SCIENTIFIC DISCUSSION

1. Introduction

Gastrointestinal stromal tumour (GIST)

Gastrointestinal stromal tumour (GIST) is a sarcoma of mesenchymal origin. In nearly 95% of cases, the primary tumour site is located in the gastrointestinal tract, where the most common locations are the stomach (50–60%) and small bowel (20–30%). Less frequently, GIST occurs in the large bowel (10%), esophagus (5%), and mesentery, omentum, or retroperitoneum (<10%)

GIST, estimated to represent up to 1% of all GI tumors, is the most common mesenchymal malignancy of the GI tract with a yearly incidence of about 7-15 per million (rising with age).

GIST often remains clinically silent until tumors reach a large size, when mass effects, bleeding, or rupture may ensue. GIST may also be discovered incidentally on computed tomography (CT) scan or during surgery performed for some other reason. Metastatic disease is present at diagnosis in nearly half of patients with GIST, most commonly to the liver (65%) and peritoneum (21%), but also to the lymph nodes, bone and lungs. After radical resection, the 5-year overall survival is approximately 50%, whereas for unresectable or metastatic GISTs, before treatment with imatinib became available, the median survival was estimated at 9 to 20 months.

Over 90% of GISTs express KIT, the receptor for stem cell factor (SCF). In the vast majority (over 80%), KIT is the abnormal product of a mutated *c-kit* gene, and shows constitutive TK activity without the presence of the normally required ligand, resulting in abnormal cell proliferation and inhibition of apoptotic cell death. Some GISTs, however, appear driven by the activity of wild type KIT, which may be inappropriately over-expressed, while 5% to 10% of GISTs are driven by mutated PDGFR-α.

Surgery is the standard treatment for non-metastatic GIST); however, recurrence is common, with reported recurrence rates ranging from 44% to 80%. Recurrence is usually local, although about half of local recurrences are accompanied by liver metastases.

Imatinib mesylate, an inhibitor of KIT, PDGFR, and the fusion protein bcr-abl, was the first effective non-surgical treatment for GIST. It is approved for the treatment of KIT-positive unresectable or metastatic GIST in the EU. A recently published, representative study, involving 946 GIST patients treated with imatinib 400 mg either once or twice daily, showed a complete response in 5% of patients, a partial response in 47%, and stable disease in 32% (median follow-up 760 days). There was no difference in response rates between the daily and twice-daily dose groups, but progression-free survival was longer with the higher dose, with 50% of patients on the high dose experiencing progression by 30 months compared to 56% on the lower dose.

Approximately 5% of patients cannot tolerate imatinib therapy, and another 15% exhibit primary resistance and fail to respond to treatment. It has also become apparent that secondary resistance, characterized by disease progression after an initial objective response, develops in many patients. Although little published data are available on longer-term follow-up of GIST patients treated with imatinib, overall, treatment failure is already known to occur in approximately 70% of patients.

Since no drug other than imatinib has demonstrated appreciable efficacy in the treatment of GIST, there remains an unmet medical need for patients who cannot tolerate imatinib, or who have tumors that are resistant to, or become resistant to, this drug. Sunitinib, by inhibiting KIT and PGDFR, is expected to exert direct anti-tumor effects in GIST. In addition, sunitinib may confer further benefit by inhibiting the angiogenesis necessary for tumor growth through its effects on VEGFR and PDGFR.

Metastatic Renal Cell Carcinoma (MRCC)

RCC, a malignancy originating from the tubular cells of the kidney, comprises 80% to 85% of all renal parenchymal malignancies reported from surgical series. Some 75% to 85% of RCCs are histologically classified as ‘clear cell’; these tumors tend to be very vascular, and typically metastasize to lung, bone, lymph nodes, and adrenal glands.

Incidence rates for RCC vary by more than 10- to 20-fold around the world, with higher rates in Western countries such as Scandinavia, France, Canada and the US, and the lowest rates in Central and South America and Asia. RCC is nearly twice as common among men than among women: for example, in the US in 2004, it is estimated that there were over 22 000 new cases in males (6% of all cancer diagnoses in males) and nearly 8000 deaths (3% of cancer deaths in males), compared to nearly 14 000 new cases and nearly 5000 deaths among females. A number of etiological associations have been described, including smoking, obesity, long-term hemodialysis, hypertension, sickle-cell trait, and genetic factors.

Receptor tyrosine kinases (RTK) activity appears to play a prominent role in the malignant transformation, growth and metastasis of many RCCs, often through inactivation of the *VHL* gene. This tumour suppressor gene codes for a protein that is responsible for regulating the transcription of VEGF, PDGF-B and a number of other hypoxia-inducible proteins. Through deletion, mutation or methylation, *VHL* is believed to be inactivated in as many as 80% of sporadic clear cell RCCs, resulting in overexpression of these ligands. Inappropriately expressed VEGF and PDGF-B promote tumour angiogenesis and, in those RCCs which also express VEGFR and PDGFR, further serve as signals in a stimulatory autocrine loop.

At least 25 to 30% of patients with RCC present with metastases. MRCC, based on 1992-1999 US data, has a 5-year survival rate of only 9.1%. Treatment of MRCC has been generally disappointing, and in some countries the poor results of systemic therapy in MRCC has resulted in the acceptance of supportive care as standard therapeutic approach. Many MRCC patients undergo nephrectomy, either for palliation of local symptoms, or because this may improve outcome when performed prior to cytokine therapy.

The only systemic first-line treatments available for MRCC are cytokines, but their efficacy is limited, and no effective second-line alternatives are available for those who fail to respond or progress after an initial response. Cytokine-based therapies include interferon-α (IFN-α). interleukin-2 (IL-2) and combinations of IL-2 and IFN-α. For patients who fail to respond to cytokine-based therapy or relapse after an initial response or period of disease stabilization, treatment options are very limited and generally ineffective, with rates of response to chemotherapy alone of less than 5%. Drug resistance may be related to the expression of the multidrug resistance transporter in proximal-tubule cells — the cells from which clear-cell and papillary renal-cell carcinoma may originate. Chemotherapy may be more efficacious for advanced non–clear-cell renal-cell carcinoma, particularly the collecting-duct type.

About the product
Sunitinib is an oral, multi-targeted tyrosine kinase inhibitor (TKI) that targets and blocks the signaling pathways of multiple selected receptor tyrosine kinases (RTKs). Through competitive inhibition ATP binding site, sunitinib inhibits the TK activity of a group of closely related RTKs, all of which are involved in various human malignancies: the vascular endothelial growth factor receptors (VEGFR-1, -2, -3), the platelet-derived growth factor receptors (PDGFR□□), the stem cell factor receptor (KIT), CSF-1R, FLT-3, and RET.

2. Quality aspects

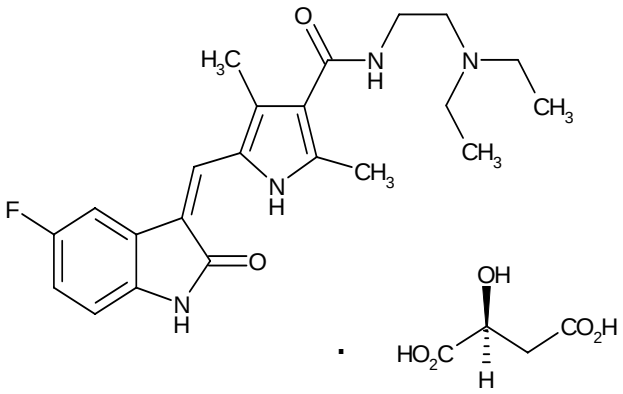
Introduction

SUTENT is presented as hard capsules containing 12.5mg, 25.0mg and 50.0mg of sunitinib malate as active substance. The excipients used in the formulation of SUTENT are mannitol, povidone, croscarmellose sodium and magnesium stearate. There are no novel excipients used in the formulation.

SUTENT is administered via oral route and is packed in HDPE bottles of 30 capsules with a polypropylene closure with heat induction seal (HIS) liner.

Active Substance

Sunitinib malate is designated chemically as (Z)-N-[2-(diethylamino) ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide(S)-2-hydrosuccinate and its structure is as follows:



Sunitinib is a yellow to orange powder soluble in acidic aqueous solutions (pH 1.2 – 6.8) at 25mg/ml. The solubility of sunitinib rapidly decreases at pH greater than 6.8. For this reason, sunitinib is classified as a low solubility compound according to the biopharmaceutical classification. Sunitinib is non-hygroscopic and the active moiety has no chiral centres, however the final substance is optically active due to the malate part of the molecule. Two different polymorphs are found during development studies by X-ray diffraction (PXRD). Form I is anhydrous, crystalline and non-hygroscopic with a typical peak melting point at approx. 205°C and is more stable than Form II at ambient conditions. The synthetic process produces Form I exclusively. Form II is highly disordered and hygroscopic and is not formed from the described synthesis/manufacturing process.

The isomer resulting from the described method of synthesis is sunitinib in the Z-isomer form. The corresponding E-isomer is limited in the drug substance specifications by specific test method (HPLC).

The dissociation constant (pKa) for sunitinib malate determined by potientiometric titration was found to be 8.95.

The permeability of sunitinib malate using a Caco-2 cell model was found to be 13 x 10^{-6} cm/s, hence sunitinib malate is considered a low permeability compound.

- Manufacture

Sunitinib malate is synthesized in 4 steps and 1 purification step. The established structure of sunitinib malate was in agreement with the method of synthesis, analytical and spectroscopic data. The molecular weight determined by mass spectroscopy was in agreement with the expected molecular weight. Definitive proof of structure was provided by X-ray crystallography.

- Specification

The specifications of the active substance include visual inspection of the appearance, identity (FT-IR spectroscopy and HPLC – comparison between main peak in test chromatogram and reference standard as well as L-malic acid reference standard), assay, residue on ignition, heavy metals, particle size by Laser Diffraction Light method), residual solvents by GC-FDI and potential impurities (HPLC).

The results obtained from thirteen batches of sunitinib malate manufactured using the proposed synthetic method showed that the active substance could be reproducibly manufactured.

The analytical methods used were sufficiently described and validated according to the ICH guideline on "Validation of Analytical Methods". The methods were suitable to control the active substance on a routine basis. The acceptance criteria for specified, unidentified unspecified, unspecified and total impurities was established based on consideration of the levels of impurities present in batches of sunitinib and sunitinib malate used in toxicological and clinical studies. In addition, the level of impurities at release and stability data of batches of sunitinib malate was also taken in consideration when establishing the acceptance criteria.

- Stability

Stability studies were performed on sunitinib malate stored in the proposed packaging, according to the ICH guideline. Stability data (12 months long term 25°C/60% RH; 6 months accelerated 40°C/75%RH) was provided on three batches manufactured at Pfizer Kalamazoo. Stability data (3 months long term and accelerated) was provided for one batch manufactured at Pfizer Cork Ltd. In addition, long-term data (36 months at 25°C/60% RH) was also completed for one batch of active substance. The test parameters selected to evaluate the stability of the active substance were appearance, assay, water content, and degradation products. DSC and X-ray studies have also been used to evaluate changes in the physical form of the active substance.

Photostability studies were carried out on one batch of sunitinib malate. The results showed that the active substance is not affected by exposure to light.

The data provided is sufficient to confirm the proposed re-test period.

Medicinal Product

- Pharmaceutical Development

The L-malate salt was chosen based on the physicochemical properties as well as acceptable processing properties.

Well known excipients were used in the preparation of the formulation, selected based on their suitability for use in a wet granulation process. The compatibility with the active substance was demonstrated with the results of the stability studies performed on the finished product. Mannitol is used as diluent, povidine as binder, croscaramellose sodium as disintegrant and magnesium stearate as lubricant. Gelatin, red iron oxide and titanium dioxide are excipients used for the orange capsule shell. Red iron oxide and yellow iron oxide are additional excipients used for the caramel capsule shell. Shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide are used in the printing ink. All excipients comply with the Ph. Eur. and the Certificate of Analysis have been provided.

Three hard capsules for immediate release of sunitinib malate were developed at doses of 12.5 mg, 25 mg and 50 mg of the free base. The qualitative composition of the three strengths is identical. A similar granule mix is used for the 25 mg and 50 mg strength capsules.

The primary packaging used for sunitinib malate capsules is HDPE bottles with heat induction seal (HIS) and polypropylene closure.

- Adventitious Agents

None of the excipients in the sunitinib malate blend are of animal origin, exception being the gelatin used in the capsule shell which is obtained from bovine/limed bone. TSE CEP from the suppliers of the gelatin used in the manufacture of the capsule shell are provided. However, the CEP provided by one of the suppliers of the bovine gelatin is expired. The Applicant therefore commits to provide an updated CEP for the gelatin sourced from this supplier and clarify the measures taken in order to ensure that only gelatin from sources covered by a valid CEP is used in the manufacture of the gelatin capsules.

- Manufacture of the Product

The manufacturing process for sunitinib malate capsules uses standard pharmaceutical equipment and unit operations.

The manufacture of the finished product comprises (1) blending of the active substance with the excipients (2) wet granulation of the blend (3) drying of the granulation (4) milling (5) addition of final excipients and blend (6) capsule filling.

Process parameter ranges are described for each manufacturing step. Process parameters that have a potential to affect the quality of sunitinib malate capsules were investigated. No critical steps or intermediates have been identified.

Batch analysis was performed on a total of 23 batches. The data confirmed that the hard capsules can be manufactured reproducibly according to the finished product specifications.

- Product Specification

The product specifications include methods for appearance, identification (HPLC and UV), assay (HPLC), content uniformity (HPLC), water content, degradation products (HPLC) and dissolution. The acceptance criterion for the dissolution test is acceptable and has suitable discriminatory properties. Therefore, satisfactory control of batch-to-batch consistency can be achieved for the finished product. Degradation products are controlled and the limits are justified by reference to stability studies.

The drug product specifications have been justified and all methods of analysis have been described and adequately validated.

- Stability of the Product

Stability data on 12 batches (3 primary batches of each strength and 1 batch from the supportive stability program for each strength) was provided. Nine primary batches were stored at 25°C/60% RH and 30°C/60% RH for 12 months and 40°C/75%RH for 6 months. Two batches (1 batch of 12.5mg and 1 batch of 50mg capsules) from the supportive stability program were stored at 25°C/60% RH for 24 months and one batch of 25 mg capsules was stored at the same conditions for 36 months. The parameters analysed were: appearance, assay, degradation products, dissolution, water content and microbiological integrity.

Three validation batches (of each capsule strength) were produced at the proposed commercial manufacturing site. The data provided demonstrates equivalence between these validation batches and the primary stability batches.

Based on the available stability data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of test 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 in the clinic.

At the time of the CHMP opinion, there were a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

Almost all pivotal non clinical studies were conducted with representative clinical grade material, in compliance with Good Laboratory Practices (GLP) with Quality Assurance documents included, and following FDA, OECD and Japanese Ministry of Health and Welfare guidelines for non clinical laboratory studies. The nonclinical development of sunitinib was consistent with the ICH guidelines including M3 guideline (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals), and ICH 7B (QT prolongation).

Pharmacology

A series of *in vitro* biochemical kinase assays have been conducted to evaluate sunitinib´s potency against intended receptor tyrosine kinase (RTK) targets as well as to determine relative selectivity against unintended RTKs. The *in vivo* efficacy of sunitinib was primarily evaluated in a xenograft tumour model where human and rat tumour cell lines derived from various different tumour types were implanted into the flanks of athymic SCID mice. Oral sunitinib treatment started when the tumours were established, which generally was considered when the tumours had reached a size of 300-500 cm^3. Studies were terminated when the tumours reached an average size of 1000 cm^3 or when the tumours were judged to adversely affect the well-being of the animals. The extent of RTK phosphorylation was determined by Western blotting.

- Primary pharmacodynamics

In vitro, sunitinib is a potent inhibitor of phosphorylation of the receptor tyrosine kinases (RTKs) VEGFR and PDGFR with K_i values in the nM range. Sunitinib inhibited VEGF-dependent endothelial cell proliferation, vascular sprouting and tube formation (IC_{50} = 4-55 nM). Similarly, sunitinib inhibited PDGF-induced proliferation of NIH-3T3 cells overexpressing PDGFRα or PDGFRβ with IC_{50} values of 69 and 39 nM, respectively. In nude athymic mice bearing human tumour xenografs, sunitinib demonstrated both time- and dose-dependent inhibition of PDGFRβ and VEGFR2 phosphorylation, where the degree and duration of RTK phosphorylation increased with increasing dose. Based on the *in vivo* results, the combined (sunitinib and SU012662) plasma concentration required to inhibit ligand-dependent phosphorylation of PDGFRβ and VEGFR2 is in the range of 50-100 ng/mL or greater. When considering that approximately 95% of the sunitinib and SU012662 are protein-bound, the total target plasma concentration at this effective dose will be in the nanomolar range (5-10 nM). Consequently, a nice correlation is seen between the *in vitro* and *in vivo* experiments. Indeed, a median C_{max} value of 104 ng/mL (sunitinib and SU012662) is reported in the clinical studies, which corresponds approximately to a free plasma concentration of 10 nM. Although a bit less potent than the parent compound (2 to 4-fold), the major sunitinib metabolite SU012662 inhibited VEGF and PDGF-dependent cell proliferation and likely contributes to pharmacologic activity against the intended targets.

Sunitinib demonstrated concentration-dependent inhibition of wild-type KIT phosphorylation in stem cell factor (SCF)-stimulated NCI-H526 human small cell lung cancer cells *in vitro* with an IC_{50} value of approximately 1 to 10 nM. A similar response was observed in SCF-stimulated MO7E human acute myeloid leukemia cells *in vitro* with an IC_{50} of approximately 10 to 100 nM. The ability of sunitinib to inhibit KIT phosphorylation was evaluated *in vivo* following repeated daily PO dosing of athymic mice xenografted with NCI-H526 lung tumour cells. Sunitinib caused a near complete inhibition of KIT phosphorylation in tumours analysed 4 hours (expected C_{max}) following administration of 40 and 80 mg/kg. KIT is implicated in the regulation of hair pigmentation and this effect was used to investigate the dose-response relationship for sunitinib inhibition of KIT. Following daily PO dosing of C57BL/6 mice for 28 days, sunitinib treatment at 80 mg/kg resulted in whitening of newly regrown hair, 40 mg/kg resulted in moderate greying of coat hair whereas lower dose levels (5 and 20 mg/kg) had no discernable effect on hair colour.

