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Human Medicines Development and Evaluation

# ASSESSMENT REPORT
# FOR
# Sutent
# (sunitinib)

## Procedure No. EMA/H/C/000687/II/0021

**Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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## List of Abbreviations

| | |
|---|---|
| APUD | Amine precursor uptake and decarboxylation |
| AT | As-treated |
| AUC | Area under plasma concentration-time curve |
| CDD | Continuous daily dosing |
| CDS | Core Data Sheet |
| CgA | Chromogranin A |
| CR | Complete response |
| CSF-1R | Colony stimulating factor-1 receptor |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| DR | Duration of response |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EGF | Epidermal growth factor |
| EGFR | Epidermal growth factor receptor |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 |
| ESRD | End-stage renal disease |
| FAS | Full Analysis Set |
| FLT-3 | Fms-like tyrosine kinase-3 |
| GEP | Gastroenteropancreatic |
| GIST | Gastrointestinal stromal tumour |
| HIF | Hypoxia-inducible factor |
| IA3 | Interim Analysis 3 |
| KIT | Stem cell factor receptor |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MUGA | Multigated acquisition |
| NET | Neuroendocrine tumours |
| NMR | Nuclear magnetic resonance |
| ORR | Objective response rate |
| OS | Overall survival |
| PDGF | Platelet-derived growth factor |
| PDGFR | Platelet-derived growth factor receptor |
| PFS | Progression-free survival |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PRRT | Peptide receptor radionuclide therapy |
| QoL | Quality of life |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RET | REarranced during Transfection |
| RSD | Reference safety document |
| RTK | Receptor tyrosine kinase |
| RTKI | Receptor tyrosine kinase inhibitor |
| SAE | Serious adverse event |
| SD | Stable disease |
| SD | Standard deviation |
| SPA | Special protocol assessment |
| TAg | T-antigen transgene |
| TTF | Time to treatment failure |
| TTP | Time to tumour progression |
| TTR | Time to tumour response |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial growth factor receptor |
| VHL | Von Hippel-Lindau |
| VIP | Vasoactive intestinal peptide |

# 1. Scientific discussion

## *1.1. Introduction*

Sunitinib is an orally active small molecule with anti-tumour properties that are mediated through the inhibition of multiple receptor tyrosine kinases (RTKs). These RTKs are important in the regulation of tumour cell growth, angiogenesis, and metastasis. Specifically, sunitinib is a potent ATP-competitive inhibitor of the catalytic activity of a group of closely related RTKs consisting of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, stem cell factor receptor (KIT), colony stimulating factor-1 receptor (CSF-1R), Fms-like tyrosine kinase-3 receptor (FLT-3), and glial cell line-derived neurotrophic factor receptor (rearranged during transfection, RET). Due to its multi-targeted profile, the activity of sunitinib is likely mediated by multiple distinct anti-tumour mechanisms. Sunitinib has demonstrated clinical efficacy with an acceptable safety profile for the treatment of gastrointestinal stromal tumour (GIST) and metastatic renal cell carcinoma (MRCC).

Sunitinib was first approved in 2006 in the United States and Europe for the treatment of GIST after failure of imatinib mesylate due to resistance or intolerance as well as for the treatment of advanced MRCC, and was subsequently approved for both indications in Japan in 2008. Sunitinib has been approved in more than 90 countries worldwide.

This type II variation has been submitted by the MAH with the aim of supporting the use of sunitinib for the treatment of patients with pancreatic neuroendocrine tumours (NET). The initially proposed indication by the MAH was:

*Treatment of patients with unresectable pancreatic neuroendocrine tumours (pNET)*

This application concerns the update of SmPC section 4.1 with a new indication and also a new dose schedule in SmPC section 4.2 for this new indication. Furthermore, related SmPC sections 4.4, 4.5, 4.8 and 5.1 have been amended. The package leaflet has been amended accordingly.

Pancreatic NET Epidemiology

Neuroendocrine tumours (NET), including pancreatic islet cell tumour, are uncommon neoplasms. Pancreatic NETs (pNETs) include a group of rare tumours of the endocrine pancreas. Collectively, these tumours are referred to as pancreatic islet cell tumours, malignant neoplasms of Islets of Langerhans (ICD-9), and gastroenteropancreatic (GEP) NET (2000 WHO classification), although individually, they may be referred to by the hormone secreted [e.g., insulinoma, gastrinoma, glucagonoma, or vasoactive intestinal peptidoma (VIPoma)]. In the WHO classification, these tumours are further classified into three groups according to malignant potential:

1) well-differentiated neuroendocrine tumour,
2) well-differentiated neuroendocrine carcinoma, and
3) poorly differentiated neuroendocrine carcinoma.

Because these three groups demonstrate differences in prognosis, treatment approaches and clinical trials for these groups are distinct. The disease under study for this variation application reflected the second group – well-differentiated neuroendocrine carcinoma – and the inclusion criteria of the pivotal trial comprised (among others) well-differentiated pancreatic islet cell tumour (according to WHO 2000 classification), locally-advanced or metastatic disease with disease progression documented, and disease not amenable to surgery, radiation, or combined modality therapy with curative intent.

Well-differentiated pancreatic islet cell tumours including pancreatic neuroendocrine carcinoma [2000 WHO classification], are often described as slow growing, although subsets of patients with documented disease progression may have more aggressive disease that leads to greater disease-related morbidity and mortality. Pancreatic NET are distinguished from the more common adenocarcinoma of the exocrine pancreas and from poorly-differentiated neuroendocrine carcinoma. Epidemiologic data on pancreatic NET are limited and potentially represent underreported data due to the lack of validated, well-defined pathologic criteria and varying nomenclature for these rare and heterogeneous tumours. In the United States, the age-adjusted annual incidence of pancreatic NET among males is 0.38 per 100,000 and among females is 0.27 per 100,000; the median age of diagnosis is 60 years (mean 59 years; SD 15) (SEER Registry for 2000 to 2004). Intriguing data from US registries (Yao, Journal of Clinical Oncology, JCO, 2008) showed that the incidence and prevalence of neurondocrine tumours, including pNETs, rose over the last three decades. Although similar epidemiology data do not exist in the European patient population, the incidence is likely consistent with that in the United States.

