitinib group than in patients who have received cytokines as part of their first-line treatment. This finding could indicate cross-resistance mechanisms that reduce the potential clinical activity of axitinib when used after sunitinib. An analysis of the relationship between time to progression on first line sunitinib and PFS on axitinib did not exclude the possibility that resistance to TKIs develop on or after first-line therapy with sunitinib, resulting in reduced activity of the second-line TKI. It is acknowledged that mechanisms of resistance to VEGF-targeted therapy in patients with advanced RCC are still to be fully elucidated, but it is not considered that the applicant has addressed the issue of resistance adequately. At present, multiple agents for mRCC with overlapping mechanisms of action are being developed concurrently, but the rationale for selection of a second TKI is weak, and whether to select an mTOR instead of a TKI in second line treatment of RCC has not been thoroughly addressed.

The uncertainty of the therapeutic value of axitinib after failure of first line sunitinib is further strengthened by the lack of a clear rationale for preferring TKIs instead of the approved mTOR inhibitor (everolimus) for second line mRCC therapy.

Axitinib is less effective in terms of PFS and OS when used as second-line therapy after prior sunitinib than when used after first-line treatment with cytokines. In first line therapy of mRCC, however, TKI therapy (sunitinib) is much more effective (PFS and OS) than therapy with cytokines. Apparently, the treatment potential of TKI therapy is released during first-line therapy, and little gain of this therapy is achieved if repeated in second-line. Overall, the additional analyses of OS of patients in the pivotal trial examined from the start of first-line treatment with either sunitinib or cytokines to the time of death on or following second-line treatment with axitinib or sorafenib further contributes to the uncertainty of whether sequential therapy with axitinib after prior sunitinib is beneficial for patients with metastatic RCC.

Therefore, in the opinion of the divergent CHMP members the benefit-risk balance in the subpopulation of patients previously treated with sunitinib is considered negative.

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Pierre Demolis

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Jan Mazag

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Karsten Bruins Slot

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Kolbeinn Gudmundsson