Sunitinib displayed affinity for RET in a receptor screen (IC_{50} = 83 nM). Sunitinib inhibited autophosphorylation of a constitutively active form of the RET RTK in human medullary thyroid cells

with an IC_{50} value of approximately 50 nM. Additionally, sunitinib inhibited thyroid cell proliferation with an IC_{50} value of approximately 50 nM.

Sunitinib inhibited FLT-ligand dependent FLT3 phosphorylation in AML cell lines expressing wild-type FLT3 with IC_{50} values of around 0.25 μM. Sunitinib potently inhibited constitutive proliferation of MV4;11 AML cells or FLT-ligand stimulated proliferation of OS-AML5 cells with IC_{50} values of 1 to 10 nM. In contrast sunitinib displayed no growth inhibiting effect in RS4;11 AML cells expressing wild-type FLT3. The ability of PO sunitinib to inhibit FLT3 phosphorylation *in vivo* was evaluated in athymic mice bearing MV4;11 AML xenografts expressing mutated and constitutively active FLT3. A single oral dose (20 mg/kg) completely inhibited FLT3 phosphorylation within 1 hour (drug plasma concentration = 277 ng/mL) and the effect lasted 16 hours following treatment (1 ng/mL).

Sunitinib inhibited constitutively active CSF-1R phosphorylation in NIH3T3 cells expressing high levels of CSF-1R with an IC_{50} value between 50 and 100 nM. Treatment caused a time and dose-dependent reduction in murine CSF-dependent development of murine osteoclasts *in vitro*.

Sunitinib was evaluated in a broad array of subcutaneous human tumour xenograft models that were derived from cell lines isolated from various solid tumour types including breast, lung, colorectal, melanoma, renal, glioblastoma, and others. Daily oral administration of sunitinib was demonstrated to result in significant growth inhibition of established tumours (100-550 mm^3) at well-tolerated doses in each xenograft model. Moreover, sunitinib caused regression of well-established tumours (250-550 mm^3) in several models including HT-29 and Colo205 colorectal and 786-O renal xenograft models (Figure 1). In the Colo205 colorectal xenograft model, a tumour regression of 13% and 38% was observed following 35 days of treatment with 40 and 80 mg/kg sunitinib, respectively. In another colorectal (HT-29) xenograft experiment, treatment with 40 mg/kg sunitinib caused a tumour regression of 62% at day 74 of treatment. Similarly, renal 786-0 tumour regression responses of 46 and 60% were reported following treatment with 40 and 80 mg/kg sunitinib, respectively.

Moreover, the efficacy of sunitinib was evaluated in tumour delay models. Following 64-days of PO sunitinib treatment (40 mg/kg/day), an increased survival (6/9) of athymic nude mice xenografted with MX-1 human breast carcinoma fragments was seen, when compared to vehicle treated mice (0/9) (animals were euthanized when the neoplasm reached a weight of 1.5 g). Sunitinib 40 mg/kg/day PO was efficient and well-tolerated in nude mice bearing LS174T human colon carcinomas with a statistically significant increase in survivors (4/5) at day 80. In mice bearing Lewis lung carcinomas, 10 mg/kg/day sunitinib produced an inhibition of tumour growth of 47%, while the higher doses levels 20, 40 and 80 mg/kg/day all inhibited tumour growth by 71-78% (day 16). Additionally, sunitinib demonstrated anti-tumour efficacy in several other cancer models including transgenic models, a carcinogen-induced model, a leukaemia model and in experimental metastasis models.

In several tumour models sunitinib demonstrated a dose-dependent effect. 40 mg/kg/day was found to be the optimal dose.

- Secondary pharmacodynamics

Sunitinib was evaluated in a radioligand binding screening assay to determine biochemical and/or cellular effects on 69 standard receptors, enzymes, or ion channels. Sunitinib inhibited the radioligand binding to several secondary targets with Ki or IC_{50} values in the μM concentration range. The most potent in vitro activity was observed in a biochemical assay, where sunitinib inhibited the human serotonin 5-HT_{2A} radioligand binding with a Ki of 26.2 nM. In follow-up experiments sunitinib demonstrated inhibition of serotonin reuptake in a cellular assay with an IC_{50} of 293 nM, and in a tissue assay, sunitinib displayed functional antagonist properties on the serotonin $5HT_{2A}$ receptor, with an IC_{50} of 28.4 μM.

- Safety pharmacology programme

The effect of 10-1000 nM sunitinib on cloned human hERG channels was investigated in stably transfected HEK293 cells using electrophysiology (n=4-5). A concentration-dependent inhibitory effect on the hERG channel was observed with an IC_{50} value of 266 nM. At a clinically relevant dose (10 nM), the hERG current was reduced by 17%. Sunitinib 10^{-6} M increased the action potential duration in canine Purkinje fibre cells, whereas no effect was observed at lower concentrations. The

major sunitinib metabolite SU012662 was a very weak hERG channel inhibitor with an IC_{50} value of 4.1 μM.

No meaningful effects on heart rate, body temperature or locomotor activity were noted at single PO administration of 5, 15, 50, or 150 mg/kg sunitinib tested dose. At both 50 and 150 mg/kg, a dose-related increase in the arterial blood pressure was observed. A dose-related prolongation of the QTc-interval was observed with peak increases of 46 ms and 66 ms in the 50 and 150 mg/kg group, respectively. The NOAEL for cardiovascular effects is 15 mg/kg.

General behaviour (Irwin's test) and body temperature were evaluated in rats following PO administration of 20, 100, or 500 mg/kg sunitinib (n=5/sex). NOAEL for behavioural effects and effects on body temperature is set at 500 mg/kg which corresponds to a safety margin of 65 (based on allometry).

Potential effects on the respiratory function was evaluated up to 4 hours following the administration of a 20, 100 or 500 mg/kg sunitinib to conscious unrestrained rats. NOAEL for respiratory effects is 500 mg/kg.

- Pharmacodynamic drug interactions

No pharmacology studies addressing pharmacodynamic drug interactions that are relevant to the present submission have been conducted.

Pharmacokinetics

- Methods

Following an extraction or protein precipitation step, plasma concentrations of sunitinib and its major metabolite SU012662 were determined by either liquid chromatography combined with tandem mass spectrometry detection (LC/MS/MS) or by high-performance liquid chromatography followed by tandem mass spectrometry detection (HPLC/MS/MS). Validation reports were provided for the quantification in rat, dog and monkey plasma. Sunitinib and SU012662 are photosensitive when in solution.

- Absorption

Plasma absorption was investigated following single dose PO and IV administration to nude mice, rat, dog and monkey. No statistically significant differences in sunitinib plasma exposure was observed between fasted and fed monkeys following single PO dosing.

Generally, the sunitinib and SU012662 plasma exposure (AUC and C_{max}) was higher at the end of a PO repeated-dosing period than on Day 1, indicating accumulation of sunitinib in rats and monkeys after multiple dosing. In rats, the increases in C_{max} or AUC were generally greater than proportional to the increase in dose level. There were no consistent gender differences in relation to plasma exposure in rats, although female rats often had higher parent drug plasma exposure and lower plasma exposure of SU012662 than the male rats. No gender differences were apparent in the monkey with respect to drug exposure. In monkeys, the SU012662 to parent compound plasma AUC ratio was around 0.5, while it appeared gender-specific in rats with ratios around 5 and 2 in males and females, respectively.

Pharmacokinetic sunitinib and SU012662 plasma data following IV infusion.

Study ID /Species	Route	N	Dose mg/kg	AUC ng*h/mL	t½, el h	Vd L/kg	Cls mL/(min*kg)
			Sunitinib				
Nude mouse/ PDM-030	IV	4 ♀	1	195	1.6	8.6	86
			10	2451	1.3	7.6	68
Rat/ PDM-033	IV	3-4 ♂	1	417	1.9	9.3	55
			4	2334	2.1	5.5	30
			8	7425	2.3	3.9	19
Rat/	IV	3[b]	2	998	2.5	8.8	40

PDM-034							
Rat/ PDM-035	IV	4 ♂	5	18832	4.8	1.8	4.6
Dog/ PDM-036[a]	IV	3[b]	1.25	515	6.1	21	41
Monkey/ PDM-064	IV	3 ♂	3	2018	14.9	21.1	25
SU012662							
Rat/ PDM-033	IV	4 ♂	4	6723	4.4	ND	ND
Monkey/ PDM-064	IV	3 ♂	3	814	119	ND	ND

Abbreviations: NA: Not Applicable. ND: Not Determined. BLQ: Below the limit of quantification
[a] : The vehicle was a Cremophor-based formulation
[b] : No data on the sex

- Distribution

In the concentration range 0.25 to 10 μM, sunitinib plasma protein binding was 98% in rat but 95% in monkey, dog and man. In athymic nude mice, plasma protein binding substituted 92% at 0.25 μM and 95% at 1 and 10 μM (PDM-060). Plasma protein binding of the metabolite SU012662 was around 98% in rat while lower binding percentages were seen in plasma from humans (90%), albino mouse (95%), dog (86%) and monkey (86%) (PDM-061). Binding of the monkey-specific metabolite M11 to plasma proteins was approximately 97%, 98% and 99% in monkey, rat and human plasma, respectively (PDM-039).

Sunitinib partitioned into red blood cells and the *in vitro* partition coefficients were 1.6, 1.4 and 4.1 in rat, human and monkey blood, respectively (PDM-040). *In vivo*, the sunitinib partition coefficients were in the range of 1.5 to 2.2 in mice and 0.5 to 1.2 in rats (PDM-037). Consequently, a discrepancy was seen with respect to the *in vitro* and *in vivo* rat blood partition data. *In vivo*, the metabolite SU012662 preferentially partitioned into red blood cells in mice but not in rats.

Sunitinib rapidly penetrated into the brain and reached brain tissue concentrations 7-fold greater than the plasma level 5 minutes post IV dosing of mice. Despite this high partitioning brain levels quickly decreased, thus 75% of the sunitinib was cleared from the brain 60 min following IV administration (PDM-095).

The tissue distribution of radiolabelled sunitinib was investigated using whole body autoradiography following oral dosing (15 mg/kg free base) of albino and pigmented rats (PDM-056). Sunitinib distributed to all sampled tissues and maximal tissue concentrations were seen at the first time point (3 h). There was a tendency for higher tissue concentrations in females than males. In both genders, sunitinib tissue levels were either very low or nondetectable 72 hours following dosing. Sunitinib displays affinity for pigmented tissues (melanin) since high concentrations were detected in the eye and uveal of pigmented rats even 336 hours following sunitinib administration.

Female monkeys were repeatedly administered 6 or 12 mg/kg/day sunitinib for 8 weeks followed by recovery, or for two cycles of 4-week daily drug treatment and a 2-week recovery (schedule 4/2) (PDM-057). At 24 hours post last dose, the combined sunitinib and SU012662 concentrations ($C_{24,\ tissue}$) in adrenal glands, bone marrow, pancreas, kidney, liver and brown fat were 13-308-fold higher than plasma concentrations ($C_{24,\ plasma}$) for both the 6 and 12 mg/kg/day group. White fat concentrations were 2- to 14-fold of $C_{24,\ plasma}$, while the ratios in brain were close to unity (1- to 3-fold). At two weeks after the last dose, the tissue concentrations were less than 1-5% of $C_{24,\ tissue}$.

- Metabolism

After IV and PO administration of ^{14}C-SU010398 (sunitinib malate salt) to rats, the sum of AUC of sunitinib and SU012662 accounted for 88-99% of plasma radioactivity AUC, indicating the absence of other significant metabolites in circulating plasma (PDM-055). However, after PO dosing of ^{14}C-SU010398 (salt form) to male and female monkeys, only intact drug and SU012662 were found as the major drug-related compounds in systemic circulation. The sum of AUC of sunitinib and SU012662 in plasma accounted for 31-42% of plasma radioactivity AUC (PDM-054).

In human liver microsomes, SU014335 (M3) was the major SU012662 metabolite (PDM-050). The formation of SU012662 from sunitinib was faster than the deethylation of SU012662 to SU014335 at all substrate concentrations tested. N-deethylation of sunitinib to its major metabolite SU012662 was catalysed by CYP3A4 in human liver microsomes (PDM-051). *In vitro* formation of SU012662 was catalysed by flavin-containing monooxygenases in rat and dog liver microsomes (PDM-049). In human hepatic microsomes, the metabolism of SU012662 was primarily catalysed by CYP3A4, but CYP1A2 may have contributed (PDM-050).

Sunitinib was detected in rat bile along with its phase I and phase II metabolites. Moreover, sunitinib, SU012662 (M1) and SU012487 (M2E) were detected at high levels in rat urine. In both rat bile and urine, SU012662 was the major metabolite regardless of the route of sunitinib administration. Similarly, sunitinib was detected in all monkey urine samples and accounted for 3-8% while SU012662 was the major metabolite (36-54%). In humans, sunitinib was excreted primarily as unchanged drug up to 72 hours post-dose while SU012662 and SU012487 were detected at lower levels.

- Excretion

In rats, the amounts of radioactivity recovered (as % of dose) over 72 hours in urine and faeces, respectively, were 9% and 77% (IV), 9% and 71% (PO) in female rats, and 9% and 75% in male rats (PO). The mean total recovery of all groups was approximately 82-87% (PDM-055). Drug-related radioactivity was excreted in bile in rats, but enterohepatic recirculation was not observed. In bile duct cannulated rats, 43% and 39% of the dose were excreted in bile and faeces, respectively, with a total recovery of 96% by 48 hours (PDM-070). In monkeys, the amounts of radioactivity recovered over 336 hours in urine and faeces, respectively, were 5% and 87% in male monkeys, and 6% and 84% in female monkeys. The mean total recovery, including cage washing, was approximately 91-94% (PDM-054).

Suntinib-related radioactivity had a higher affinity for the milk than the plasma at all time point following PO administration of 20 mg/kg ^{14}C-SU01398 (sunitinib malate salt) to lactating rats.

- Pharmacokinetic drug interaction studies

Sunitinib inhibited the CYP3A4-catalysed 1'-hydroxylation of midazolam by human hepatic microsomes with IC_{50} values ranging from 19 to 56 μM. The corresponding IC_{50} value for SU012662 was higher than 200 μM (PDM-052).

Toxicology

- Single dose toxicity

Exploratory acute oral toxicity studies were conducted in mice and dogs, while rats and monkeys were selected as the nonclinical animal models for full development. All animals were observed for clinical signs and mortality daily for up to 14 days, body weights were recorded weekly, and selected clinical laboratory parameters were measured. In studies with terminal endpoints, all animals were examined for gross pathologic changes at necropsy and selected tissues were examined histopathologically. Results are summarised in the table below:

Single dose toxicity studies

Study ID/ GLP status	Species/ Sex/Number/ Group	Dose (mg/kg) /Route	Approx. lethal dose / observed max non-lethal dose	Major findings
E-002059 Non-GLP	mice female CD-1 (5/group)	50, 150, 300, 500 oral gavage	NOAEL > 500	No-drug related changes
2000-0184 non-GLP	dogs Male/female Beagle (1/sex /group)	Dose-escalating 50, 250, 500 oral	MNLD > 500	No mortality Emesis in all animals on the day of treatment, diarrhea, mild hematology changes (increase in platelet and fibrinogen) at the highest dose
7039-152 non-GLP	Monkeys Female (2)	Oral followed by Intravenous 50 / 2		No mortality and clinical signs were observed
E-002066 nonGLP	rats Sprague Dawley Male/female (4/sex/group)	50, 150, 300, 500 oral	MNLD > 500	No treatment related deaths* Hypoactivity and slight decrease in body weight at 500 mg/kg
2000-0314 GLP	Cynomolgus monkeys (2/sex/group)	Dose-escalating 50, 150, 300, 600, 1200 (oral)	MNLD>1200	No mortality. Emesis in all animals on the day of treatment, diarrhea and decreased food intake, decrease in body weight, hematolgy changes (decrease in WBC counts, increase in fibrinogen, increase in AST, ALT, bilirubin, glucose, LDH, CK, HBDH) at doses >300 mg/kg. Minimal decrease in zymogen granules in the acinar cells of the pancreas at histological examination (only one female)

* two accidental deaths due to malintubation.

- Repeat dose toxicity (with toxicokinetics)

The pivotal repeat-dose toxicology studies were performed in rats and monkeys. The studies included an oral repeat-dose study of three months duration and a study applying 5 to 8 treatment cycles of 28 days duration separated by a recovery period of one week. Recovery was addressed in the pivotal studies. In the clinical setting, sunitinib is taken daily for 28 days followed by a 2-week rest period. Mortalities were observed in rats and monkeys during the course of the repeat-dose studies.

In both rats and monkeys, bone marrow hypocellularity (erythroid and lymphoid cell lineages), anaemia and lymphoid depletion of thymus, spleen and lymph nodes were observed at clinically relevant plasma exposures. Moreover, secondary infections were observed in monkeys treated daily for approximately two months. In a mechanistic study, sunitinib treatment significantly decreased the percent and numbers of rat bone marrow cells in the S-G2/M synthesis/tetraploidy phase of the cell cycle. At the end of the recovery period, bone marrow hypocellularity was resolved in monkeys exposed to clinically relevant drug (sunitinib and SU012662) levels when treated according to the clinical 4/2 schedule. Decreased neutrophil and platelet counts of grade 3 and 4 severity were reported in patients thus complete blood counts are performed at the beginning of each treatment cycle.