These tumours may be either functional, producing peptides which cause characteristic hormonal syndromes (insulinoma, gastrinoma, glucagonoma, VIPoma), or non-functional but capable of causing general symptoms. The putative cells of origin for this malignancy have been referred to as APUD cells for their ability for amine precursor uptake and decarboxylation, and they form clusters within the pancreatic parenchyma. Specific cell types, such as alpha, beta, delta, G, and PP, produce the hormones glucagon, insulin, somatostatin, gastrin, and pancreatic polypeptide, respectively. The mechanism of malignant transformation of these cells remains unknown; however, these tumours do occur as part of inherited predisposition syndromes, including MEN1 and VHL. MEN1 is an autosomal dominant condition caused by mutation in the MEN1 gene, which encodes menin, a putative inhibitor of transcription, and is associated with several tumour types; approximately 75% of these individuals develop NET of the pancreatic islet cells or duodenum. VHL is an autosomal dominant disorder caused by mutation in the von Hippel-Lindau (VHL) tumour suppressor gene. The resulting protein can no longer function in targeting hypoxia-inducible factor (HIF) for breakdown, leading to increased and abnormal blood vessel formation; this disorder is characterized by a predisposition for several vascular tumours, including renal cell carcinoma and pancreatic NET (Glenn et al., 1992). Although there are limited data describing a direct mechanistic link between dysfunctional menin and angiogenesis, an angiogenic association has been described in the setting of VHL, where angiogenesis in several tumour types, including pancreatic NET and renal cell carcinoma, putatively plays an important role in carcinogenesis. The mechanism for increased angiogenesis in the setting of VHL includes overexpression of VEGF. Indeed, pancreatic NET and their associated stroma have been shown to overexpress both, VEGF and PDGF, as well as their receptors, VEGFR and PDGFR (Reidy et al., 2009). The VEGF pathway may be particularly important in promoting tumour growth and angiogenesis through direct effects on the tumour vasculature (Christofori et al., 1995; Terris et al., 1998; La Rosa et al., 2003), while the PDGF pathway may be important for supporting pericytes within the tumour stroma and thereby cooperating with VEGF in tumour neoangiogenesis. Expression of VEGF has been associated with relatively short disease-free and overall survival. Additionally, a recent study demonstrated that low KIT expression (assessed by immunohistochemistry) in pancreatic NET biopsies was associated with prolonged survival, suggesting that KIT may similarly be a disease-specific target for pancreatic NET (Zhang et al., 2009). Together, these data suggest that VEGFR, PDGFR, and KIT are rational molecular targets in pancreatic NET.

The rationale for the development of sunitinib for pNETs mainly relies on the anti-angiogenic mechanism of action of the medicinal product, because of the inhibition of VEGFR 1-3 and PDGFR. Angiogenesis has been shown to be directly implicated in cancer growth and progression for various tumour types, including pNETs. Nevertheless, basic, clinical and translational research should aim to

identify for each tumour type its own biological "hub" (Yosef Yarden, SABCS 2009), that could consequently be blocked by selective medicinal products.

IGF-1R and mTOR pathways seem to play a key role in pNET progression and a number of mTOR genetic mutations as outlined above (tuberosclerosis, neurofibromatosis, Von Hippel-Lindau syndrome) are associated with pNET development. Moreover, preclinical data support a close interaction between IGF and mTOR pathways, fuelling the rationale to combine medicinal products which selectively could block the aforementioned "hubs" (YAO, ASCO 2009). So far, the following pathways have been more extensively studied in the context of clinical trials: IGF-1 pathway, mTOR pathway and the angiogenic pathway.

Treatment of Pancreatic NET

Although pancreatic NET (pNET) is typically considered an indolent disease, patients with unresectable, locally advanced or metastatic disease and recent disease progression represent a subset with a poor prognosis and an expected survival of 1-3 years. Many of these patients may be variably treated with surgery of primary and metastatic lesions and/or treated with liver-directed therapies such as hepatic artery chemoembolization, radiofrequency ablation therapy, or ethanol injection (Clark, 2009).

Although somatostatin analogs may be useful in ameliorating some hormonally related symptoms such as diarrhoea, demonstrated antitumour efficacy has been limited primarily to low-volume midgut (but not pancreatic) tumours (Rinke et al., 2009). The role of somatostatin analogues has been recently re-launched based on the evidence provided by US registries of prolonged overall survival after the introduction of octreotide (YAO, JCO 2008). The use of these compounds in non-functional tumours is still debated. Preclinical studies suggest an impact on angiogenesis and a decrease of the IGF-1 mediated signals. NCCN and European Neuroendocrine Tumour Society (ENETS) state that somatostatin analogues may stabilize the tumour growth in up to 50% of patients. The speculation was reinforced by the results of the PROMID trial (ASCO 2009) that showed almost a three-fold increase in PFS among patients that were treated with octreotide for midgut NETs. The study did not enrol pNETs. However, many other studies did and octreotide is currently investigated in combination with other new medicinal products for pNETs.

Trials of systemic chemotherapy have been conducted with agents including streptozocin, doxorubicin, and fluorouracil but have yielded low response rates and have been associated with adverse events that may outweigh any benefit (Oberg and Eriksson, 1991; Kouvaraki et al., 2004; Vilar et al., 2007; Delaunoit et al., 2008). However, in metastatic setting chemotherapy has a limited impact.

Exploratory studies have also been conducted with newer agents, including temozolomide and thalidomide in Phase 2 trials (Kulke et al., 2006), and with peptide receptor radionuclide therapy (PRRT) (Hörsch et al., 2008). The therapeutic options beyond failure of first line are scant and highly debated. Thus, there is no standard of care, and there remains considerable unmet medical need for an effective agent with an acceptable safety profile for the treatment of patients with pancreatic NET.

## *Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended the application included an EMA decision (P35/2009) for the following condition(s):

- Gastro-intestinal stromal tumour

on the agreement of a paediatric investigation plan (PIP).

- Treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney)

on the granting of a class waiver.

- Treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma)

on the granting of a class waiver.

The PIP is not yet completed.

### *Information relating to Orphan Market Exclusivity*

Not applicable

## *1.2. Non-clinical aspects*

Pre-clinical data supporting the use of sunitinib in pNET are based on bibliographic references.

Nonclinical proof of concept for sunitinib in pancreatic islet cell carcinoma was first observed in the RIP1-TAG2 transgenic mouse model. The RIP1-TAG2 model comprises a strain of transgenic mice for which the rat insulin promoter (RIP) directs expression of the SV40 Large T antigen transgene (TAg) in beta cells of the pancreatic islets. The Large TAg oncogene is expressed beginning at embryonal day 8, and hyperplastic islets begin to appear by 3-4 weeks of age. Solid tumours consistently and reproducibly emerge initially as small encapsulated adenomas at about 10 weeks that progress into large adenomas by 12 to 13 weeks and to invasive cancer by 14 weeks.

Sunitinib was evaluated in both regression and regression/survival trials in the RIP1-TAG2 model. In regression or regression/survival trials, sunitinib was administered to 12-week-old RIP1-TAG2 mice bearing multiple large established adenomas. In these studies, sunitinib was associated with reduced tumour burden and stable disease over the 4-week administration cycle and with a significant survival advantage (Pietras and Hanahan, 2005). In longer term studies utilizing RIP1-TAG2 mice, administration of sunitinib starting at 12 weeks was markedly efficacious, producing a significant survival benefit and a 65% decrease in tumour burden after 5 weeks of treatment when compared to age-matched control animals (Pàez-Ribes, et al., 2009).

Mechanistic studies in the RIP1-TAG2 islet cell carcinoma model reported that treatment with sunitinib for 7 days reduced both the endothelial cell population (69% reduction) and pericyte coverage (71% reduction) of tumour vessels (Yao, et al., 2007), consistent with the importance of inhibition of VEGF effects on blood vessels and PDGF effects on pericytes in islet cell tumours.

**Ecotoxicity/environmental risk assessment**

The CHMP agreed that no updated environmental risk assessment is required for this Type II variation applied for the treatment of pancreatic neuroendocrine tumours. Assuming a prevalence rate of about 10 per million an increase in the predicted environmental exposure can be considered as insignificant.

## *1.3. Clinical aspects*

**Clinical Development program for sunitinib**

The use of sunitinib in pNET is supported by the results of one pivotal Phase 3 study (A6181111) and a supportive Phase 2 study (RTKC-0511-015). Two additional Phase 2 studies (A6181047 and A6181061) in GIST and MRCC, respectively, are included in this submission to support the continuous daily dosing (CDD) schedule used in the pivotal trial.

| Protocol | Design and Objectives | N; Status |
|---|---|---|
| **Pivotal Phase 3 Study** | | |
| A6181111 | Double-blind, randomized, controlled Phase 3 study to evaluate the efficacy and safety of sunitinib 37.5 mg (on Schedule CDD*) versus placebo in patients with progressive advanced/metastatic well-differentiated pancreatic islet cell tumours | 171; Stopped early due to efficacy |
| **Supportive Studies** | | |
| *Studies in Subjects with Pancreatic Neuroendocrine Tumours* | | |
| RTKC-0511-015 | Open-label, randomized, multicenter, 2-cohort, Phase 2 study to investigate the efficacy and safety of single-agent sunitinib 50 mg (on Schedule 4/2) in subjects with unresectable neuroendocrine tumours; carcinoid tumours or pancreatic neuroendocrine tumours | 66 (Pancreatic NET); 41 (Carcinoid); Completed |
| *Other Studies Evaluating Continuous Daily Dosing* | | |
| A6181047 | Open-label, uncontrolled, multicenter Phase 2 study to investigate the efficacy, safety/tolerability, and PK of sunitinib 37.5 mg (on Schedule CDD) in patients with advanced GIST | 60; Completed |
| A6181061 | Open-label, nonrandomized, multicenter Phase 2 study to investigate the efficacy, safety/tolerability, and pharmacokinetics of sunitinib 37.5 mg (on Schedule CDD) in patients with cytokine-refractory MRCC | 107; Completed |

*Sunitinib Schedules: CDD=continuous daily dosing, and 4/2=4 weeks on treatment followed by 2 weeks off treatment.
GIST=gastrointestinal stromal tumour.
MRCC=metastatic renal cell carcinoma.

**GCP**

All studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with the International Congress on Harmonization Good Clinical Practices Guidelines, as reported by the marketing authorisation holder.

The CHMP requested a GCP inspection for the single pivotal study A6181111.

**Scientific Guidelines and Regulatory Agency Advice**

The marketing authorisation holder did not seek EMA Scientific Advice for the development of sunitinib in pNET.

***1.3.1 Clinical Pharmacology***

Continuous Daily Dosing (CDD)

One of the main objectives was to provide supporting PK data for administration of sunitinib 37.5 mg on a CDD schedule as investigated in the pivotal study A6181111 for the treatment of advanced/metastatic pancreatic neuroendocrine tumours (pNET). The supporting clinical pharmacology studies were conducted to evaluate the safety/tolerability and PK of sunitinib as a single agent on Schedule 4/2 (RTKC-0511-015) in patients with advanced unresectable NET, including carcinoid tumour and pancreatic islet cell tumours (also referred to as pNET), and as a single agent on a CDD schedule (A6181047 and A6181061) in patients with GIST or cytokine-refractory MRCC.