Adrenal gland haemorrhage was observed in both rats and monkeys at clinically relevant plasma exposures (AUC). Additionally, necrosis, fibrosis and blood-filled cysts were observed in rats along with decreased corticosterone and aldosterone levels. With exception of the necrotic lesions observed in the rat, the adrenal findings were reversible within approximately 6 weeks. In monkeys treated according to the 4/2 schedule, adrenal gland haemorrhage was the only residual finding at the end of the two-week recovery period. During the clinical trials (safety data, CT/MRI scanning and ACTH stimulation test), where only 1 subject out of 1400 experienced adrenal gland abnormality.

In repeat-dose studies performed in monkeys, treatment caused a modest decrease in heart rate and in a single study sunitinib treatment caused a decrease in cardiac preload and contractility. In a mechanistic study, QT-prolongation and compromised ventricular function were observed at 5-8 times

the clinical exposure level. No effect on ECG parameters was observed in the repeat-dose toxicity studies conducted in monkeys or in the clinic. Hypertension, on the other hand, was very common in the clinic.

Thickening of the epiphyseal cartilage (physeal dysplasia) was consistently observed in rats and monkeys, respectively, at clinically relevant plasma exposures. This effect was reversible within two weeks in monkeys treated according to the 4/2 schedule.

Degranulation of pancreatic acini occurred in both rats and monkeys without safety margin. In some cases also pancreatic inflammation was observed in the rat. In the clinical trials, two subjects have been reported with pancreatitis. Moreover, elevations in amylase and lipase were observed at greater frequency in the sunitinib-treated patients when compared to placebo patients.

A consistent finding in rats and monkeys was an increase in liver enzymes (ALT, AST), indicating a liver effect. Moreover, an increased urea and a reduced albumin plasma level were consistently seen in rats. However, the increase in liver enzymes was only higher than 2-fold in the high-dose groups following approximately three months of repeated dosing in which case it occurred at a rat/human exposure (AUC) multiple of 5.5 and 20 in monkeys and rats, respectively.

Following three months of repeated dosing of rats, pathological changes were observed in the bile ducts i.e. bile duct dilatation, inflammation, hyperplasia and necrosis. Overall, the bile duct changes occurred only in one species and at high exposure multiples when the animals were allowed a week recovery in between the treatment cycles.

Degenerative changes of corpora lutea but also decreased uterus, ovary and prostate weight were observed at clinically relevant plasma concentrations in rats and monkeys were. Following three months treatment of monkeys, the reduced ovary and uterus weights were not reversed at the end of a 6-week recovery period. At high dose levels, a wide range of effects were seen in the reproductive systems, which were not fully recovered following a 6-weeks treatment-free period.

Teeth caries and broken incisors was a common finding in treated rats. In rats, incisors erupt continuously. Similarly, bloody gums, oral cavity and tongue necrosis were reported in monkeys. Moreover, diarrhea, body weight loss and acinar hypertrophy in the salivary glands were common findings even at low dose levels.

Yellow discolouration of fur, skin, internal organs and urine was observed. Similarly, yellow discolouration of the skin is a common adverse effect in patients.

- Genotoxicity

Sunitinib did not induce reverse mutations in selected strains of Salmonella typhimurium and Escherichia coli. Treatment of human lymphocytes caused a decrease in the mitotic index following phytohemagglutinin stimulation starting from approximately 1 μg/mL. No increase in the incidence of chromosomal aberrations was observed in the concentration range tested, however, sunitinib induced numerical aberrations (polyploidy) in cultured lymphocytes at 10-20 μg/mL with and without metabolic activation. Although sunitinib induced evidence of toxicity and mortality in rats administered 1500 mg/kg (high-dose group), no statistically significant increase in micronucleated polychromatic erythrocytes was observed. As evidenced in the PO distribution studies, sunitinib does reach the bone marrow in rats.

- Carcinogenicity

Carcinogenicity studies using sunitib have not been performed**.**

- Reproduction Toxicity

An overview of the conducted reproductive and developmental toxicity studies is given in the table below.

Study type/ Study ID / GLP	Species; Number sex/ group	Route;dose (mg/kg free base)	Dosing period	Major findings	NOAEL (mg/kg) & $AUC_{sunitinib\ \&\ SU012662}$
Dose-range studies					
Embryo-fœtal development/ 2002-0254/No	Rat; 8 ♀/group	PO; 1, 5, 15, 30	GD 6 - GD 12	↑litter loss ↓foetal weight, foetal malformation	1 (910 ng*h/mL)
Embryo-fœtal development/ 2002-0613/No	Rabbit; 6 ♀/group	PO; 0.5, 1, 5, 20	GD 7 - GD 20	↑litter loss ↑resorptions, ↑post-implantation loss, foetal malformation	0.5 (288 ng*h/mL)
Pivotal studies					
Male fertility/ 2003-0370/Yes	Rat; 22 ♂/group	PO; 1, 3, 10	58 Days prior to mating - sacrifice	None	10 (49710 ng*h/mL)
Female fertility & early embryonic development/ 2003-0370/Yes	Rat; 22 ♀/group	PO; 0.5, 1.5, 5	14 Days prior to mating - GD7	Fertility: None Embryonic: ↑ dead embryos, ↑pre- and post-implantation loss	Fertility: 5 (9800 ng*h/mL) Embryonic: 1.5 (1667 ng*h/mL)
Embryo-fœtal development/ 2003-0372/Yes	Rat; 22 ♀/group	PO; 0.3, 1.5, 3, 5	GD 6 – GD 17	↑litter loss, ↓live foetuses, ↓foetal weight, ↑resorptions, ↑postimplantation loss, skeletal malformations	F0: 5 (10,600 ng*h/mL) F1: 3 (Maternal AUC: 4430 ng*h/mL)

GD, gestation day

Fertility and early embryonic development

In the male fertility study, rats were PO administered 1, 3 and 10 mg/kg sunitinib (free base) 58 days prior to mating with untreated females. Four males in the high-dose group were either found dead or euthanised during the pre-treatment period. Moreover, other signs of a toxic reaction in the high-dose males were observed in the form of clinical signs and decreases in body weight and food consumption. Sperm morphology, concentration, and motility were unaffected by treatment. At necropsy, two cases of small seminal vesicles and a case of flaccid testes were detected in high-dose males. Potential effects on female fertility was investigated by treating the females with 0.5, 1.5 and 5 mg/kg sunitinib 14 days prior to mating with untreated males. No effects on body weight, food consumption, oestrous cycle, copulation or fertility data were observed.

Female rats were treated with 0.5, 1.5 and 5 mg/kg PO sunitinib until Gestation Day (GD) 7. Subsequently, the females were sacrificed and necropsied on GD 14. Treatment-related findings were made in the 5 mg/kg treatment group, consisting of increases in the mean number of corpora lutea, mean number of dead embryos (foetuses), and mean percent pre- and post-implantation loss (2003-0370).

Embryo-foetal development

In a non-GLP rat dose-range finding study, dams were treated with 1, 5, 15 and 30 mg/kg sunitinib (free base) at GD 6 through GD 12. The dams were sacrificed on GD 20 and a caesarean section was subsequently performed. Maternal toxicity was evident in the 15 and 30 mg/kg treatment groups along

with two cases of mortality in the 30 mg/kg group. Total litter loss was observed in 3 of 8 litters in the 5 mg/kg group and in all litters in the higher dose groups. Corresponding decreases in gravid uterine weights and increases in post-implantation loss were noted. A reduction in mean foetal body weights was seen in the 5 mg/kg group. Foetal malformations (2 cases of acephalostomia in 1 litter) occurred with a NOAEL of 1 mg/kg. Consequently, the NOAEL for embryo effects is below clinical plasma exposure levels.

Rabbit does were PO treated with 0.5, 1, 5 and 20 mg/kg sunitinib on GD 7 through 20 as a part of a dose-range finding study. The high dose was not tolerated since the does were either found dead or euthanized on GD 14 or 15. Complete litter loss was observed in 4 of 6 does in the 5 mg/kg group. Increases in the number of resorptions (early and total) and post-implantation losses were detected, accompanied by reductions in uterine weights and the number of live foetuses. Treatment-related malformations were observed in both the 1 and 5 mg/kg dose groups. One foetus in the 5 mg/kg group had both a cleft lip and a cleft palate, while another foetus in the same litter was observed with a cleft lip. Moreover, one foetus in the 1 mg/kg group was observed with a cleft lip. There was no safety margin with respect to malformations since the malformation seen in the 1 mg/kg group occurred at approximately ¼ of the clinical plasma exposure level (AUC).

In the pivotal rat embryo-foetal study, the dams were treated with 0.3 to 5 mg/kg sunitinib at GDs 6 to 17. Caesarean section was performed on GD 21. Treatment-related embryo-foetal mortality was evident at 5 mg/kg by significant reductions in the number of live foetuses, increased numbers of resorptions (early and total), and corresponding increased post-implantation loss. In addition, total litter loss (complete reorption) occurred in 8 of 28 of the pregnant females at this dose. Furthermore, foetal body weight was reduced. Skeletal malformations were observed in 26.5% of foetuses (55% of litters) in the 5 mg/kg dose-group. The malformations consisted of thoracic and lumbar vertebral anomalies i.e. hemi centric, misaligned, and absent vertebral centra and/or arches. Moreover, skeletal variations characterized as decreased ossification was detected in the 5 mg/kg dose group along with a single case in the 3 mg/kg group. The NOAEL for the embryo-foetal effects was 3 mg/kg corresponding to an AUC based safety margin of 2.3. Body weight decrease and reduced gravid uterine weight was seen in the dams in the 5 mg/kg group and is attributed to the foetal loss at this dose level.

- Local tolerance

No dermal irritation was observed in three female rabbits exposed to 500 mg sunitinib for 4 hours via a patch (2000-0508). One hour following ocular administration of 100 mg sunitinib to three female rabbits slight conjunctival redness (3/3) and slight conjunctival oedema (2/3) were observed in the test animals. Conjunctival redness was still detected in two of animals 24 hours following ocular administration (2000-0509).

- Other toxicity studies

Phototoxicity

The UV absorption coefficient for sunitinib is 4.4×10^5 L mol^{-1} cm^{-1} at pH 7 and sunitinib enters the skin via systemic circulation and binds to melanin, thus photosafety is required as described in CPMP/SWP/398/01. As recommended in the guideline, the phototoxic potential of sunitinib was determined in the 3T3 neutral red uptake phototoxicity assay. A photo irritation factor of 1.995 and a mean photo effect of 0.042 were derived when testing sunitinib concentrations up to 8 mg/mL in the presence or absence of UVA light.

Wound healing

Sunitinib's potential effect on wound healing was evaluated in female SKH1 mice PO administered 40 and 80 mg/kg for up to five consecutive weeks (n=4-10). On day six, a full-thickness incision was made on the back of all mice, which then were sealed with nylon sutures. Subsequently, the strength of the healed wounds was evaluated on Days 13, 20, and 34. Mice treated with 40 mg/kg/day had wound tensile strength comparable to control, at all time points evaluated. Transient treatment-related effects were observed in mice treated with 80 mg/kg/day, corresponding to a 40% decrease in wound tensile strength on Day 20 (ex5144, non-GLP). Consequently, the NOAEL for wound healing effects in mice is 40 mg/kg/day. At treatment Day 20, combined sunitinib and SU012662 plasma exposure (C_{max}) in this dose group was 1792 ng/mL, which corresponds to 16 times the clinical C_{max}.

Ecotoxicity/environmental risk assessment

Based on the estimated value of predicted environmental concentration (PEC surface water) for SUTENTof 0.38 µg/L phase II Environmental Effect Analysis has been performed. Both the PEC and the revised PEC are approximately 2 orders of magnitude lower than the lowest no observed effect concentration (NOEC) determined under the test conditions for various species tested. The PEC/PNEC surfacewater is determined to be 0.04.

- **Discussion on the non-clinical aspects**

In vitro data showed that Sunitinib potently inhibited KIT phosphorylation in cells expressing exon 11 mutations whereas a lower affinity was observed toward exon 9 mutants. Patients with primary KIT exon 11 mutations appear to be less likely to derive clinical benefit (11%) from Sunitinib treatment than are patients with primary exon 9 mutations, wild-type KIT or PDGR-α, or PDGFR-α mutations. Moreover, a reduced clinical benefit (15%) was observed in patients with a secondary KIT exon 17 or 18 mutations regardless of the primary KIT genotype. It should be considered that these preliminary conclusions are based on a low patient number. Molecular analyses of tumours from a phase III study are ongoing.

The finding in the non-clinical (in vitro and in vivo) safety pharmacology studies indicate that Sunitinib after single dose has the potential to inhibit the cardiac action potential repolarization process (eg, prolongation of QT interval). No respiratory function impairment (except a slight and transient increase of total tidal volume (30% 30 min after treatment) are observed after single oral administration of 500 mg/kg in rats. No specific safety studies on kidney have been presented.

Pharmacokinetics

Sunitib shows a PK profile characterised by a dose-dependent but not dose-proportional increase in Cmax and AUC values [greater than proportionality in rats (non linear kinetics in this species), lower in monkeys] and increases in elimination half-lives with increasing dose that were accompanied by decreasing clearance rates. This profile in non human primates is probably due to the significant saturation of the absorption at high doses. No evidence of accumulation derived from findings of the PK studies, but accumulation has been observed in humans. Accumulation is independent of dosing schedule, and no further accumulation of Sunitinib or SU012662 occurs beyond the first dosing cycle in any of the dosing schedules tested (from the Overall Clinical Summary).

SU011248 and its metabolites cross the blood-brain-barriers, are distributed into CNS and their brain concentrations decreased with time, similar to the decline of plasma concentrations with time.

Neither Sunitinib nor SU012662 are anticipated to be potent inhibitors of major CYP450 enzymes or to have significant inductive effect on the activity of CYP1A2, CYP2E1, and CYP3A4/5. Thus, both Sunitinib and SU012662 are predicted to have low potential to increase or inhibit the clearance of concomitantly administered drugs that are metabolized by these major CYP450 enzymes. The overall available data indicate that a sufficient higher exposure has been obtained in preclinical studies using suitable animal models. No gender-related differences in disposition were observed across species except in the rat in which higher plasma levels have been obtained in female animals. Pregnancy does not appears to alter disposition in rats and rabbits.

Toxicology

Rats and monkeys were chosen by the Applicant as species for the evaluation of the toxicological potential of Sunitinib. The primary target organs of Sunitinib were the hemolymphopoietic system (bone marrow hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node), the exocrine pancreas (acinar cell degranulation with single cell necrosis in rats), the adrenal gland (cortical congestion and hemorrhage in rats and monkeys, with necrosis followed by fibrosis in the rat), the salivary gland (acinar hypertrophy), the gastrointestinal system (emesis and diarrhea in monkeys, and single incidences of intestinal necrosis associated with erosion/ulceration), the developmental and reproductive system. All findings showed reversibility following termination of treatment, except for effects on adrenal, pancreas and reproductive system. Sunitinib has shown to affect reproductive system both in male and female animals at systemic exposure comparable to the mean human exposure at recommended dose of 50mg/day: based on the available non-clinical data, Sunitinib treatment may result in adverse effects on reproductive function and fertility in humans.

In addition, other findings on cardiovascular system, kidney, liver, and bone growth plate have been observed. Evidence of QT prolongation, left ventricular dysfunction, bradychardia and mild diastolic dysfunction have been observed at 6mg/kg/day in the cardiovascular investigative study and in the 39-week monkey study. A chronic progressive nephrosis in the 6 months rat study (1.5 mg/kg/day: day168 AUC = 2128 ng-h/mL), was still present at the end of the 8-week recovery period. In a 9-month monkey study increased mesangial matrix in the kidney cortex was observed. Changes in liver weight and increase in liver parameters suggest a treatment related hepatic dysfunction. Thickening (physeal dysplasia) of the growth plate, characterized by disrupted endochondral ossification of long bones was observed in Sunitinib-treated rats and monkeys.

Sunitinib was not mutagenic in bacteria using metabolic activation.

The carcinogenic risk of Sunitinib to humans is unknown, as carcinogenicity studies have not been conducted.

Sunitinib should be labelled "probably phototoxic". An evaluation of photogenotoxicity and photocarcinogenicity is not considered necessary.

Embrio-fetal development study in rats and rabbits have shown maternal toxicity and treatment related malformation at doses comparable to the mean human exposure at recommended dose of 50mg/day. No peri- and post-natal toxicity study program has been performed. Based on the available non-clinical data, Sunitinib should not be taken during pregnancy or by any woman who is not using adequate contraception, unless the potential benefit justifies the potential risk to the fetus. Additionally, women should be advised against breastfeeding while taking Sunitinib. Section 4.6 and 5.3 of the SPC have been revised accordingly.

SUTENT does not present an environmental risk following patient use.

4. Clinical aspects

Introduction

All clinical studies were conducted in accordance with good clinical practice (GCP) and were consistent with each local country's guidelines on drug development.

Pharmacokinetics

In support of this marketing application, the following pharmacokinetic studies were conducted:

- 2 single-dose studies in healthy volunteers (248-ONC-0511-001 and A6181031)
- 4 single-dose bioequivalence/bioavailability studies in healthy volunteers (248-ONC-0511-004, A6181032, A6181033 & A6181046)
- 2 single-dose drug-interaction studies in healthy volunteers (RTKC-0511-009 & A6181001)
- 1 dose-escalating study in patients with malignant disease (248-ONC-0511-006)
- 6 multiple-dose studies in patients with malignant disease (248-ONC-0511-002, RTKC-0511-005, RTKC-0511-013, RTKC-0511-014, RTKC-0511-016, RTKC-0511-018)

In total, the Applicant conducted 15 clinical Phase 1-3 studies with sunitinib – including 8 studies in healthy subjects, 1 study in patients with acute myeloid leukaemia (AML) and 6 studies in patients with solid malignant tumours.

Summary of Sunitinib and SU012662 PK Parameters in Healthy Subjects by Study and Treatment Group Following a Single-Dose of Sunitinib

Parameter	Statistic	Study 001	Study 004		Study 009	Study 1001	Study 1031	Study 1032	Study 1033			Study 1046	
			Trt. A	Trt. B				Fasted	Trt. 1	Trt. 2	Trt. 3	Trt. 1	Trt. 2
		50 mg (n = 6)	50 mg (n = 14)	50 mg (n = 13)	10 mg (n = 27)	50 mg (n = 25)	50 mg (n = 6)	50 mg (n = 16)	50 mg (n = 23)	50 mg (n = 22)	50 mg (n = 23)	12.5 mg (n = 16)	12.5 mg (n = 16)
Sunitinib													
C_{max}[a] (ng/mL)	Mean	37.7	24.1	25.5	23.8	30.1	24.4	26.3	31.5	31.0	31.3	23.0	22.4
	%CV	25	26	24	23	24	16	32	38	36	32	25	24
$AUC_{0\text{-}last}$[a] (ng*hr/mL)	Mean	943	996	1108	1267	1318	1052	1534	1582	1575	1556	1373	1374
	%CV	25	35	35	37	23	25	28	35	35	32	22	24
$AUC_{0\text{-}\infty}$[a] (ng*hr/mL)	Mean	1350	1029	1131	1318	1328	1063	1546	1592	1587	1566	1418	1418
	%CV	32	34	36	36	23	25	28	34	35	31	22	24
T_{max} (hr)	Median Min, Max	6 5, 16	7 4.5, 10	6 4.5, 12	8 5, 16	8 7, 12	8 8, 8.1	8 8, 16	8 8, 12	8 8, 12	8 8, 12	12 8, 16	12 8, 16
$T_{1/2}$ (hr)	Mean	26.9	38.1	39.0	42.2	48.9	50.9	60.0	51.7	52.0	51.9	55.6	53.7
	%CV	27	23	16	20	23	13	18	21	24	21	23	24
CL/F (L/hr)	Mean	40.4	54.3	50.9	42.7	39.5	49.9	35.0	34.3	34.8	34.6	37.0	37.2
	%CV	32	35	42	35	21	28	30	27	31	28	24	24

%CV = Percent Coefficient of Variation; $AUC_{0\text{-}\infty}$ = Area Under the Plasma Concentration Time Curve From 0 Extrapolated to Infinity; $AUC_{0\text{-}last}$ = Area Under the Plasma Concentration Time Curve From 0 to Time of the Last Measurable Concentration; CL/F = Oral Clearance; C_{max} = Maximum Concentration; $T_{1/2}$ = Terminal Half-Life; T_{max} = Time to Maximum Concentration; Trt. = Treatment.

Data shown are for the following sunitinib treatments:

Study 001: 50-mg sunitinib free-base; Study 004: 50-mg free-base fasted (Trt. A), 50-mg L-malate fasted (Trt. B); Study 009: 10-mg sunitinib L-malate alone; Study 1001: 50-mg sunitinib L-malate alone; Study 1031: 50-mg [^{14}C]-sunitinib L-malate; Study 1032: 50-mg sunitinib L-malate proposed commercial formulation (fasted); Study 1033: 50-mg sunitinib L-malate clinical trial formulation (Trt. 1), 50-mg sunitinib L-malate proposed commercial formulation (Trt. 2), Four x 12.5-mg sunitinib L-malate proposed commercial formulation (Trt. 3); Study 1046: 12.5-mg sunitinib L-malate clinical trial formulation (Trt. 1), 12.5-mg sunitinib L-malate proposed commercial formulation (Trt. 2).

[a] C_{max} and AUC parameters have been normalized to a 50 mg sunitinib dose, where appropriate. To normalize to a 50 mg sunitinib dose in Study A6181046, C_{max} and AUC were multiplied by 4.

- Absorption

After oral dosing, both sunitinib and SU012662 reach Cmax at around 6 to 12 hours, followed by a bi-exponential decline in concentrations. Terminal half lives range from 40 to 60 hours for sunitinib and from 80 to 110 hours for SU012662. Consistent with these half-lives, accumulation with daily dosing is 3- to 4-fold for sunitinib and 7- to 10-fold for SU012662, or 3.5 to 4.5-fold for total active drug (sunitinib + SU012662). Accumulation is independent of dosing schedule, and no further accumulation of sunitinib or SU012662 occurred beyond the first dosing cycle in any of the dosing schedules tested.

With daily dosing, steady-state conditions are achieved by day 14 for sunitinib, SU012662 and total active drug. With a daily dose of 50 mg, trough levels of total drug are in the pre-clinically determined therapeutic range (> 50 ng/mL) by day 7.

- Distribution

Sunitinib/SU012662 binding to human plasma proteins were 95% and 90% respectively, with no apparent concentration dependence at concentration ranges of 99.6 to 3985 ng/mL for sunitinib and 92.6 to 3700 ng/mL for SU012662

The blood to plasma partitioning of sunitinib in humans was evaluated both *in vitro* and *ex vivo*, showing that sunitinib preferentially partitions into erythrocytes.

The apparent (Vd/F) of sunitinib has not been estimated because sunitinib has not been administered intravenously in humans. From a cross-study population PK analysis in HVs and patients, the Applicant estimated a Vd/F of sunitinib of approximately 2230 L; this is consistent with the large Vd/F (4-21 L/kg) observed in rats and monkeys.

- Elimination

Sunitinib was the primary species identified in plasma, faeces, and urine, followed by SU012662.

Faecal excretion was the major route of elimination of sunitinib. Over a 21-day collection period, total recovery of radioactivity was approximately 77%, with 61% in the faeces and 16% in urine, of which the majority was excreted within the first 7 days.

- Dose proportionality and time dependencies

The dose proportionality of sunitinib, SU012662, and total drug (sunitinib + SU012662) has been evaluated in oncology patients following single dosing with sunitinib doses ranging from 50 to 350 mg, and multiple (QD) dosing with doses of 25 to 100 mg (Schedule 4/2). Based on regression analyses of these data, the PK of these analytes appeared to be dose proportional over this dose range (95% CIs on the slopes of log-log regressions included a value of 1 or were close to 1).

Accumulation per cycle was approximately 3- to 4-fold for sunitinib and 3.5- to 4.5-fold for total drug (sunitinib + SU012662) with repeat dosing, and was independent of dosing schedule (ie, 14- or 28-day dosing). In the case of SU012662, accumulation was 7- to 10-fold across schedules and appeared to be slightly higher with 28-day than with 14-day dosing, but the difference was small.

No accumulation between cycles was noted.

- Special populations

No clinical studies have been conducted to evaluate the PK of sunitinib in patients below 18 years of age. The development of a paediatrics programme has been planned by the company

No clinical study was conducted to evaluate the PK of sunitinib in subjects with hepatic or renal impairment. No relationship was observed between hepatic or renal function and sunitinib PK in the population PK analysis.

The dataset used for population PK analysis included ages ranging from 18 to 84 years. No age effect on CL/F of either sunitinib or SU012662 was shown. Therefore, AUC is not affected by age.

The dataset used for population PK analysis included 195 males and 83 females. Females showed a 31% decrease in CL/F of sunitinib and a 26% decrease in CL/F of SU012662, relative to males. Weight was positively correlated with Vd/F of sunitinib, and CL/F and Vd/F of SU012662.

This was translated to a 16% (due to decreased CL/F of SU012662 only) increase in total drug mean steady-state AUC, with a similar effect on C_{max} for lower weight subjects ($\leq$40 kg) and to a 5% decrease in both AUC and C_{max} of total drug in higher weight individuals ($\geq$ 100 kg).

- Pharmacokinetic interaction studies

In vitro

Sunitinib had little or no effect on the activities of CYP1A2, CYP2E1, and CYP3A4/5 in cultured human hepatocytes. SU012662 caused a concentration-dependent increase in CYP1A2 activity (up to

2.2-fold at 10 μM [3.70 μg/mL], on average). As an inducer of CYP1A2 activity, SU012662 was as effective as rifampin, but only 25% as effective as β-naphthoflavone. SU012662 had little or no effect on other P450 isoenzymes.

Data from HCT-8 and Caco-2 cell lines indicated that sunitinib was either not a substrate or was, at most, a moderate substrate of the transporter protein, P-glycoprotein (P-gp); sunitinib was not a substrate for the breast cancer resistant protein (BCRP) transporter. At clinically relevant concentrations (50 ng/mL or greater), these transporters are not expected to affect the PK of sunitinib.

In vivo

In Study RTKC-0511-009 (single-dose, randomized, open-label, 2-way crossover design study) subjects were randomized to receive either sunitinib malate 10 mg PIB on Day 1 or ketoconazole 400 mg QD on Days 1 through 7 with a single 10-mg dose of sunitinib malate on Day 3. Subjects were then crossed-over with at least a 4-week washout period between treatment periods.

Administration of ketoconazole with sunitinib resulted in a significant increase in mean sunitinib C_{max} (59%), $AUC_{0\text{-last}}$ (76%), and $AUC_{0\text{-}\infty}$ (74%). Sunitinib T_{max} and $T_{1/2}$ were not affected. Mean SU012662 C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ decreased by 29%, 16%, and 12%, respectively, and T_{max} was prolonged following ketoconazole coadministration. $T_{1/2}$ of SU012662 was not affected.

Study A6181001 was a single-dose, randomized, open-label, 2-way crossover design study to investigate the potential for PK interaction when sunitinib was given in combination with rifampin. Subjects were randomized to receive either a single dose of sunitinib malate 50 mg or rifampin 600 mg QD for 17 days combined with a single dose of sunitinib malate 50 mg on Day 8. Subjects were then crossed over with at least 2 weeks separating treatments.

Administration of rifampin with sunitinib resulted in an approximate 80% mean reduction in sunitinib $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ as compared with sunitinib alone. A 56% mean reduction was observed in sunitinib C_{max} with the combination sunitinib and rifampin. Sunitinib T_{max} was not affected. Consistent with CYP3A4 induction, $T_{1/2}$ decreased with rifampin coadministration. The values of most SU012662 PK parameters (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$) increased after administration of the combination of sunitinib and rifampin relative to administration of sunitinib alone. Mean SU012662 $AUC_{0\text{-}\infty}$ increased by 27%, $AUC_{0\text{-last}}$ by 29% and C_{max} by 137% when sunitinib was administered with rifampin as compared to sunitinib alone. The magnitude of change in SU012662 exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$) with rifampin coadministration was not as large as that seen with sunitinib. No difference was observed in SU012662 T_{max}. Consistent with an increase in metabolism, SU012662 $T_{1/2}$ was slightly decreased (approximately 20%) with rifampin coadministration.

Pharmacodynamics

The PD sunitinib has not been studied directly in humans since no adequate biomarker reaction has been identified.

Relationship between plasma concentration and effect

Data collected from 6 clinical studies were pooled for the population PK/PD analysis. Tentative relationships with exposure were identified for time to progression, fatigue (both linked to steady-state AUC of total drug), diastolic blood pressure (linked to concentration of total drug), and absolute neutrophil count (linked to cumulative AUC of total drug, dropping contributions preceding a 28-day window).

Modelling of fatigue suggested that total steady-state AUC affects incidence but not severity of fatigue; fatigue achieves steady-state levels after one cycle; and there is less drug-related fatigue in GIST and MRCC patients than solid tumor patients. For a typical GIST patient, the model predicts that the probability of any fatigue would increase from 65% at 50 mg QD to 80% at 75 mg QD, and would fall to 46% at 25 mg QD. For a typical MRCC patient, the model predicts that the probability of any fatigue would increase from 74% at 50 mg QD to 86% at 75 mg QD, and would fall to 57% at 25 mg QD. For a typical Solid Tumor patient, the model predicts that the probability of any fatigue would increase from 92% at 50 mg QD to 96% at 75 mg QD, and would fall to 85% at 25 mg QD. Modelling of neutrophil data suggested that absolute neutrophil counts (ANC) are negatively correlated with exposure and achieve steady-state levels after one cycle; and there are more drug related ANC changes

in GIST and MRCC patients than solid tumor patients. For a typical GIST patient, the model predicts that mean ANC would decrease 36% at 50 mg QD, 54% at 75 mg QD, and only 18% at 25 mg QD. For a typical MRCC patient, the the model predicts that ANC would decrease 30% at 50 mg QD, 45% at 75 mg QD, and 15% at 25 mg QD. For a typical Solid Tumor patient, the model predicts that ANC would decrease 26% at 50 mg QD, 39% at 75 mg QD, and 13% at 25 mg QD.

Diastolic blood pressure (DBP) modelling predicted that a typical patient on 25 mg QD or 75 mg QD would experience a maximum DBP elevation of 5 mmHg and 9 mmHg above pre-treatment DBP levels, respectively, vs. 8 mmHg at 50 mg QD.

Clinical efficacy

- Dose response study(ies)

The dose and schedule of sunitinib was based upon an assessment of dose limiting toxicities (DLTs) in 2 Phase 1 studies in patients with advanced malignancies. Starting doses of 25 to 100 mg QD were administered to patients in escalating dose cohorts on Schedules: 4/2 (4 weeks on /2 weeks off) , 2/2 and 2/1. The maximum tolerated dose determined in each of these studies was 50 mg regardless of the schedule tested and there was no difference in the safety profile between the schedules. Schedule 4/2 provided the greatest sunitinib exposure and because of the anti-tumours activity observed in Phase 1, Schedule 4/2 was chosen by the Applicant as the recommended schedule for further exploration.

The Applicant conducted a Phase 1/2 open-label, single-arm, dose-escalating study at 2 centres in the United States (Study RTKC-0511-013). The study was originally designed as an open-label, dose-escalation Phase 1 study, to identify sunitinib regimens suitable for Phase 2 development. This was accomplished with the selection of 50 mg QD of sunitinib on Schedule 4/2. At that point a Phase 2 portion was added to evaluate the clinical benefit of this regimen. Fifty-five patients were enrolled at a starting dose of 50 mg QD on Schedule 4/2 and their data are provided by the applicant as an additional supportive study to the main study.

Gastrointestinal Stromal Tumour (GIST)

The clinical efficacy of sunitinib for the GIST indication is based on data from 1 pivotal Phase 3 and 1 main supportive phase 1/2 trial. These are listed in Table GIST-1, along with the continuation protocol open to patients who have completed sunitinib studies.

Table GIST-1 SUTENT: Supportive and Pivotal Clinical Trials (GIST) With Continuation Protocols

Protocol	Study Status	Study Design	N
RTKC-0511-013 Phase 1/2	Completed	Single-arm, open-label, multi-center, dose-escalating in GIST patients (US based)	55 [a]
Pivotal			
A6181004 Phase 3	Ongoing	Double-blind, placebo-controlled, multinational in GIST patients	312 [b]
Continuation			
RTKC-0511-017, A6181030	Ongoing	Open-label continuation study for patients with GIST, MRCC, and other cancers who would benefit from further sunitinib treatment.	24 GIST [c,d], 18 MRCC [c]

[a] Study RTKC-0511-013 also included 42 patients who received sunitinib at a starting dose other than 50 mg QD, or on a schedule other than Schedule 4/2.
[b] as of 01 January 2005
[c] As of 01 December 2004.
[d] The 24 GIST patients include 1 patient from Study A6181004 who was transferred to this protocol after a decline in performance status.

Both studies RTKC-0511-013 and Study A6181004 were confined to patients with malignant GIST who had tumours that were resistant to imatinib, or who were intolerant of imatinib. Enrollment in both studies is closed and the supportive study has been completed. In Study A6181004, a planned interim analysis of efficacy was performed on the database as of 01 January 2005, which included results from 125 patients with disease progression (44% of the planned total number of events). The

analysis revealed that the primary objective had been met. The Independent Drug SafetyMonitoring Board therefore recommended that the study be unblinded and that all patients receiving placebo should receive sunitinib.

- Main studies

METHODS

Study Participants

Patients eligible for Study A6181004 were to have experienced failure during prior imatinib treatment due to disease progression defined by RECIST or World Health Organization (WHO) criteria (confirmed retrospectively by the core imaging laboratory) or intolerance defined as life-threatening toxicity at any dose or unacceptable toxicity at a moderate dose (ie, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 toxicity or Grade 2 toxicity that was unacceptable to the patient, such as nausea). Patients were to be at least 18 years of age, have histologically-proven GIST that was not amenable to therapy with curative intent, measurable disease, adequate organ function as defined in the entry criteria and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were not eligible for the study if they had received treatment including chemotherapy, chemoembolization, immunotherapy, or an investigational agent after failure of imatinib or radiotherapy to all sites of disease progressing on imatinib.

Treatments

Patients were randomized to either sunitinib 50 mg QD on Schedule 4/2 (4-week treatment followed by a 2-week off-drug per treatment cycle) or matched placebo capsules in a 2:1 fashion; at the time of interim analysis, 207 patients were randomized to the active drug and 105 to placebo. Dose reductions were allowed for tolerability.

Objectives/outcomes/endpoints

For the pivotal trial, Study A6181004, TTP was the primary endpoint, defined as the time from the first dose of study medication to first documentation of PD. For patients who did not have objective disease progression, died due to any cause, or were given antitumor treatment other than the study treatment prior to PD, TTP was censored on the day after the date of the last disease assessment documenting absence of PD. For patients who lacked on-study assessments, TTP was censored at the date of the first dose of study medication. Secondary efficacy endpoints included PFS, OS, ORR, and DR. The primary analyses for all efficacy endpoints were performed in the ITT population. Tumours-related endpoints were evaluated using RECIST and the primary analyses used results of assessment by the independent core imaging laboratory.

Sample size

The study was designed to test whether treatment with sunitinib resulted in at least 50% improvement in median TTP over placebo; the median TTP was assumed to be 4 months in the placebo group based on an investigator survey. The planned sample size was 357 patients (238 on sunitinib and 119 on placebo) to obtain 281 PD events. Other assumptions included a planned accrual period of 18 months, a minimum follow-up period of 6 months, and an expectation that approximately 5% of patients might be lost to follow-up.