**Table 1. Overview of Clinical Studies with PK Evaluable Subjects or Patients**

| Protocol No. (Study Type) | Design and Objectives | Starting Dose/ Formulation/ Schedule | Study Population (N) | Full PK Profile Sampling | Trough Concentration Sampling | Noncompartmental PK Analysis |
|---|---|---|---|---|---|---|
| **Multiple-Dose Single-Agent Studies in Patients with Malignant Disease** | | | | | | |
| **RTKC-0511-015** | 2-Cohort (Schedule 4/2), open-label, multicenter, Phase 2 study to evaluate the efficacy and safety of single-agent sunitinib in patients with carcinoid tumours or pancreatic islet cell tumours. | 50 mg; L-malate salt capsules; Schedule 4/2 | NET (107 total) Carcinoid (41) Pancreatic NET (66) | N/A | X | N/A |
| **A6181047** | Open-label, uncontrolled, multicenter Phase 2 study to investigate the efficacy, safety/tolerability, and PK of AM and PM sunitinib administered on a CDD schedule in patients with advanced GIST | 37.5 mg; L-malate salt capsules; Schedule CDD, administered AM or PM | GIST (60) | N/A | X | N/A |
| **A6181061** | Open-label, non-randomized, multicenter Phase 2 study to investigate the efficacy, safety/tolerability, and PK of AM and PM sunitinib administered on a CDD schedule in patients with cytokine-refractory MRCC | 37.5 mg; L-malate salt capsules; Schedule CDD, administered AM or PM | MRCC (107) | N/A | X | N/A |

AM = morning; CDD = continuous daily dosing; ESRD = end-stage renal disease; GIST = gastrointestinal stromal tumour; MRCC = metastatic renal cell carcinoma; N = total number of subjects or patients; NET = neuroendocrine tumours; N/A = not applicable; No. = number; PK = pharmacokinetics; PM = evening; QD = daily; X = study had PK sampling schedule indicated, and study was included in analysis indicated.

Continuous Daily Dosing versus Intermittent Dosing

The dose proportionality of plasma exposures to sunitinib, SU012662 and total drug has been previously evaluated in advanced cancer patients following single sunitinib doses ranging from 50 to 350 mg, and multiple daily dosing with doses of 25 to 100 mg (on Schedule 4/2). The dose-corrected maximum and total plasma exposures were comparable between doses and showed no dose-related trends, demonstrating that the PK of sunitinib, SU012662 and total drug were dose-proportional or

close to dose-proportional over the dose ranges evaluated following both single and multiple dosing. Similarly, the dose-corrected AUC24 values (at steady state) after multiple day dosing were similar to AUC∞ values after single dosing, supporting lack of time-dependence in the PK of sunitinib, SU012662, and total drug. Consistent with the linearity in PK, it has been observed that the PK disposition of sunitinib, SU012662 and total drug was similar among dosing Schedules 4/2, 2/1, and 2/2. To further support the linearity in the PK of sunitinib, SU012662 and total drug on Schedule CDD, the steady state trough values for sunitinib, SU012662 and total drug on Schedule CDD were compared to Schedule 4/2.

The steady state trough concentrations of sunitinib, SU012662 and total drug on Schedules CDD and 4/2 are presented in table 2. The dose-corrected mean $C_{trough}$ values for sunitinib ranged from 40.9-64.2 ng/mL on Schedule CDD and 42.6-57.9 ng/mL on Schedule 4/2. In addition, for SU012662, mean dose-corrected $C_{trough}$ values ranged from 15.9-25.3 ng/mL on Schedule CDD and 21.0-32.7 ng/mL on Schedule 4/2. Similarly, for total drug, mean dose-corrected $C_{trough}$ values ranged from 58.2-87.5 ng/mL on Schedule CDD and 63.6-87.2 ng/mL on Schedule 4/2. There was a significant overlap between the dose-corrected trough plasma concentrations for sunitinib, SU012662, and total drug between Schedule CDD and Schedule 4/2, supporting lack of schedule dependence in the PK of sunitinib and SU012662. Therefore, it would be expected that the total plasma exposure to sunitinib and SU012662 following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2 (i.e., 37.5 mg × 42 days ≈ 50 mg × 28 days).

**Table 2. Summary of Sunitinib, SU012662 and Total Drug Steady State Dose-Corrected Trough Concentrations Following Multiple 37.5-mg or 50-mg Doses of Sunitinib (Studies A6181004, A6181006, A6181047, and A6181061)**

| Parameter | Arithmetic Mean (CV%) [Median] | | | |
|---|---|---|---|---|
| | Schedule CDD | | Schedule 4/2 | |
| | Study 1047 GIST Cycles 2-13 Day 1 (n=4-25) | Study 1061 MRCC Cycles 2-12 Day 1 (n=6-22) | Study 1004 GIST Cycle 1-8 Day 28 (n=5-84) | Study 1006 MRCC Cycles 1-4 Day 28 (n=9-38) |
| **Sunitinib** | | | | |
| DC-$C_{trough}$ (ng/mL) | 41.9-58.6 (30-61) [33.5-53.3][a] | 40.9-64.2 (25-89) [40.0-59.1][a] | 42.6-57.9 (16-55) [44.9-61.8] | 48.7-56.2 (42-50) [48.3-56.2] |
| **SU012662** | | | | |
| DC-$C_{trough}$ (ng/mL) | 17.4-25.3 (34-56) [16.1-24.9][a] | 15.9-24.9 (32-65) [14.5-23.3][a] | 21.0-31.1 (31-74) [18.1-26.9] | 29.4-32.7 (47-70) [22.2-34.8] |
| **Total Drug** | | | | |
| DC-$C_{trough}$ (ng/mL) | 60.0-83.7 (26-57) [56.7-79.7][a] | 58.2-87.5 (24-78) [54.9-78.9][a] | 63.6-86.7 (18-54) [67.3-87.4] | 80.9-87.2 (43-50) [76.0-91.9] |

CDD: continuous daily dosing; CV: coefficient of variation; DC-$C_{trough}$: dose-corrected trough concentration; GIST: gastrointestinal stromal tumours; n: number of patients with observations; MRCC: metastatic renal cell carcinoma.
[a] Dose corrected to 50 mg.