Randomisation

Patients were randomized 2:1 to receive sunitinib capsules or matching placebo capsules The stratification factors were 1) prior progressive disease (PD) within 6 months of the start of imatinib treatment vs. PD beyond 6 months from the start of imatinib treatment vs. intolerance, and 2) baseline McGill Pain Questionnaire's Present Pain Intensity (MPQ-PPI) score (0 vs. $\geq$ 1).

Blinding (masking)

A double-blind study design was used. Patients were to continue blinded treatment until PD or withdrawal for other reasons. At the time of PD, treatment was unblinded; patients randomized to

placebo were offered crossover to open-label sunitinib and patients randomized to sunitinib were permitted to continue treatment.

An independent DSMB monitored the conduct of this pivotal trial through quarterly data analysis and meetings. Analyses for the DSMB were prepared by an unblinded third-party statistician who was not otherwise involved in the study conduct.

Statistical methods

Standard statistical methods were used. The primary analysis of TTP was based on a two-sided unstratified log rank test. Secondary analyses were stratified by previous imatinib treatment (≤ vs. > 6 months), baseline MPQ-PPI score (0 vs. ≥ 1), age (< vs. ≥ 65 years), sex (male vs. female), race (white vs. nonwhite), ECOG performance status (0 vs. 1), time since initial diagnosis (< vs. ≥ 6 months), and baseline weight (continuous).

RESULTS

Participant flow

The ITT population consisted of 312 randomised patients, 207 to sunitinib and 105 placebo respectively, with 5 and 3 patients not treated or without available treatment record, respectively.

Recruitment

Patient enrolment (randomization) began 17 December 2003 and ended 01 January 2005.

Conduct of the study

The first planned interim efficacy analysis was performed when approximately 50% of the required number of progression events had occurred. The data cutoff for the analysis was 01 January 2005; on that date 312 patients had enrolled on the study. During discussions within the independent DSMB between 24-26 January 2005, the board concluded that the study had met the primary endpoint, as well as demonstrating survival advantage, and recommended that the blinded study be discontinued and all remaining patients allowed access to open-label sunitinib.

Baseline data/Numbers analysed

Overall, the baseline disease characteristics and prior treatment history of the patients were similar between the sunitinib group and placebo group in Study A6181004 and between the 2 studies. Approximately 88% of patients in each study were white. In Study A6181004, males comprised 63.8% and 61.0% of the sunitinib and the placebo populations respectively. The median age ranged from 55 to 58 years among the studies/treatment arms. All patients entered the studies with an ECOG performance status <2 at the screening visit.

History of Malignancy and Prior Tumours Treatment

Overall, the baseline disease characteristics and prior treatment history of the patients were similar between the sunitinib group and placebo group in Study A6181004 and between the 2 studies. Summaries of type of malignancy and prior treatment are given in Table GIST-4.

Table GIST-4 SUTENT: Summary of Disease Characteristics and Prior Tumours Treatment (Intent-to-Treat Population)

Parameter	Phase 3 Study A6181004 50 mg QD, Schedule 4/2		Phase 1/2 Study RTKC-0511-013 50 mg QD, Schedule 4/2 (N = 55)
	Sunitinib (N = 207)	Placebo (N = 105)	
Histology (n [%])[a]			
Epithelioid	18 (8.7)	7 (6.7)	9 (16.4)
Spindle cell	126 (60.9)	75 (71.4)	22 (40.0)
Epithelioid and spindle cell	33 (15.9)	13 (12.4)	19 (34.5)
Not categorized	29 (14.0)	9 (8.6)	5 (9.1)
Missing	1 (0.5)	1 (1.0)	0 (0)
Time since initial diagnosis (weeks)			
n	207	104	55
Mean (SD)	194.8 (142.9)	206.1 (147.5)	182.7 (165.1)
Median	166.6	176.3	153.3
Range	8.6, 1398.6	12.4, 854.4	22.6, 922.9
Previous surgery (n [%])			
Yes	204 (98.6)	104 (99.0)	55 (100)
No	3 (1.4)	1 (1.0)	0 (0)
Previous radiotherapy (n [%])			
Yes	13 (6.3)	12 (11.4)	9 (16.4)
No	186 (89.9)	91 (86.7)	34 (61.8)
Missing	8 (3.9)	2 (1.9)	12 (21.8)
Average daily dose (mg) of previous imatinib treatment			
N	205	105	55
Mean (SD)	553.6 (214.3)	532.4 (178.4)	483.8 (128.2)
Median	502.9	484.6	447.0
Range	203.8, 1600.0	235.3, 1393.6	263.9, 800.0
Maximum daily dose (mg) of previous imatinib treatment			
N	205	105	55
Mean (SD)	750.2 (277.9)	739.0 (255.9)	618.2 (177.5)
Median	800.0	800.0	600.0
Range	300.0, 1600.0	400.0, 1600.0	400.0, 1000.0
Duration of previous imatinib treatment (weeks)			
N	205	105	55
Mean (SD)	98.2 (52.4)	101.6 (50.7)	91.5 (35.3)
Median	105.3	106.9	97.9
Range	0.3, 205.1	11.4, 187.7	10.3, 164.4
Time since last imatinib treatment (weeks)[b]			
N	200	102	55
Mean (SD)	8.2 (13.5)	7.8 (13.0)	6.9 (12.1)
Median	3.3	3.3	2.9
Range	1.1, 117.9	0.1, 80.3	0.1, 77.4

Table GIST-4 SUTENT: Summary of Disease Characteristics and Prior Tumours Treatment (Intent-to-Treat Population) (Continued)

Parameter	Phase 3 Study A6181004 50 mg QD, Schedule 4/2		Phase 1/2 Study RTKC-0511-013 50 mg QD, Schedule 4/2
	Sunitinib (N = 207)	Placebo (N = 105)	(N = 55)
Best response to imatinib treatment[c], n(%)			
Complete response	6 (2.9)	1 (1.0)	NA
Partial response	51 (24.6)	36 (34.3)	NA
Stable disease	87 (42.0)	36 (34.3)	NA
Progressive disease	58 (28.0)	30 (28.6)	NA
Not applicable	4 (1.9)	2 (1.9)	NA
Missing	1 (0.5)	0 (0)	NA
Outcome of previous imatinib treatment n(%)			
Intolerant of imatinib	9 (4.3)	4 (3.8)	2 (3.6)
Disease progression on imatinib			53 (96.4)
≤6 months	36 (17.4)*	17 (16.2)	
>6 months	162 (78.3)	84 (80.0)	
Location of metastases [n (%)][d]			
Liver	130 (62.8)	68 (64.8)	51 (92.7)
Peritoneal	96 (46.4)	44 (41.9)	20 (36.4)
Lymph nodes	37 (17.9)	28 (26.7)	10 (18.2)
Stomach mass	12 (5.8)	7 (6.7)	NA
Lung	8 (3.9)	5 (4.8)	12 (21.8)
Visceral organs	10 (4.8)	3 (2.9)	16 (29.1)
Soft tissue	8 (3.9)	0 (0)	18 (32.7)

[a] For Study RTKC-0511-013, histology was classified by medical review of the data.
[b] Time since last imatinib treatment was calculated based on the number of weeks between the last dose of imatinib treatment and the first dose of sunitinib or placebo.
[c] Best response to previous imatinib treatment was not available from Study RTKC-0511-013.
[d] Location of metastases were recoded by medical review of the data; in some cases, similar terms were collapsed.
* One patient initially randomized to sunitinib was found retrospectively as an eligibility error due to lack of documentation for progression on imatinib and was thus withdrawn by the investigator.

Outcomes and estimation

Time to Tumour Progression

TTP results using the core imaging laboratory assessment in the ITT population for Study A6181004 are presented in Table GIST-5 and Figure GIST-1. TTP results using the investigator's assessment in the ITT population for Study A6181004 are presented in Table GIST-5.

Table GIST-5 SUTENT: Summary of Time to Tumours Progression (Intent-to-Treat Population)

Efficacy Parameter	Phase 3 Study A6181004 50 mg QD, Schedule 4/2		Phase ½: Study RTKC-0511-013 and Continuation Study A6181030 50 mg QD, Schedule 4/2 (N = 55)
	Sunitinib (N = 207)	Placebo (N = 105)	
Core Imaging Laboratory Assessed[a]			
With disease progression[a,b], n (%)	82 (39.6)	67 (63.8)	NA
Time to Tumours Progression (weeks)[a,b]			
Quartile (95% CI)	9.6 (4.3, 10.1)	4.1 (4.0, 4.3)	NA
25%	27.3 (16.0,	6.4 (4.4, 10.0)	NA
50%	32.1)	10.1 (10.0,	NA
75%	35.0 (34.0,	16.1)	
	45.9)		
Hazard ratio (sunitinib vs. placebo)[c]	0.329		
95% CI	0.233, 0.466		
p-value[d]	< 0.001		
Investigator Assessed			
With disease progression[b] n (%)	77 (37.2)	67 (63.8)	32 (58.2)
Time to Tumours Progression (weeks)[b]			
Quartile (95% CI)	10.1 (9.1, 12.4)	4.1 (4.0, 4.3)	21.4 (10.1, 22.0)
25%	28.9 (21.3,	5.1 (4.4, 10.1)	34.0 (22.0, 46.0)
50%	34.1)	10.6 (10.1,	58.0 (44.0, *)
75%	45.9 (39.9,	16.1)	
	46.9)		
Hazard ratio (sunitinib vs. placebo)[c]	0.281		
95% CI	0.198, 0.399		
p-value[d]	< 0.001		

Note: Investigator assessments were derived from Investigator measurements, reason for discontinuation from study ('lack of efficacy') and disease progression AE data; the results also include patients who completed Study RTKC-0511-013 and transferred to Study A6181030.

[a] Disease progressions were not reviewed by the core imaging laboratory for Study RTKC-0511-013.

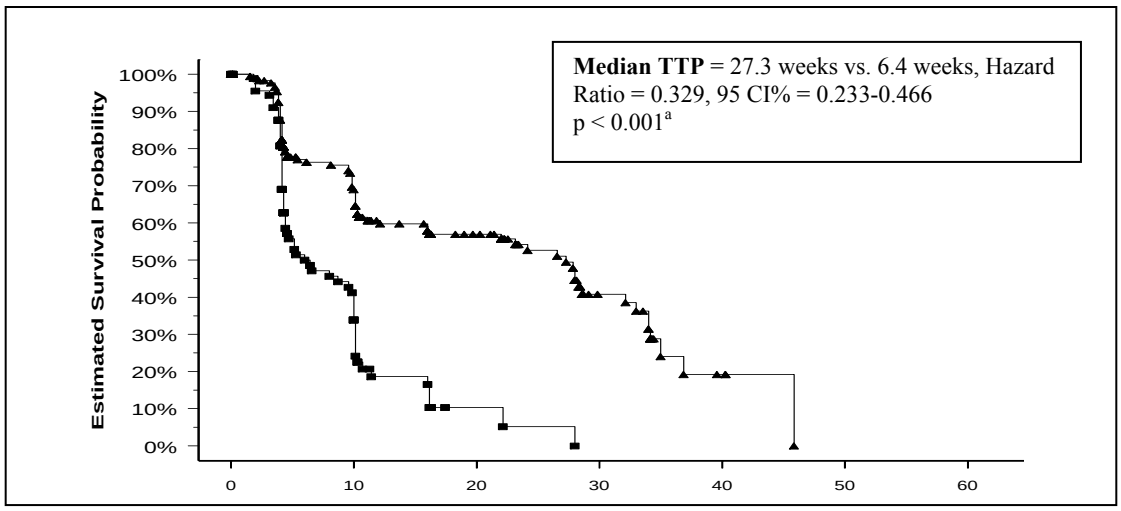
[b] For patients who progressed while on study. For Study A6181004, for patients who progressed during blinded period.

[c] Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of sunitinib; a hazard ratio greater than 1 indicates a reduction in hazard rate in favor of placebo.

[d] p-value is from a 2-sided, unstratified log-rank test.

* Unable to calculate due to immaturity of the study.

Figure GIST-1 SUTENT: Kaplan-Meier Curves of Time to Tumours Progression, Core Imaging Laboratory Assessment in Study A6181004 (Intent-to-Treat Population)



▲ Sunitinib ■ Placebo

[a] p-value is from a 2-sided, unstratified log-rank test.

The difference in TTP between the treatment arms was statistically and clinically significant with median TTP of 27.3 vs. 6.4 weeks for the sunitinib and placebo arms, respectively (hazard ratio 0.329; 95% CI: 0.233 – 0.466, $p < 0.001$). Median TTP for the group of patients treated with sunitinib was greater than 4-fold that for patients receiving placebo. The study outcome using the investigator assessments was consistent with that of the Core Imaging Laboratory.

Progression Free Survival

PFS is a composite endpoint that includes as events disease progression and deaths due to any cause while on-study (within 28 or 30 days of last dose, depending on the protocol conduct). PFS results, using the core imaging laboratory assessment in the ITT population for Study A6181004, are presented in Table GIST-7 and Figure GIST-4. Median PFS was 24.6 weeks vs. 6.4 weeks for the sunitinib and placebo arms, respectively (hazard ratio 0.333; 95% CI: 0.238 - 0.467, $p < 0.001$). The study outcome as analyzed using the investigator assessments is similar. These results are consistent with the analysis of TTP in this study. Results of the supportive trial, Study RTKC-0511-013, are again consistent with the pivotal trial, with median PFS 34.0 weeks (Figure GIST-5).

Table GIST- 7 SUTENT:Summary of Progression-Free Survival (Intent-to-Treat Population)

Efficacy Parameter	Phase 3 Study A6181004 50 mg QD, Schedule 4/2		Phase 1/2 Study RTKC-0511-013 Continuation Study A6181030 50 mg QD, Schedule 4/2
	Sunitinib (N = 207)	Placebo (N = 105)	(N = 55)
Core Imaging Laboratory Assessed			
With progression or death due to any cause while on study [a b]	89 (43.0)	70 (66.7)	NA
Progression-free survival (weeks) Quartile (95% CI)			
25%	7.9 (4.3, 10.0)	4.1 (4.0, 4.3)	NA
50%	24.6 (12.1, 28.3)	6.4 (4.4, 10.0)	
75%	35.0 (33.0, 45.9)	10.1 (10.0, 16.0)	
Hazard ratio (sunitinib vs. placebo)[c]	0.333		
95% CI	0.238, 0.467		
p-value[d]	< 0.001		
Investigator Assessed			
With progression or death due to any cause while on study [a b]	82 (39.6)	70 (66.7)	33 (60.0)
Progression-free survival (weeks) Quartile (95% CI)			
25%	9.9 (7.4, 11.4)	4.1 (4.0, 4.3)	21.4 (10.1, 22.0)
50%	27.9 (17.4, 34.1)	5.1 (4.4, 10.0)	34.0 (22.0, 46.0)
75%	45.9 (39.9, 46.9)	10.6 (10.1, 16.1)	58.9 (44.0, *)
Hazard ratio (sunitinib vs. placebo)[c]	0.293		
95% CI	0.209, 0.412		
p-value[d]	< 0.001		

[a] Disease progressions were not reviewed by the core imaging laboratory for Study RTKC-0511-013.

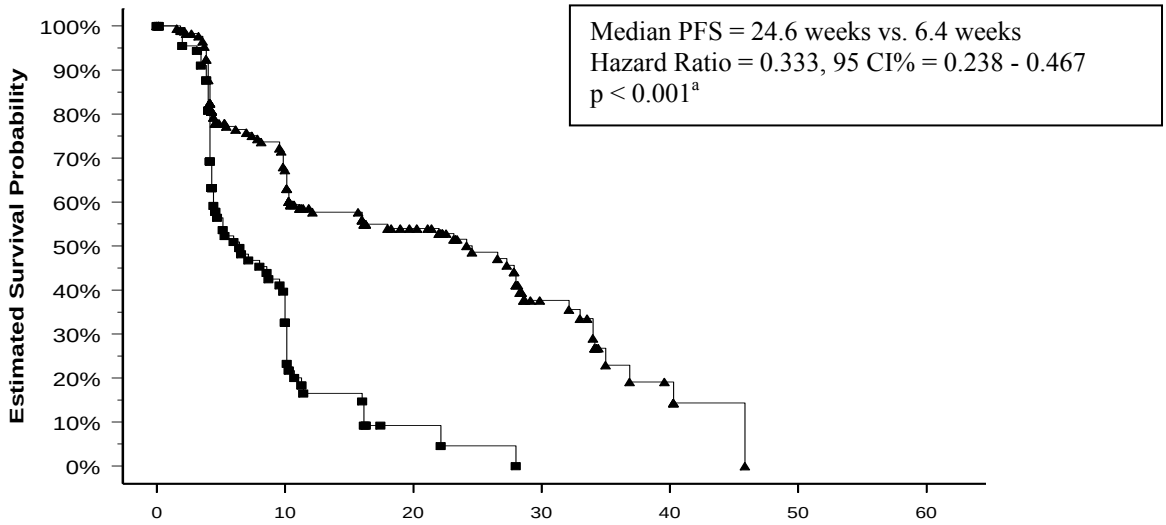
[b] For patients who progressed while on study. For Study A6181004, for patients who progressed during blinded period.

[c] Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of sunitinib; a hazard ratio greater than 1 indicates a reduction in hazard rate in favor of placebo.

[d] p-value is from a 2-sided, unstratified log-rank test.

* Unable to calculate due to immaturity of the study.