Based on the PK data in pNET, the predicted steady state trough mean plasma concentrations in pancreatic NET following administration of sunitinib 37.5 mg on Schedule CDD would be 39.6 ng/mL for sunitinib, 18.5 ng/mL for SU012662, and 58.1 ng/mL for total drug. These predicted trough concentrations in pancreatic NET would be similar to the trough concentrations for sunitinib, SU012662, and total drug following administration of sunitinib 37.5 mg on Schedule CDD in GIST (e.g., 38.4 ng/mL, 13.6 ng/mL, and 52.0 ng/mL on Day 1 of Cycle 2, respectively) and RCC (e.g., 41.6 ng/mL, 15.4 ng/mL, and 56.9 ng/mL on Day 1 of Cycle 2, respectively).

RTKC-0511-015

There were no clinically relevant differences observed in the steady state trough sunitinib and SU012662 concentrations in the pNET subpopulation as compared to the carcinoid tumour subpopulation. Steady-state conditions for sunitinib and SU012662 were likely achieved by Day 14 of Cycle 1 in both cohorts. No disproportionate accumulation of sunitinib or SU012662 was observed in either cohort across cycles. Sunitinib caused increases in VEGF and IL-8 plasma concentrations and decreases in sVEGFR-2 and sVEGFR-3 plasma concentrations in both pNET and carcinoid tumour subpopulations.

A6181047

Based on the mean dose-corrected trough values for sunitinib, SU012662 and total drug, the PK of sunitinib and SU012662 appeared to be similar (45.0-62.8 ng/mL vs. 47.7-65.0 ng/mL for total drug) between this CDD schedule and on Schedule 4/2 in a Phase 3 study of patients with GIST (A6181004). No disproportionate accumulation of sunitinib and SU012662 was observed throughout the study. Sunitinib caused significant increases in VEGF and decreases in sVEGFR-2, sVEGFR-3, and sKIT plasma concentrations. Significant correlations were observed over multiple treatment cycles between plasma VEGF ratios to baseline and trough concentrations of both SU011248 and total drug (SU011248 + SU012662).

Discussion on clinical pharmacology

Data from supportive clinical Study RTKC-0511-015, in which sunitinib was administered at 50 mg daily on Schedule 4/2, and from supportive clinical Studies A6181047 and A6181061, in which sunitinib was administered at 37.5 mg daily on a CDD schedule to subjects with GIST and MRCC, respectively, support the comparability of the dosing regimens and disease types.

The steady state trough plasma exposures to sunitinib and its active metabolite SU012662 in subjects with pancreatic NET appeared to be similar to that in subjects with GIST and MRCC, indicating that the PK of sunitinib and SU012662 were not tumour-type dependent. In addition, the PK of sunitinib and SU012662 appeared to be similar between the CDD schedule and Schedule 4/2 in subjects with GIST and MRCC. Therefore, it was predicted that the total plasma exposure to sunitinib and SU012662 following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2, supporting the selection of 37.5 mg dose on the CDD schedule in subjects with pNET.

The proposed starting dose of Sunitinib 37.5 mg once daily on a CDD schedule is adequately supported by the submitted PK data.

The MAH has submitted an indirect justification for the proposed 37.5 mg daily dosing in pNET: It has been demonstrated that steady state trough plasma concentrations of sunitinib were similar between GIST and MRCC patients and the pNET subpopulation, respectively, indicating that the PK of sunitinib were not dependent of the tumour type. Furthermore, the observed PK of sunitinib was similar between Schedules CDD and 4/2 in both GIST and MRCC patients. As a consequence, it is concluded that the exposure to sunitinib following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2, supporting the selection of the proposed 37.5 mg dose CDD schedule in subjects with pancreatic NET.

### *1.3.2 Clinical efficacy*

The efficacy of sunitinib for the treatment of pNET was evaluated in pivotal Study A6181111. One additional study of subjects with pancreatic NET (RTKC-0511-015) was also submitted in support of the efficacy of sunitinib for pNET.

**Table 3. Pancreatic NET Studies of Sunitinib Presented in the Summary of Clinical Efficacy**

| Study Number<br>**Title**<br>**Status** | Study Design | Treatment | N |
|---|---|---|---|
| **Pivotal Phase 3 Study** | | | |
| **A6181111**<br>A Phase III Randomized, Double-blind Study of Sunitinib versus Placebo in Patients with Progressive Advanced/Metastatic Well-differentiated Pancreatic Islet Cell Tumours<br>*Completed* | Phase 3, randomized, double-blind, placebo-controlled | Sunitinib 37.5 mg/day or Placebo CDD | Sunitinib: 86<br>Placebo: 85 |
| **Supportive Phase 2 Study** | | | |
| **RTKC-0511-015**<br>A Phase II Study of the Efficacy and Safety of Sunitinib in Patients with Advanced Unresectable Neuroendocrine Tumour<br>*Completed* | Phase 2, open-label, 2-cohort, 2-stage | Sunitinib 50 mg/day Schedule 4/2 | 66* |

#### *1.3.2.1 Main study*

Study A6181111 was a multinational, randomized, double-blind, placebo-controlled, Phase 3 clinical trial. Subjects had progressive, well-differentiated pancreatic islet cell tumours (pNET), not amenable to surgery, radiation, or combined modality therapy with curative intent.

- **Methods**

*Study Participants*

Subject Eligibility: Inclusion criteria included histologically or cytologically proven diagnosis of well-differentiated pancreatic islet cell tumour (according to WHO 2000 classification), locally-advanced or metastatic disease with disease progression documented radiographically (CT, MRI, or Octreoscan) within the prior 12 months, disease not amenable to surgery, radiation, or combined modality therapy with curative intent, at least one measurable target lesion according to RECIST, adequate organ function, ECOG performance status 0 or 1, and life expectancy ≥3 months.

Subjects were excluded from the study if they had poorly differentiated pancreatic NET, were on current treatment for the disease other than somastostatin analogs, had prior treatment with any tyrosine kinase inhibitors or anti-VEGF angiogenic inhibitors, presented with diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ carcinoma of the cervix uteri.