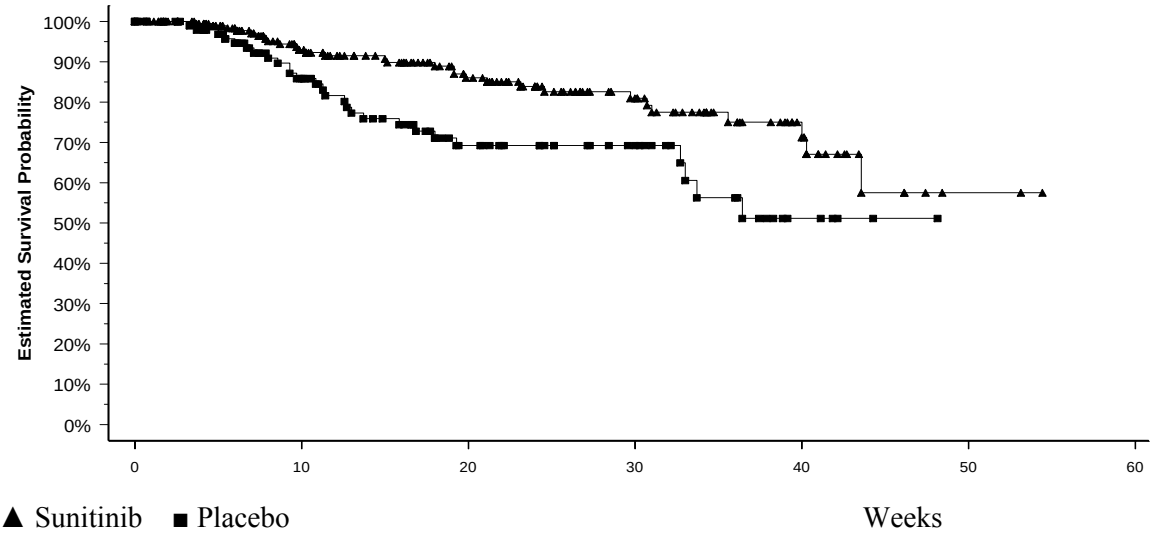
Figure GIST-4. SUTENT: Kaplan-Meier Curves of Progression-Free Survival in Study A6181004, Core Imaging Laboratory Assessment (Intent-to-Treat Population)



Overall Survival

OS results in the ITT population for Study A6181004, including the open-label portion of the study, are presented in Figure GIST-6 and Table GIST-8. The difference in OS between the treatment arms was statistically significant (hazard ratio 0.491; 95% CI: 0.290 – 0.831, p = 0.007). The risk of death was 2 times higher in patients in the placebo arm of the study compared to the sunitinib arm. Median OS had not yet been reached in either treatment arm at the time of the analysis. The proportion of patients expiring was 14.0% vs. 25.7% for sunitinib vs. placebo, respectively. OS was not an endpoint in Study RTKC-0511-013.

Figure GIST-6. SUTENT: Kaplan-Meier Curves of Overall Survival, Including Open-Label Portion of Study A6181004 (ITT Population)



Note: For Study A6181004, the open-label portion of data is included and kept under the original treatment group.

For patients known to be alive at the time the database was closed for analysis, survival data were censored on the date they were last known to be alive.

Table GIST-8 SUTENT: Summary of Overall Survival Including the Open-Label Portion of Study A6181004 (Intent-to-Treat Population)

	Phase 3 Study A6181004 50 mg QD, Schedule 4/2	
Efficacy Parameter	**Sunitinib (N = 207)**	**Placebo (N = 105)**
Patient status (n [%])[a]		
Alive	178 (86.0)	78 (74.3)
Dead	29 (14.0)	27 (25.7)
Survival time (weeks)		
Quartile (95% CI)		
25%	40 (29.7, *)	15.9 (11.3, 33.7)
50%	* (43.6, *)	* (30.0, *)
75%	* (*, *)	* (*, *)
Hazard ratio (sunitinib vs. placebo)[b]	0.491	
95% CI	0.290, 0.831	
p-value[c]	0.007	

Note: Includes 1 patient who transferred to Study A6181030.
The open-label portion of data is included and kept under the original treatment group.
QD = once daily, N = number of patients included in the population, CI = confidence interval.

[a] For patients not known to be dead at the time the database was closed for analysis, survival data were censored on the date they were last known to be alive.

[b] Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of sunitinib; a hazard ratio greater than 1 indicates a reduction in hazard rate in favor of placebo.

[c] p-value is from a 2-sided, unstratified log-rank test.

* Unable to calculate due to immaturity of the study.

Median OS had not yet been reached in pivotal Study A6181004, at the time of data cut-off

Ancillary analyses
Analyses were performed on the endpoints of TTP, PFS, OS, ORR, and DR to assess the efficacy of sunitinib in subpopulations defined by age, gender, and race. No clinically meaningful differences could be detected.

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

No formal meta-analysis was performed across the trials.

- Clinical studies in special populations

None performed.

Study RTKC-0511-013

This study was an open-label, multicenter, dose-escalation, Phase 1/2 study in patients with GIST after failure of imatinib due to resistance or intolerance.

The primary objective of this study was to identify 1 or more sunitinib regimens suitable for Phase 2 development. The original protocol examined Schedule 2/2 (2-week treatment followed by a 2-week off-drug period) using dose levels of 25, 50, and 75 mg QD. The protocol was subsequently amended to allow investigation of other regimens including Schedule 2/1 at 50 mg QD and Schedule 4/2 at 50 mg QD. The 50 mg QD Schedule 4/2 regimen was selected for Phase 2 development because it was well tolerated, provided exposure at drug levels consistent with preclinically determined target inhibition, and had demonstrated antitumor activity in several patients. The data included in the SCE are for 55 patients treated using the 50 mg QD Schedule 4/2.

The study included patients that were at least 18 years of age, had histologically proven metastatic or unresectable GIST, had an ECOG performance status of 0 or 1, and had adequate organ function as defined in the entry criteria.

The TTP was 34.0 weeks (95% CI, 22.0 – 46.0 weeks), based on investigator measurements. The investigator-assessed ORR was 9.1%.

Metastatic Renal Cell Carcinoma (MRCC)

The clinical efficacy of sunitinib for the RCC is based on data from 1 pivotal large Phase 2 and 1 supportive Phase 2 trial. These are summarized in Table RCC-1, along with the continuation protocol open to patients who have completed the supportive study.

Table RCC-1 Supportive and Pivotal Clinical Trials (GIST and MRCC Indications), With Continuation Protocols

Protocol	Study Status	Study Design	N
Supportive			
RTKC-0511-014	Completed	Single-arm, open-label, multi-center in MRCC patients	63
Pivotal			
A6181006	Ongoing (enrolment completed)	Single-arm, open-label, multi-center in MRCC patients	106
Continuation RTKC-0511-017, A6181030	Ongoing	Open-label continuation studies for patients with GIST, MRCC, and other cancers who would benefit from further sunitinib treatment.	24 GIST [a,b], 18 MRCC [a]

[a] As of 01 December 2004.
[b] The 24 GIST patients include 1 patient from Study A6181004 who was transferred to this protocol after a decline in performance status.

- Main studies

The 2 trials in patients with MRCC had similar designs and methods and are described in parallel in the following sections.

METHODS

Study Participants

Patients eligible for these studies were at least 18 years of age, had histologically-proven MRCC that was not amenable to therapy with curative intent and had measurable disease, adequate organ function as defined in the entry criteria and ECOG performance status of 0 or 1. All patients were to have experienced failure during (or intolerance to (Protocol RTKC-0511-017) previous cytokine therapy. Prior treatment failure was in study A6181006 based on radiographic evidence of disease progression defined by RECIST or WHO criteria during or within 9 months of completion of 1 cytokine therapy treatment (IL-2, IFN, or IL-2 + IFN); patients who were treated with IFN alone were to have received treatment for at least 28 days.

Treatments

Patients received 50 mg SU011248 daily for 4 weeks followed by 2 weeks of rest in repeated 6-week cycles. Doses could be reduced to 37.5 mg or 25 mg in the event of toxicity. No dose increases were allowed in Study A6181006, but could go up to 75 mg/d in RTKC-0511-017. Sutinib treatment continued on-study until PD or withdrawal for other reasons.

Objectives/Outcomes/endpoints

The primary endpoint for the studies was ORR. Secondary endpoints included assessment of DR, TTP, PFS, and OS; evaluation of the safety of sunitinib; evaluation of exposure to sunitinib and its active metabolite (SU012662); and patient reported outcomes for quality of life (in Study RTKC-0511-014 only).

The protocol defined efficacy assessments were based on core imaging laboratory assessments for the pivotal Study A6181006, and on investigator assessments for supporting Study RTKC-0511-014. Radiographic (CT or MRI) assessment was performed at screening and after every cycle for the first 4 cycles (first 2 cycles for Study RTKC-0511-014) and every other cycle thereafter for the remainder of the study, as well as at the end of treatment/withdrawal visit. Additional scans were performed to confirm response, or whenever disease progression was suspected. All images were interpreted by the investigator. In Study A6181006, all images were also interpreted by an independent central core laboratory, which was blinded to the investigator's interpretation, but in Study RTKC-0511-014, core laboratory interpretations were only done on images which the investigator had already interpreted as responses by RECIST.

Sample size

The calculation of sample size for both studies was based on the null hypothesis of ORR ≤ 5% (which was considered to be not clinically meaningful). For Study A6181006, the sample size of 100 patients had 90% power for testing that the ORR was ≥ 15% (overall 2-sided significance level of 0.05, exact binomial test). For Study RTKC-0511-014, a Simon 2-stage minimax design was used. With a one-sided alpha level of 5% and 85% power for testing that the ORR was ≥ 15%, up to a maximum of 63 treated patients were required.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods
Standard statistyical methods were used. The proportion of responders was estimated using 95% exact confidence intervals. Patients with no on-study assessments were counted as non responders

RESULTS
Participant flow

In Study A6181006 106 patients were entered and constitute the ITT population. All 106 patients started at least one treatment administration. In study **Study RTKC-0511-014 63 patients** were entered and constitute the ITT population. All 63 patients started at least one treatment administration.

Recruitment

Enrollment for Study A6181006 began in February 2004 and was complete in November 2004; for Study RTKC-0511-014, enrollment began in January 2003 and was complete in July 2003. Thus, the last patient enrolled in Study A6181006 approximately 2 months prior to the data cutoff date, as compared to Study RTKC-0511-014, in which the last patient enrolled 17 months before the data cutoff date for the continuation studies.

Conduct of the study

An independent Drug Safety Monitoring Committee oversaw the conduct of the pivotal trial, Study A6181006. The committee met at least every 4 months to review conduct of the study as well as accumulating safety and efficacy data. The committee met on 3 occasions prior to 28 January 2005; the conclusion for each meeting was that the study should continue as planned.

Baseline data

The baseline age, gender, race and ECOG performance statuses of the patients were generally comparable between Studies A6181006 and RTKC-0511-014; patient baseline characteristics for the 2 studies are presented in the following table.

Table 6. Summary of Patient Baseline Characteristics (Intent-to-Treat Population)

Patient Baseline Characteristics	Pivotal Study A6181006 (N = 106)	Supportive Study RTKC-0511-014 (N = 63)	RTKC-0511-014 and A6181006 Pooled (N = 169)
Age (years)			
N	106	63	169
Mean (SD)	55.8 (10.3)	59.3 (10.0)	57.1 (10.3)
Median	56	60	57
Range	32.0, 79.0	24.0, 87.0	24.0, 87.0
Age (n [%])			
18 - <65 years	87 (82.1)	43 (68.3)	130 (76.9)
≥65 years	19 (17.9)	20 (31.7)	39 (23.1)
Sex (n [%])			
Male	67 (63.2)	43 (68.3)	110 (65.1)
Female	39 (36.8)	20 (31.7)	59 (34.9)
Race (n [%])			
White	100 (94.3)	54 (85.7)	154 (91.1)
Black	0 (0.0)	3 (4.8)	3 (1.8)
Asian	2 (1.9)	4 (6.3)	6 (3.6)
Not listed	4 (3.8)	2 (3.2)	6 (3.6)
ECOG performance status (n [%])			
0	58 (54.7)	34 (54.0)	92 (54.4)
1	47 (44.3)	28 (44.4)	75 (44.4)
2*	1 (0.9)	1 (1.6)	2 (1.2)

Note: Baseline is defined as the last observation prior to the first dose of study drug.
N = total number of patients included in the population, n = number of patients, SD = standard deviation, ECOG = Eastern Cooperative Oncology Group.
* Patients having ECOG performance status 2 at baseline were eligible for study with performance status <2 at earlier screening assessment.

History of Malignancy and Prior Tumor Treatment

Overall, the baseline malignancy and prior treatment history of patients were comparable between Studies A6181006 and RTKC-0511-014. All patients entering both studies had received prior treatment with cytokine therapies. Summaries of type of malignancy and prior treatment are presented in Table

Summary of Malignancy and Prior Treatment (Intent-to-Treat Population)

Parameter	Pivotal Study A6181006 (N = 106)	Supportive Study RTKC-0511-014 (N = 63)	RTKC-0511-014 and A6181006 Pooled (N = 169)
Histology (n [%])[a]			
Clear cell	106 (100.0)	55 (87.3)	161 (95.3)
Not categorized	0 (0.0)	7 (11.1)	7 (4.1)
Missing	0 (0.0)	1 (1.6)	1 (0.6)
Time since initial diagnosis (weeks)			
Mean (Std)	131.0 (154.3)	215.2 (315.6)	162.4 (230.9)
Median	79.4	89	84.4
Range	10.0, 918.1	9.6, 1473.0	9.6, 1473.0
Previous nephrectomy (n [%])			
Yes	106 (100.0)	58 (92.1)	164 (97.0)
No	0 (0.0)	5 (7.9)	5 (3.0)
Previous radiotherapy (n [%])			
Yes	20 (18.9)	25 (39.7)	45 (26.6)
No	86 (81.1)	38 (60.3)	124 (73.4)
Prior cytokine treatment (n [%])			
Yes	106 (100.0)	63 (100.0)	169 (100.0)
Type of prior cytokine or systemic therapy (n [%])			
IFN Only	47 (44.3)	27 (42.9)	74 (43.8)
IFN + Other	0 (0.0)	8 (12.7)	8 (4.7)
IFN + IL-2 Only	9 (8.5)	7 (11.1)	16 (9.5)
IFN + IL-2 + Other	0 (0.0)	2 (3.2)	2 (1.2)
IL-2 Only	50 (47.2)	18 (28.6)	68 (40.2)
IL-2 + Other	0 (0.0)	1 (1.6)	1 (0.6)
Best response to previous cytokine therapy [n (%)]			
Complete response	3 (2.8)	1 (1.6)	4 (2.4)
Partial response	9 (8.5)	3 (4.8)	12 (7.1)
Stable disease	29 (27.4)	15 (23.8)	44 (26.0)
Progressive disease	63 (59.4)	44 (69.8)	107 (63.3)
Not applicable	1 (0.9)	0 (0.0)	1 (0.6)
Missing	1 (0.9)	0 (0.0)	1 (0.6)
Number of sites of metastases [n (%)]			
1	17 (16.0)	11 (17.5)	28 (16.6)
2	39 (36.8)	15 (23.8)	54 (32.0)
≥3	50 (47.2)	37 (58.7)	87 (51.5)
Location of common sites of metastases [n (%)]			
Lung metastases	86 (81.1)	51 (81.0)	137 (81.1)
Lymph nodes	62 (58.5)	34 (54.0)	96 (56.8)
Bone metastases	27 (25.5)	32 (50.8)	59 (34.9)
Liver metastases	29 (27.4)	10 (15.9)	39 (23.1)
Local recurrences	21 (19.8)	13 (20.6)	34 (20.1)

[a] For Study RTKC-0511-014, histology was characterized by medical review of the data.

Numbers analysed
A total of 169 patients enrolled in Studies A6181006 and RTKC-0511-014 and received the treatment regimen of 50 mg QD sunitinib on Schedule 4/2. In Study A6181006, the median duration of sunitinib treatment was 23.6 weeks. In Study RTKC-0511-014, the median duration of treatment, including participation in the continuation studies, was 34 weeks.

Outcomes and estimation
The ORR, the primary efficacy endpoint, is summarized for the ITT population in Table RCC-. In Study A6181006, the ORR was assessed both by the investigator and an independent core laboratory, while in Study RTKC-0511-014, assessment was first made by the investigator and only images considered to represent objective responses were sent for evaluation by the core laboratory.
The core laboratory-assessed ORR was very similar in the pivotal and the supportive study: 25.5% and 25.4%, respectively. Likewise, the investigator-assessed rate was very consistent between studies: 35.8% (Study A6181006) and 36.5% (Study RTKC-0511-014).

Table RCC-5 Objective Response Rate in MRCC Studies (Intent-to-Treat)

	Study A6181006 (N = 106)	Study RTKC-0511-014 [a] (N = 63)	Pooled MRCC (N = 169)
Core Laboratory Assessed			
Patients with baseline assessment, n (%)	106 (100.0)	NA	NA
Patients with measurable disease at baseline	105 (99.1)	NA	NA
Best overall response			
Complete response	0	0	NA
Partial response	**27 (25.5)**	**16 (25.4)**	NA
Stable disease	**65 (61.3)**	NA	NA
Progressive disease	14 (13.2)	NA	NA
Not valuable [b]	0	NA	NA
ORR (CR+PR), % (95% CI)	**25.5 (17.5 – 34.9)**	**25.4 (15.3 – 37.9)**	NA
Investigator Assessed			
Patients with baseline assessment, n (%)	106 (100.0)	63 (100.0)	169 (100.0)
Patients with measurable disease at baseline	105 (99.1)	63 (100.0)	168 (99.4)
Best overall response			
Complete response	1 (0.9)	0	1 (0.6)
Partial response	**37 (34.9)**	**23 (36.5)**	**60 (35.5)**
Stable disease (≥ 6 weeks)	**44 (41.5)**	**25 (39.7)**	**69 (40.8)**
Progressive disease	17 (16.0)	7 (11.1)	24 (14.2)
Not valuable [b]	7 (6.6)	5 (7.9)	12 (7.1)
Missing	0	3 (4.8)	3 (1.8)
ORR (CR+PR), % (95% CI)	**35.8 (26.8 – 45.7)**	**36.5 (24.7 – 49.6)**	**36.1 (28.9 – 43.8)**

[a] Includes data from Studies A6181030 and RTKC-0511-017, from 18 patients who transferred after completing Study RTKC-0511-014

[b] Patients were considered "Not Valuable" if all target and non-target lesions documented at baseline were not followed on-study For the investigator-assessed responses, patients with less than 6 weeks on-study observation time were also considered "Not Valuable", unless they had disease progression.