*Treatments*

The starting dose of sunitinib was 37.5 mg administered once daily orally on a CDD schedule. Subjects experiencing severe toxicity could receive treatment breaks inserted into the regimen as needed. Intrasubject dose reduction to 25 mg was permitted depending on toxicity. Intrasubject re-escalation of study medication back to a previous dose level was permitted at the discretion of the investigator upon consideration of the subject's clinical status. Dose escalation to 50 mg daily was recommended for subjects who had not yet achieved an objective disease response and who had not experienced progression or prohibitive toxicity.

No other approved or investigational anticancer treatments were permitted during the study period, including chemotherapy, biological response modifiers, hormone therapy, or immunotherapy. Use of somatostatin analogs for symptomatic control was permitted. This medication was recorded as a concomitant medication.

Subjects were to be treated until progression of disease, unacceptable toxicity, or death.

Crossover and Treatment on Extension Study: During this study, subjects developing documented objective disease progression could be unblinded and, if assigned to placebo, offered access to treatment with open-label sunitinib in one of two companion extension trials (Study A6181114 or Study A6181078). Subjects who were unblinded at the time of disease progression and found to be receiving sunitinib were withdrawn unless assessed by the investigator as having the potential to experience clinical benefit from further treatment with sunitinib. In this case, the opportunity to receive open-label sunitinib in one of the extension studies may have been offered on an individual case basis. At the end of the study, all remaining subjects were also unblinded and offered access to open-label sunitinib in one of the extension studies.

*Objectives*

The primary objective of the study was to compare progression free survival (PFS) (defined as the time from the date of randomization to the date of first documentation of objective tumour progression or death due to any cause, whichever occurred first) in subjects treated with sunitinib with those treated with placebo.

Secondary objectives were to compare the Overall Survival (OS), Overall Response Rate (ORR), duration of response (DR), time to tumour response (TTR), patient-reported outcomes (PROs), and safety in the sunitinib and placebo treatment arms. Safety evaluations included adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs and ECOG performance status.

*Outcomes/endpoints*

PFS was chosen as the primary endpoint to evaluate the efficacy of sunitinib in subjects with pNET.
*Sample size*

The initial target sample size was determined based on 90% power to demonstrate a 50% improvement in PFS using a 2-sided, unstratified log-rank test at a significance level of 0.05. The assumptions included a median PFS for placebo-treated subjects of 22 weeks, median PFS for sunitinib-treated subjects of 33 weeks, enrolment period of 26 weeks with an accrual rate of 13 subjects per week, and a 10% dropout rate. Approximately 340 subjects were required to observe 260 events assuming a 44-week follow-up after the last subject was enrolled.

The design included an interim efficacy analysis using the Lan-DeMets spending function with O'Brien-Fleming stopping boundaries to ensure the overall type I error was maintained at 0.05 for two-sided tests. The interim analysis was to be conducted when 50% of the PFS events required for the final analysis had occurred, i.e. an interim analysis was planned when 130 events had occurred, and the final analysis was to be conducted when 260 events had occurred. The possibility of an increase in sample size based on the interim analysis was included.

The conduct of the study was overseen by an independent DMC.

*Randomisation*

Subjects were randomized in a 1:1 ratio to receive sunitinib or matching placebo plus best supportive care. Randomization was balanced by country/region (grouped as Americas/Australia, Europe, Asia), with a maximum of 180 subjects per region.

*Blinding (masking)*

This was a double-blind study.

*Statistical methods*

Intent-to-treat (ITT): The ITT population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received any study drug or received a different drug from that to which they were randomized. The ITT population was the primary population for evaluating the efficacy endpoints.

The population as treated (AT) included all subjects who received at least 1 dose of study treatment with assignment designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety.

PRO analysis set: The PRO population included subjects from the ITT population who completed baseline plus at least one on-study EORTC QLQ-C30 assessment while on treatment. This analysis set was the primary analysis for evaluating PRO endpoints.

The analysis populations in these studies are summarized in table 4. An overview of planned statistical analyses used to assess the efficacy of sunitinib in Studies A6181111 and RTKC-0511-015 is presented in table 5.

**Table 4. Summary of Analysis Populations**

| | Phase 3 Study A6181111 | | Phase 2 Study RTKC-0511-015 |
|---|---|---|---|
| **Study Population** | **Sunitinib (N = 86)** | **Placebo (N = 85)** | **Pancreatic NET (N = 66)** |
| ITT (n [%]) | 86 (100) | 85 (100) | 66 (100) |
| AT (n [%]) | 83 (96.5) | 82 (96.5) | 66 (100) |

Source: CSR A6181111, Table 13.1.1; CSR RTKC-0511-015, Table 8.
ITT = intent-to-treat; AT = as treated; NET = neuroendocrine tumours.

**Table 5. Summary of Efficacy Analyses for Studies A6181111 and RTKC-0511-015**

| Endpoint | Statistical Method | Interpretation |
|---|---|---|
| PFS | K-M method (median and 95% CI) | A6181111: Primary analysis<br>RTKC-0511-015: None |
| ORR | Binary endpoint<br>(n and exact 95% CI) | A6181111: Secondary analysis<br>RTKC-0511-015: Primary analysis |
| DR | K-M method (median and 95% CI)<br>Arithmetic median and range also provided in A6181111 | A6181111: Secondary analysis<br>RTKC-0511-015: Secondary analysis |
| TTR | K-M method (median and 95% CI)<br>Arithmetic median and range also provided in A6181111 | A6181111: Secondary analysis<br>RTKC-0511-015: Secondary analysis |
| OS | K-M method (median and 95% CI) | A6181111: Secondary analysis<br>RTKC-0511-015: Secondary analysis |
| TTP | K-M method (median and 95% CI) | A6181111: None<br>RTKC-0511-015: Secondary analysis |
| PRO | Repeated measures mixed-effects models | A6181111: PRO assessment<br>RTKC-0511-015: None presented |

Source: CSR A6181111, Appendix A10.1; CSR RTKC-0511-015, Appendix A10.1
1PFS = progression-free survival, ORR = objective response rate, DR = duration of response, TTR = time to tumour response, OS = overall survival, TTP = time to tumour progression, PRO = patient-reported outcome.
K-M = Kaplan-Meier, CI = confidence interval, n = number of subjects.

The time to event endpoints were compared between the 2 treatment arms with a 2-sided unstratified log-rank test at the $\alpha = 0.05$ significance level. The rates of the binary endpoint, ORR, for the 2 treatment arms were compared with a significance level of 0.05 using a 2-sided Pearson $\chi 2$ test and Cochran-Mantel-Haenszel (CMH) test.

Two sensitivity analyses for PFS were planned and performed to test the robustness of the primary PFS analysis:

1) One sensitivity analysis corrected for potential bias in tumour assessment schedules by assigning dates for events only to scheduled visit dates.

2) The second sensitivity analysis expanded the definition of PFS events to include symptomatic deterioration, administration of a new anti-tumour treatment, and PD after a significant gap in disease assessments, in addition to the PFS events defined in the primary analysis. The unstratified log-rank test (two-sided, $\alpha = 0.05$) was used to evaluate the primary efficacy endpoint, PFS, in the ITT population in these analyses.

Disease assessments were scheduled at the fixed time points indicated in the protocol. Imaging studies at screening included at least a CT or MRI scan of the chest, abdomen, and pelvis. Subsequent imaging studies were required only for areas of known or suspected tumours during Week 5, Week 9, and every 8 weeks thereafter and were required only for areas of known or suspected tumours. Additional disease assessments were performed if progressive disease (PD) was suspected. Clinical assessment of disease coincided with the imaging studies. Brain CT or MRI and bone scan were performed at screening and repeated if metastases were present or suspected. The determination of tumour response and progression was made by the investigator and was based on objective tumour assessments made according to RECIST. A minor modification was adopted to accommodate standard practice in use of spiral CT scanning (i.e., reconstruction interval up to 8 mm). The same imaging modality and technique were used throughout the study to measure disease.

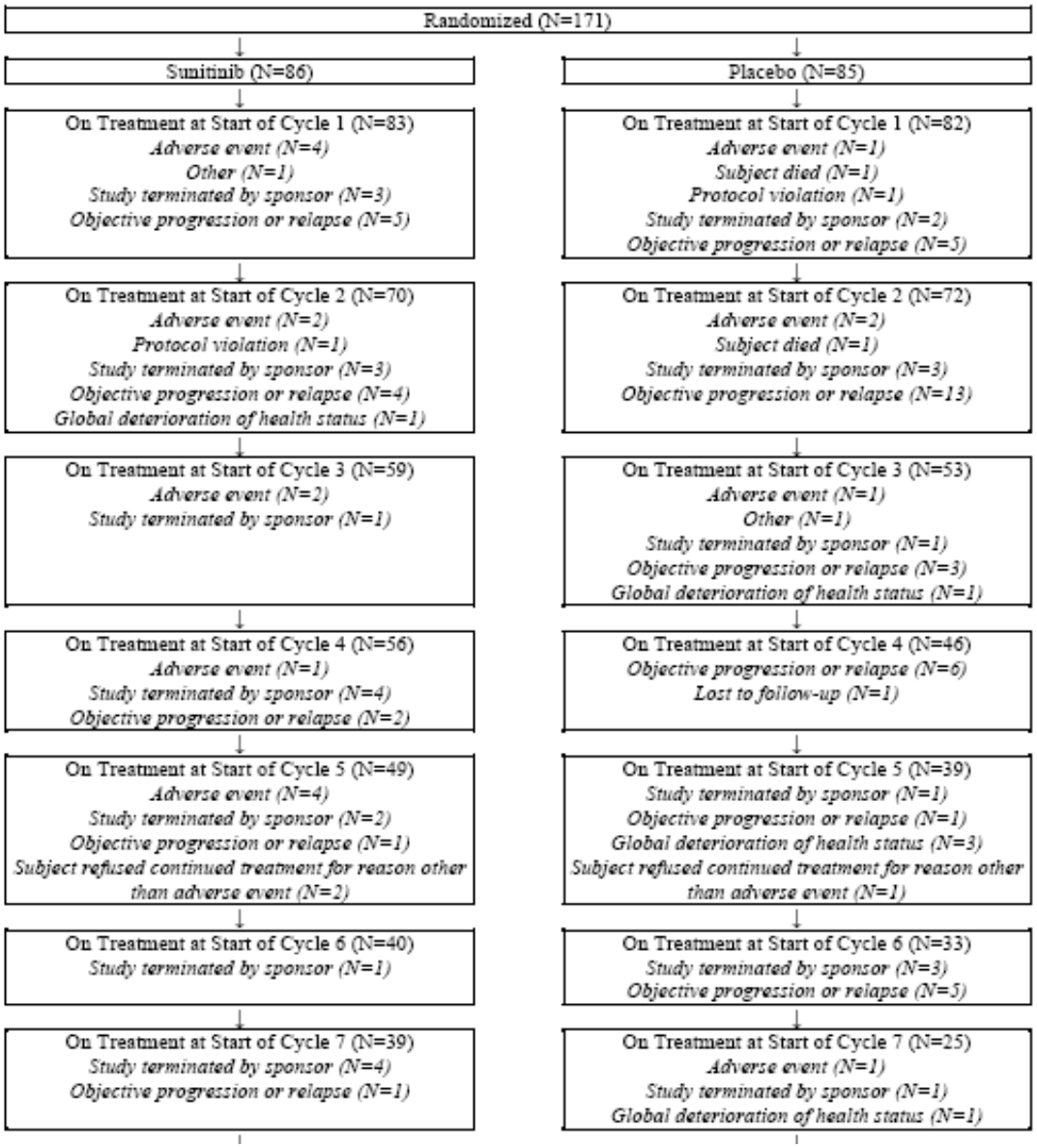
An independent DMC monitored the safety of the subjects on a periodic basis.