The median PFS in Study A6181006 using the core laboratory assessments was 34.0 weeks (95% CI: 23.3 – 36.0); median PFS using the investigator assessments was 34.0 weeks (95% CI: 22.3 – 35.3). In Study RTKC-0511-014, median PFS was 37.7 weeks (95% CI: 24.0 – 46.4). Analysis of OS for Study A6181006 was premature as 89 of 106 patients were still alive.

Ancillary analyses

Analyses of DR, TTP, PFS, and OS in subpopulations defined by age, gender, and race found that no clinically meaningful differences in these endpoints with respect to any of these groups could be established.

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

No formal meta-analysis was performed across the trials.

- Clinical studies in special populations

Hepatic Insufficiency: No clinical studies have been performed in patients with impaired hepatic function. Studies excluded patients with ALT or AST >2.5 x Upper Limit of Normal(ULN) or, > 5.0 x ULN, if due to underlying disease. Population pharmacokinetic analyses performed by the Applicant

show that sunitinib pharmacokinetics were unaltered in a range of hepatic function evaluated by ALT (4-156 IU/L).

Renal Insufficiency: No clinical studies have been performed in patients with impaired renal function. Studies excluded patients with serum creatinine > 2.0 x ULN.

The Applicant performed a Population pharmacokinetic analysis which showed that sunitinib pharmacokinetics were unaltered in the range of renal function evaluated by creatinine clearance (42-347 mL/min).

- Supportive study(ies)

Given the similiarity in terms of study design and analysis plan, Study RTKC-0511-014 has been described and discussed together with the pivotal trial A6181006 for ease of comparison.

- Discussion on clinical efficacy

The demonstration of efficacy in the treatment of patients with malignant gastrointestinal stromal tumour (GIST) who were resistant or intolerant to imatinib is based on a double blind, placebo controlled Phase III study (A6181004) and a single-arm, open-label, dose-escalation study (RTKC-0511-013). In this study, the TTP and overall survival for sunitinib were significantly longer than for placebo.

The demonstration of efficacy in patients with metastatic renal cell carcinoma (MRCC) who were refractory to prior cytokine therapy with interleukin-2 or interferon-α is based on the proportion of patients achieving an objective response observed in two single-arm, open-label phase II studies (A6181006 and RTKC-0511-014). In study RTKC-0511-014 the ORR was 36.5% (95% C.I. 24.7% - 49.6%). In study A6181006, ORR was 35.8% (95% C.I. 26.8% – 45.7%). The applicant also announced the results of an interim analysis of ORR in treatment-naïve patients enrolled in a randomized, multi-centre, Phase 3 study, but no detailed study report was available at the time of assessment (data not shown). However, no randomized controlled trials with SUTENTin MRCC in patients who were refractory to prior cytokine therapy have been submitted. Evaluation of treatment effects in terms of time-related endpoints is difficult in the context of non-randomized studies. Thus, comprehensive clinical data referring to the efficacy of the medicinal product SUTENTin the MRCC indication have not been supplied. The CHMP consulted the Oncology Scientific Advisory Group seeking confirmation about the interpretation of the efficacy results in the context of the non-randomized studies presented. The advisory group concluded that the phase 2 data provided sufficiently convincing evidence of clinical benefit (see Risk-benefit assessment).

Clinical safety

Safety analyses are based on patients whose starting dose was 50 mg QD on Schedule 4/2. This includes not only the 257 GIST and 169 MRCC patients in the 2 pivotal and 2 supportive studies who were on this regimen, but also a further 36 patients with other malignancies from early clinical trials. Safety data for 126 subjects in Phase 1 single-dose studies, which relate primarily to DLTs, are also presented.

A number of other clinical trials of sunitinib are currently ongoing. Critical safety data (as of 01 December 2004) will be presented for 424 subjects in 10 ongoing studies, including 34 subjects with MRCC and 4 with GIST treated with sunitinib as a single agent. These data include subject demographic and other characteristics, treatment-emergent all-causality serious adverse events (SAEs) (including deaths), and discontinuations due to treatment-emergent all-causality adverse events (AEs).

- Patient exposure

Extent of exposure to sunitinib is summarized in Table 19. Exposure tended to be longer among MRCC patients than GIST patients. To a great extent, this is a consequence of the positive outcome of the Study A6181004 interim analysis, which occurred while patients were still being recruited: the result was that about half the patients were enrolled during the last 5.3 months of the patient recruitment period (25 July 2004 – 01 January 2005), and the median number of treatment cycles possible was 3. Placebo subjects in GIST Study A6181004 had the option of crossing-over to open-label sunitinib treatment after demonstration of disease progression; 59 subjects did so, accounting for

the relatively short time they stayed on this treatment relative to patients who were initially randomized to sunitinib.

Table 19. Exposure to Study Drug

	Solid Tumors	MRCC	GIST	
			Sunitinib	Placebo
	(N=450)	(N=169)	(N=257)	(N=102)
Days of drug administration[a]				
Mean (SD)	98 (71.4)	114 (75.1)	90 (65.5)	46 (32.8)
Median (min-max)	84 (1-334)	106 (5-297)	69 (1-324)	30 (2-168)
Patients on treatment, n (%)				
≥1 day	450 (100.0)	169 (100.0)	257 (100.0)	102 (100.0)
≥1 month	418 (92.9)	160 (94.7)	237 (92.2)	95 (93.1)
≥6 months	171 (38.0)	81 (47.9)	82 (31.9)	6 (5.9)
≥12 months	33 (7.3)	21 (12.4)	9 (3.5)	0 (0)
Mean (SD) [b]	158 (112.7)	184 (117.6)	142 (103.3)	73 (50.6)
Median (min-max) [b]	131 (6-531)	169 (6-484)	125 (15-496)	43 (16-252)

[a] Excludes 2-week rest period
[b] Includes 2-week rest period

- Adverse events

The most important treatment-related serious adverse events associated with SUTENTtreatment of solid tumour patients were pulmonary embolism (1%), thrombocytopenia (1%), tumour hemorrhage (0.9%), febrile neutropenia (0.4%), and hypertension (0.4%). The most common treatment-related adverse events (experienced by at least 20% of the patients) of any grade included: fatigue; gastrointestinal disorders, such as diarrhea, nausea, stomatitis, dyspepsia and vomiting; skin discoloration; dysgeusia and anorexia. Fatigue, hypertension and neutropenia were the most common treatment-related adverse events of Grade 3 maximum severity and increased lipase was the most frequently occurring treatment-related adverse event of Grade 4 maximum severity in patients with solid tumours.

Adverse reactions

Adverse reactions that were reported in >5% of solid tumor patients are listed below, by system organ class, frequency and grade of severity. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	***Frequency***	***Event***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and lymphatic system disorders	Very Common	Anaemia	57 (12.7%)	21 (4.7%)	1 (0.2%)
		Thrombocytopenia	49 (10.9%)	12 (2.7%)	4 (0.9%)
		Neutropenia	48 (10.7%)	26 (5.8%)	2 (0.4%)
		Leukophenia	38 (8.4%)	18 (4.0%)	0 (0.0%)
Metabolism and nutrition disorders	Very Common	Anorexia	97 (21.6%)	2 (0.4%)	0 (0.0%)
Nervous system disorders	Very Common	Dysgeusia	125 (27.8%)	0 (0.0%)	0 (0.0%)
		Headache	56 (12.4%)	3 (0.7%)	0 (0.0%)
	Common	Dizziness	25 (5.6%)	2 (0.4%)	0 (0.0%)
Vascular disorders	Very Common	Hypertension	74 (16.4%)	26 (5.8%)	0 (0.0%)
Respiratory,	Common	Epistaxis	34 (7.6%)	0 (0.0%)	0 (0.0%)

System Organ Class	*Frequency*	*Event*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
thoracic and mediastinal disorders		Dyspnoea	23 (5.1%)	2 (0.4%)	1 (0.2%)
Gastrointestinal disorders	Very Common	Diarrhoea	176 (39.1%)	18 (4.0%)	0 (0.0%)
		Nausea	160 (35.6%)	4 (0.9%)	0 (0.0%)
		Stomatitis	122 (27.1%)	8 (1.8%)	0 (0.0%)
		Dyspepsia	108 (24.0%)	3 (0.7%)	0 (0.0%)
		Vomiting	100 (22.2%)	3 (0.7%)	0 (0.0%)
		Constipation	47 (10.4%)	1 (0.2%)	0 (0.0%)
		Glossodynia	46 (10.2%)	0 (0.0%)	0 (0.0%)
	Common	Abdominal pain.	36 (8.0%)	6 (1.3%)	1 (0.2%)
		Oral pain	32 (7.1%)	1 (0.2%)	0 (0.0%)
		Flatulence	31 (6.9%)	0 (0.0%)	0 (0.0%)
		Dry mouth	27 (6.0%)	0 0.0%)	0 (0.0%)
		Gastro-oesophageal reflux disease	23 (5.1%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very Common	Skin discolouration	132 (29.3%)	0 (0.0%)	0 (0.0%)
		Palmar-plantar erythrodysaesthesia syndrome	77 (17.1%)	20 (4.4%)	0 (0.0%)
		Rash	76 (16.9%)	3 (0.7%)	0 (0.0%)
		Hair colour changes	56 (12.4%)	0 (0.0%)	0 (0.0%)
		Alopecia	27 (6.0%)	0 (0.0%)	0 (0.0%)
	Common	Dry skin	39 (8.7%)	0 (0.0%)	0 (0.0%)
		Erythema	32 (7.1%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Common	Pain in Extremity	42 (9.3%)	2 (0.4%)	0 (0.0%)
		Myalgia	29 (6.4%)	1 (0.2%)	0 (0.0%)
		Arthralgia	23 (5.1%)	2 (0.4%)	0 (0.0%)
General disorders and administration site conditions	Very common	**Fatigue**	219 (48.7%)	37 (8.2%)	0 (0.0%)
		Mucosal Inflammation	65 (14.4%)	2 (0.4%)	0 (0.0%)
	Common	**Asthenia**	41 (9.1%)	10 (2.2%)	0 (0.0%)
Investigations	Common	Lipase increase	33 (7.3%)	17 (3.8%)	8 (1.8%)
		Blood creatine phosphokinase increase	24 (5.3%)	1 (0.2%)	2 (0.4%)
		Any adverse event	412 (91.6%)	176(39.1%)	40 (8.9%)

- Serious adverse event/deaths/other significant events

6.4% of patients with solid tumors died during the treatment period or the follow-up period (28 to 30 days, depending on the protocol). The death rate was comparable in the GIST and MRCC populations. *Study disease* was the most common cause of death in all groups.

On-Study Deaths

	Solid Tumors	MRCC	GIST	
			Sunitinib	Placebo
	(N=450)	(N=169)	(N=257)	(N=102)

Study drug [a]	5 (1.1)	1 (0.6)	4 (1.6)	2 (2.0)
Study disease	25 (5.6)	7 (4.1)	15 (5.8)	8 (7.8)
Other	0	0	0	0
Not determined	1 (0.2)	1 (0.6)	0	0
Total	*29 (6.4)* [b]	*9 (5.3)* [b]	*17 (6.6)* [b]	*8 (7.8)* [b]

[a] If the relationship to study drug was unknown, the event was considered to be related to treatment

[b] Dual causality (*study drug* and *study disease*) was assigned to 2 of the deaths in the sunitinib-treated GIST group (which is included in the Solid Tumor group) and to 2 deaths in the placebo-treated group.

Among all patients with solid malignant tumors, 174 of 450 (38.7%) patients experienced at least 1 treatment-emergent all-causality SAE. The overall incidence of all-causality SAEs was comparable in the sunitinib-treated GIST and MRCC populations. Fewer SAEs were reported from the placebo-treated GIST population.

Among solid tumor patients, 87 of the 450 patients (19.3%) experienced at least 1 such SAE. Treatment-related SAEs were reported more frequently in the sunitinib-treated GIST population (23.0%) than in the MRCC population (14.2%), and only 4.9% of the placebo-treated subjects from GIST Study A6181004 were reported with a treatment-related SAE. To some extent, the lower SAE rate among placebo patients may be related to their shorter time on treatment. Although nearly 20% of solid tumor patients experienced a treatment-related SAE, there was a diverse assortment of such events, with none really predominating and no clear pattern emerging. No individual event was reported as a treatment-related SAE in more than 2% of patients in any group.

- Laboratory findings

The most common Grade 4 chemistry abnormalities in the All Solid Tumours group were hyperuricemia (40/423, 9.5%) and increased lipase (9/423, 2.1%). No other Grade 4 laboratory abnormality occurred in more than 1% of patients. The most common (>5%) Grade 3 chemistry abnormalities in this group were hyperlipasemia (50/423, 11.8%), hypophosphatemia (27/432, 6.3%), and hyperamylasemia (23/423, 5.4%).

These laboratory changes were generally not associated with signs and symptoms of disease. Only 2 adverse events relating to pancreatitis were reported from these studies: a GIST patient with a history of chronic pancreatitis diagnosed at least 2 years prior to her first dose of sunitinib was reported with an SAE of ‘acute pancreatitis’ during treatment cycle 5, and an MRCC patient, whose radiologic reports raised the possibility of evidence of direct tumours extension to the pancreas, was reported with an SAE of ‘pancreatitis’ in cycle 3. There were no reported cases of gout or other manifestations of hyperuricemia.

For hematologic abnormalities, decreases of Grade 3 or 4 severity in the solid tumours group were seen for decreases in lymphocyte count (73/429, 17.0%), absolute neutrophil count (60/429, 14.0%), total white blood cell count (34/429, 7.9%), and platelet count (19/429, 4.5%). However, corresponding clinical conditions were considerably rarer: for instance, febrile neutropenia was reported as an adverse event in only 2 solid tumours patients (0.4%), both of whom were sunitinib-treated GIST patients .

- Safety in special populations

Sunitinib is indicated in adults only, and had not been studied in children or adolescents as of the data cutoffs used for these data analyses.

The integrated safety database includes 335 subjects between the ages of 18 and 65 and 115 subjects 65 or older. Analysis of adverse event data shows that the safety profile was broadly similar between these 2 age groups, with no particular safety concerns particular to either group

No clinical studies have been conducted to evaluate the PK of sunitinib in patients with renal or hepatic impairment. Angiogenesis is a critical component of embryonic and fetal development. In preclinical studies, sunitinib was embryolethal, and when administered to rats during organogenesis at a dose approximately equivalent to the registration clinical dose of 50 mg daily, it was a

developmental toxicant, resulting in an increased incidence of foetal skeletal malformations, especially thoracic/lumbar vertebral alterations (retarded ossification). No clinical studies with sunitinib have been conducted in pregnant women, and no pregnancies occurred during clinical studies of sunitinib.

- Safety related to drug-drug interactions and other interactions

Concurrent administration of a single dose of sunitinib (10 mg) with the potent CYP3A4 inhibitor, ketoconazole (400 mg QD), to healthy subjects in Study RTKC-0511-009 resulted in an increase of the mean sunitinib C_{max} by 59% and area under the plasma concentration-time curve from time 0 to time of the last measurable concentration ($AUC_{0\text{-last}}$) by 76%, as compared with administration of sunitinib alone. At the same time, a decrease in the mean SU012662 Cmax by 29% and $AUC_{0\text{-last}}$ by 16% was observed upon combined administration of sunitinib and ketoconazole.

Concurrent administration of a single dose of sunitinib (50 mg) with the repeated doses of a potent CYP3A4 inducer, rifampin (600 mg QD), to healthy subjects in Study A6181001 resulted in reduction of the mean sunitinib C_{max} by 56% and $AUC_{0\text{-last}}$ by 79%, as compared with administration of sunitinib alone. The mean SU012662 Cmax and $AUC_{0\text{-last}}$ increased, however, by 137% and 29%, respectively, upon combined administration of sunitinib and rifampin.

- Discontinuation due to adverse events

The following table displays the treatment-related adverse events that were associated with treatment discontinuations. Few of these occurred in more than 1 patient.

	Solid Tumors	MRCC	GIST	
	(N=450)	(N=169)	Sunitinib (N=257)	Placebo (N=102)
Patients with AEs,n, %	28 (6.2)	15 (8.9)	13 (5.1)	2 (2.0)
Anemia	3 (0.7)	0	3 (1.2)	0
Ejection fraction abnormal	3 (0.7)	3 (1.8)	0	0
Astenia	2 (0.4)	0	2 (0.8)	0
Dyspnea	2 (0.4)	1 (0.6)	1 (0.4)	0
Nausea	2 (0.4)	2 (1.2)	0	0
Other AEs (each reported by only 1 patient)	29	14	15	2

- Discussion on clinical safety

Fatigue, gastrointestinal disorders (such as nausea, diarrhea, stomatitis, dyspepsia, constipation, and vomiting), and anorexia were the most commonly reported all-causality adverse events. Anemia, thrombocytopenia, and neutropenia were also noted, as was hypertension, the latter supported by vital sign data. Most adverse events were mild or moderate in severity, and in general were manageable through specific therapies, decreases in dosage, or by delaying the next treatment cycle. Although elevations in amylase and lipase were among the more common laboratory abnormalities, clinical pancreatitis was rare, occurring in only 2 of 450 solid tumor patients (1 of whom had a history of chronic pancreatitis). Deaths related to cardiovascular event are reported in the treatment arm. In solid tumor patients, 19% experienced a treatment-related SAE. Adverse events that most commonly led to dose reductions or delays on SUTENT included gastrointestinal disorders (23 patients, 11%) and blood and lymphatic disorders (13 patients, 6%).

Important identified risks with sunitinib are cardiac and hepatic toxicity. QT interval prolongation was investigated in a trial in 24 patients, aged 20-87 years, with advanced malignancies.

At approximately twice therapeutic concentrations, SUTENT has been shown to prolong the QTcF interval (Frederica's Correction). There were no patients with greater than grade 2 (CTCAE v3.0) QT/QTc interval prolongation and no patient presented with a cardiac arrhythmia. The clinical relevance of the effects observed is unclear and will depend on individual patient risk factors and susceptibilities present. SUTENT should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing

cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of SUTENT reduced.

Important missing information is long tern toxicity data on cardiovascular safety. Even if toxicity was manageable with dose delay or reduction, long term safety needs to be further investigated for patients who will receive a long term treatment with the drug. Adequate information has been provided in the SPC to help treating physicians minimize potential sunitinib toxicity, and to minimise the incidence and severity of cardiac toxicity.

There is no experience of acute over-dosage with SUTENT. There is no specific antidote for over-dosage with SUTENT and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage.

5. 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 MAA submitted a risk management plan. A number of safety issues, including long-term toxicity will require routine pharmacovigilance, periodic monitoring and review of target adverse events from ongoing clinical trials (quarterly basis or earlier) and SAEs (monthly basis). The following studies have been conducted or are ongoing and are of particular relevance to address some of the safety issues:

- A6181005 is the completed QT study consisting of a 10 day treatment regimen: LD: 200-225 mg/day, MD: 50mg/day to achieve drug concentration around 200ng/mL.
- A6181077 is an ongoing randomized phase 2 study of sunitinib vs. standard of care for patients with previously treated advanced triple receptor negative (ER, PR, and HER2) breast cancer.
- A6181079 (hepatic impairment study) is a Phase 1 study to evaluate the effects of mild and moderate impaired hepatic function on the single-dose pharmacokinetics of sunitinib and its active metabolite, SU012662 and to assess the safety and tolerability of a single dose of SU011248 in subjects with mild and moderate impaired hepatic function.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
QT prolongation	A6181005 QT study Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4)
Hypertension	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4 and 4.8)
Haemorrhage (including tumour)	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4, 4.5, and 4.8)
Anaemia, neutropenia, thrombocytopenia	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4 and 4.8)
Hypothyroidism	Study A6181077 with TSH testing Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4 and 4.8)
Use in patients with hepatic	A6181079 hepatic impairment study Periodic review data from ongoing	Provide information in the SPC (see section 5.2)

impairment	clinical trials and SAE	
Thromboembolic events	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4 and 4.8)
Phototoxicity and skin discolouration	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4 and 4.8)
Gastrointestinal perforation	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.4)
Carcinogenicity	Rodent carcinogenicity studies Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 5.3)
Fatigue & asthenia	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.8)
Drug-drug interaction caused by inhibition or induction of CYP3A4 and CYP1A2	Periodic review data from ongoing clinical trials and SAE	Provide information in the SPC (see section 4.2, 4.4, 4.5 and 5.2)

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

An updated Risk Management Plan, as per the CHMP Guideline on Risk Management Systems for medicinal products for human use, should be submitted at the same time as the PSURs, within 60 days of an important (Pharmacovigilance or Risk minimisation) milestone being reached or when the results of a study becoming available or at the request of the Competent authority.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The Quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

At the time of the CHMP opinion, there were a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and diarrhoea in monkeys), adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats), haemolymphopoietic system (bone morrow hypocelularity, and lymphoid depletion of thymus, spleen, and lymph node), exocrine pancreas (acinar cell degranulation with single cell necrosis), salivary gland (acinar hypertrophy), bone joint (growth plate thickening), uterus (atrophy) and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included QTc interval prolongation, LVEF reduction, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in kidney, haemorrhage in GI tract and oral mucosa, and hypertrophy of anterior pituitary cells. Changes in the uterus (endometrial atrophy) and bone growth plate (physeal thickening or dysplasia of cartilage) are thought to be related to the pharmacological action of sunitinib. Most of these findings were reversible after 2 to 6 weeks without treatment.

The *g*enotoxic potential of sunitinib was assessed *in vitro* and *in vivo*. Sunitinib was not mutagenic in bacteria using metabolic activation provided by rat liver. Sunitinib did not induce structural chromosome aberrations in human peripheral blood lymphocyte cells *in vitro.* Polyploidy (numerical chromosome aberrations) was observed in human peripheral blood lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Sunitinib was not clastogenic in rat bone marrow *in vivo.* The major active metabolite was not evaluated for genetic toxicity potential.

Carcinogenicity studies with sunitinib malate have not been performed.

No effects on fertility were observed in male rats dosed for 58 days prior to mating with untreated females. No reproductive effects were observed in female rats treated for 14 days prior to mating with untreated males, at doses resulting in systemic exposures approximately 5 times the systemic exposure in patients. However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea, endometrial changes in the uterus and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Moreover in repeat-dose toxicity studies conducted in rats, effects on male fertility were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididimes and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than is observed in clinic. Not all the effects observed in male rats were reversible at the end of the recovery period (6 weeks).

No specifically designed perinatal and postnatal development animal studies have been conducted.

In rats, treatment-related embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions (early and total); corresponding increased postimplantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than is observed in clinic. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions (early and total), increases in postimplantation loss and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3-fold higher than is observed in clinic.

Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisted of increased incidence of foetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae. Developmental effects in rats occurred at plasma exposure levels 6-fold higher than is observed in clinic. In rabbits, developmental effects consisted of increased incidence of cleft lip at plasma exposure levels approximately equal to that observed in clinic, and cleft lip and cleft palate at plasma exposure levels 2.7-fold higher than is observed in clinic.

A definitive rabbit embryo-foetal development toxicity study was not conducted as embryo-foetal effects were clearly demonstrated in the rat and reported in the preliminary study conducted in rabbits.

Efficacy

The demonstration of efficacy in the treatment of patients with malignant gastrointestinal stromal tumour (GIST) who were resistant or intolerant to imatinib is mainly based on a double blind, placebo controlled Phase III study (A6181004) that showed an increased TTP and overall survival for sunitinib compared to placebo. The demonstration of efficacy in patients with metastatic renal cell carcinoma (MRCC) who were refractory to prior cytokine therapy with interleukin-2 or interferon-α is based on two single-arm, open-label phase 2 studies showing outstanding results in terms objective response rate in a homogenous group of progressive patients with a predictable outcome of the disease. The CHMP considers that efficacy results from a trial in first line will provide comprehensive clinical data about the product, particularly as these will allow to confirm that treatment with SUTENT is associated with an effect on important time-related clinical endpoints such as progression-free survival and overall survival independent of patients with MRCC who have failed prior cytokine based treatment. The trial for which data is requested is ongoing, recruitment has been completed and the requested results are expected in September 2006

Safety

The most important treatment-related serious adverse events associated with SUTENT treatment of patients with solid tumours were pulmonary embolism (1%), thrombocytopoenia (1%), tumour haemorrhage (0.9%), febrile neutropoenia (0.4%), and hypertension (0.4%). The most common

treatment-related adverse events (experienced by at least 20% of the patients) of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; dysgeusia and anorexia. Fatigue, hypertension and neutropoenia were the most common treatment-related adverse events of Grade 3 maximum severity and increased lipase was the most frequently occurring treatment-related adverse event of Grade 4 maximum severity in patients with solid tumours.

Important identified risks with sunitinib are cardiac toxicity, thrombocytopenia / leucopenia and hypertension. Important missing information is data on long term safety especially for cardiotoxicity. Adequate information has been provided in the SPC to help treating physicians minimize potential sunitinib toxicity, and to minimise the incidence and severity cardiac toxicity. However, regarding the safety profile of sunitinib there are still uncertainties due to the limited size of the safety database. This is justified in view of the unmet medical need of these patients with no other treatment options, but requires for the applicant to introduce specific procedures concerning the safety of the product. A risk management plan was submitted.

The Applicant performed a user consultation testing on the package leaflet. The testing of the Patient Information Leaflet for SUTENT has proved the document to be well designed and informative. It exceeds all of the standards set for this form of testing with the answers to 98% of the questions asked found 'easily' or 'very easily'. Only 2% of the answers to the questions were found with 'some difficulty'.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

Risk-benefit assessment

The clinical benefit of sunitinib in the treatment of GIST has been demonstrated in terms of relevant clinical endpoints such as time to progression and overall survival in patients who had failed or been unable to tolerate prior imatinib therapy. Taking into account the manageable toxicity, the risk-benefit of sunitinib in the claimed GIST indication is positive.

Concerning the MRCC indication, the CHMP considered that comprehensive clinical data related to the efficacy of SUTENT have not been supplied. In particular the submitted studies were non-randomized, and the effect of SUTENT in terms of relevant clinical endpoints such as PFS and OS is difficult to quantify using historically comparisons. The CHMP consulted the Oncology Scientific Advisory Group (SAG) seeking confirmation about the interpretation of the efficacy results in the context of the non-randomized studies presented, and whether the population in the two studies representative for the claimed indication. The advice of the SAG was that clearly, a randomized controlled study would have provided the most convincing evidence of efficacy and clinical benefit. However, the response rate observed in the phase 2 trials was very high and it is very likely that this effect will translate into a clinically relevant effect on PFS and OS. Concerning the single-arm study and the historical comparison to placebo, the effect in terms of ORR is unprecedented, even with the most active available agents in a non-refractory population. The phase 2 data appeared to be of high quality, with radiological confirmation of the progressive disease at study entry, and independent evaluation of responses. The population in the two studies is considered to be representative for patients resistant or intolerant to first line cytokine based therapy. By protocol, all patients included in the studies were progressive to cytokine treatment as specified by the study design, and this was indeed confirmed. The results were consistent across the two studies. Although the majority of patients had kidney cancer of clear cell type, the data are few and the potential implications for efficacy or safety in different subtypes of MRCC are unknown. Although the issue is of some academic interest, due to the small number of patients with other histology, and the number of potentially important factors, it is difficult to address these scientific issues within a reasonable timeframe. It is unlikely that the preliminary information available would allow to select responders. The disease and patient characteristics for patients recruited in the studies should be made clear in the SPC as this may help to guide treatment decisions, together with all other information but not to restrict the potential indication. Overall, the advisory group concluded that the phase 2 data provide sufficiently convincing

evidence of clinical benefit, and a manageable toxicity. When available, results from the randomized trial in first line might provide useful supportive evidence and add to the overall confidence of the conclusions based on the phase 2 data.

The CHMP considered the advice from the advisory group and concluded that although comprehensive clinical data related to the efficacy of SUTENT in MRCC have not been supplied, a dramatic effect unlikely to have occurred spontaneously has been observed in terms of objective response rate in patients with MRCC who have failed prior cytokine-based treatment. The population is considered sufficiently homogeneous with a predictable outcome to allow reliable conclusions about the efficacy of SUTENT in terms of ORR from a historical comparison to no active treatment. However, ORR per se cannot be considered a direct measure of clinical benefit. In this setting, due to the poor prognosis and the lack of effective treatment, a clinical benefit would generally require the presence of effects in terms of PFS or OS.

Due to the design, it is difficult to estimate the size of the effect in terms of time-related clinical endpoints such as PFS or OS. In terms of these endpoints, a reliable historical comparison to no active treatment is not possible based on the available data. Nevertheless, the magnitude of the observed biological effect in terms of ORR provides sufficient confidence to conclude that this will also translate into some effect in terms of PFS or OS in patients with MRCC who have failed prior cytokine-based treatment, although the exact size of the effect is difficult to assess. Thus, despite the existing uncertainty about the precise effect in terms of time-related clinical endpoints, the efficacy can be considered sufficiently established to allow a conclusion on the benefits in this indication.

The efficacy results from the ongoing randomized trial in first line could in principle provide comprehensive clinical data to confirm that treatment with SUTENT is associated with an effect on important clinical endpoints. Although the ongoing trial involves an active control and patients in an earlier stage of treatment, based on pharmacological and biological grounds, the demonstration of a favourable effect in first-line would be considered relevant also for patients with MRCC who have failed prior cytokine-based treatment confirming the existence of an effect in terms of relevant clinical endpoints even if the precise magnitude of this effect would not be known in this indication.

The data presented support a clinical benefit for sunitinib in the treatment of patients with MRCC who have failed prior cytokine-based treatment. Taking into account the favourable safety profile observed, the risk-benefit of sunitinib in the MRCC indication is considered positive. However, comprehensive clinical data in the MRCC indication are not yet available, and the CHMP, having consulted with the applicant, has proposed the granting of a conditional marketing authorization.

The CHMP considers, that the medical product SUTENT (sunitinib malate) falls within the scope of Regulation (EC) No 507/2006, with particular reference to Article 2, based on the following grounds:

SUTENT (sunitinib malate) has been designated as orphan medicinal product in accordance with Article 3 of Regulation (EC) No 141/2000. In addition, patients with GIST that are not amenable to curative treatment and that have failed imatinib mesylate treatment, and patients with MRCC that have failed prior cytokine-based treatment have a poor long-term prognosis in terms of overall survival. Thus, SUTENT is a medicinal product, which aims at the treatment of a seriously debilitating and life-threatening disease.

The CHMP considers, that SUTENT fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

(a) The clinical benefit of sunitinib in the treatment of GIST has been demonstrated in terms of relevant clinical endpoints such as time to progression and overall survival in patients who had failed or been unable to tolerate prior imatinib therapy. For the MRCC indication, sunitinib has shown an outstanding antitumor activity in terms of objective response rate.

The safety profile was considered acceptable for both indications.
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Sutent, as defined in Article 1(28a) of Directive 2001/83/EC, for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance, and for the treatment of metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy, was positive.

(b) The CHMP considers that efficacy results from the study A618034 in cytokine-naive MRCC patients will provide comprehensive clinical data, particularly as these will allow to confirm that treatment with SUTENT is associated with an effect on important time-related clinical endpoints such as progression-free survival and overall survival independent of patients with MRCC who have failed prior cytokine based treatment. The trial for which data is requested is ongoing, recruitment has been completed and the requested results are expected in September 2006. Thus, the CHMP considers that it is likely that the applicant will be in a position to provide the comprehensive clinical data.
(c) No satisfactory methods of treatment that have been authorised, exist in the Community for patients with GIST after failure of imatinib mesylate treatment due to resistance or intolerance. The clinical benefit observed for sunitinib in terms of overall survival and progression-free survival will fulfil an unmet need in these patients.
No satisfactory methods of treatment that have been authorised, exist in the Community for patients with metastatic renal cell carcinoma (MRCC) who have failed prior cytokine-based treatment. Despite other agents that have shown activity in this setting, such as different regimens of cytokines and novel tyrosine kinase inhibitors such as sorafenib, there remains a large unmet medical need in the treatment of this condition. The demonstration of efficacy in patients with MRCC who were refractory to prior cytokine therapy with interleukin-2 or interferon-α is based on the proportion of patients achieving an objective response (i.e. a major shrinkage of the overall tumor burden) observed in two single-arm, open-label phase II studies. In one study the objective response rate (ORR) was 36.5% (95% C.I. 24.7% - 49.6%). In the second study, ORR was 35.8% (95% C.I. 26.8% - 45.7%). These results were observed in a homogenous group of progressive patients with a predictable outcome of the disease. The effect in terms of ORR was unprecedented, even with the most active available agents in a non-refractory population for which response rates in the order of 5 to 15% have been reported. Also, the response rate observed for sunitinib was much higher than the reported proportion of patients with an objective response for the novel targeted kinase agent sorafenib (2.1%). Overall, compared to other agents that have shown activity in this MRCC, sunitinib appeared to have a distinct pharmacodynamic profile, and the proportion of patients achieving an objective response observed for sunitinib in this MRCC patient population was very high compared to what has been reported for other agents including sorafenib.
Therefore the CHMP considers that unmet medical needs will be fulfilled for patients with MRCC who have failed prior cytokine-based treatment.

(d) New treatments having an effect in terms of relevant clinical endpoints are of immediate relevance to patients with GIST after failure of imatinib mesylate treatment or MRCC who have failed prior cytokine-based treatment. Although comprehensive data are not available to allow precise estimation of the benefits in patients with MRCC who have failed prior cytokine-based treatment, in view of the efficacy of the product and the poor prognosis, lack of comprehensive data poses no risks that outweigh the benefits. Therefore the CHMP considers that the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Similarity with authorised orphan medicinal products

The Applicant has claimed that at the time of submission of the application the orphan medicinal product Glivec has been granted a marketing authorisation in the EU, and that SUTENT is not similar to any of the authorised Orphan medicinal products (as defined in Art. 3 of Commission Regulation (EC) No 847/2000) for a condition relating to the proposed therapeutic indication.

The CHMP concluded, having considered the arguments presented by the applicant, the Rapporteurs assessment, and the conclusions of the Quality working Party, there are substantial differences in the mechanism of action of the two active substances. Imatinib does not inhibit sunitinib target receptor tyrosine kinases including VEGFR-1, VEGFR-2, FLT-3, or CSF-1R at concentrations up to 10 μM. Furthermore, secondary mutations in the ATP-binding site of KIT that cause resistance to inhibition by imatinib, seems to be still sensitive to inhibition by sunitinib.

In addition, the CHMP concluded that sunitinib and imatinib are not similar in terms of molecular structural aspects on the basis of the difference in principal molecular structural features of the active

moieties in each case. Both molecules belong to different classes of tyrosine kinase inhibitors, and the only identical chemical feature present in both chemical structures of sunitinib and imatinib is the amide group, a very common structural group in pharmaceutical substances.

The CHMP is of the opinion that SUTENT is not similar to any authorised orphan medicinal products within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. (See Appendix 1)

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of SUTENT in the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance, and in the treatment of advanced and/or metastatic metastatic renal cell carcinoma after failure of cytokine-based therapy was favourable and therefore recommended the granting of the conditional marketing authorisation, subject to the following specific obligation: to provide results of an ongoing study in cytokine-naive patients with metastatic renal cell carcinoma by September 2006.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers SUTENT not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to authorised orphan medicinal products for the same therapeutic indication.