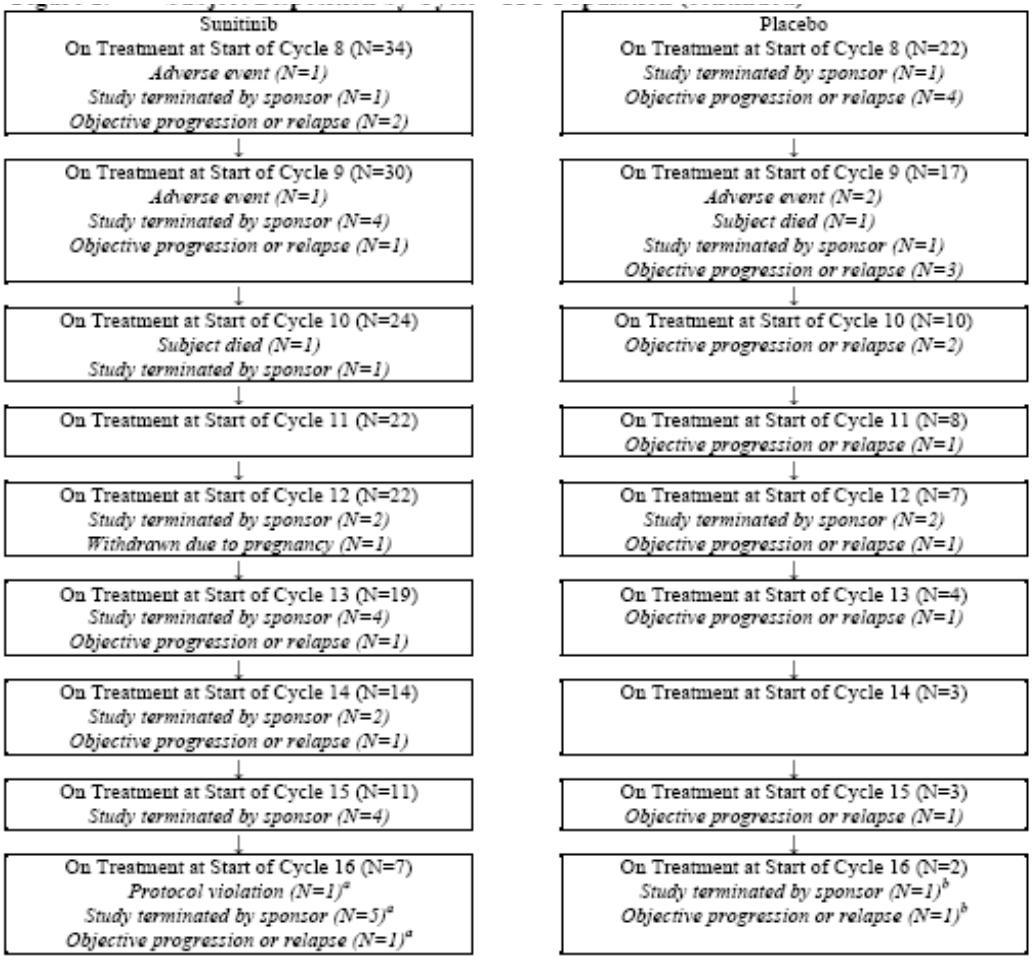
- **Results**

*Participant flow*

The ITT population included 171 subjects, 86 subjects randomized to sunitinib and 85 subjects randomized to placebo. Three subjects in each treatment arm did not receive study treatment (5 due to the study termination and 1 due to ineligibility).

**Figure 1. Subject Disposition by Cycle – ITT Population**






Source: Table 13.1.4
N= number of subjects randomized
[a] During Cycles 16-20
[b] During Cycles 16-22

*Study population and disposition*

**Table 6. Summary of Subject Disposition (Intent-to-Treat Population)**

| | Phase 3 Study A6181111 | | Phase 2 Study RTKC-0511-015 |
|---|---|---|---|
| Reason for Study Discontinuation | Sunitinib (N = 86) | Placebo (N = 85) | Pancreatic NET (N = 66) |
| | n (%) | | |
| Randomized but not treated | 3 (3.5) | 3 (3.5) | NA |
| **Adverse event** | 15 (17.4) | 7 (8.2) | 7 (10.6) |
| Global deterioration of health status | 1 (1.2) | 5 (5.9) | NA |
| Lack of efficacy (disease progression) | 19 (22.1) | 47 (55.3) | 28 (42.4) |
| Study terminated by sponsor | 41 (47.7) | 16 (18.8) | NA |
| Protocol violation | 2 (2.3) | 1 (1.2) | 1 (1.5) |
| Consent withdrawn | 2 (2.3) | 1 (1.2) | 9 (13.6) |
| Subject died | 1 (1.2) | 3 (3.5) | 0 |
| Withdrawn due to pregnancy | 1 (1.2) | 0 | NA |
| Lost to follow-up | 0 | 1 (1.2) | 0 |
| Other | 1 (1.2) | 1 (1.2) | NA |
| Completed study | NDe | NDe | 21 (31.8) d |

More subjects in the placebo arm (55.3%) discontinued from study due to disease progression than in the sunitinib arm (22.1%). Termination of the study was the reason for discontinuation for more subjects in the sunitinib arm (47.7%) than in the placebo arm (18.8%), reflecting the greater number of ongoing subjects in the sunitinib arm.

Protocol deviations that were reported in the CSR included one subject who carried a diagnosis of rectal NET and 15 subjects who did not meet other entry criteria that were unrelated to laboratory testing (eg haematology, coagulation, chemistry, TSH abnormality) or blood pressure measurements.

*Conduct of the study*

Subject enrolment began 7 June 2007. The independent DMC reviewed safety data on 3 occasions: May 2008, November 2008 and February 2009. PFS data were apparently provided at the request of the DMC as part of the safety data package. Although the study was designed with an interim analysis at 130 PFS events and a final analysis at 260 events, the DMC recommended in February 2009 that the study be closed based on their review of safety and efficacy data after 73 events had been recorded. According to the DMC: 1) the study's primary objective had been met, 2) HRs for PFS had been stable and in favour of sunitinib over 3 evaluations, 3) the conditional power analysis indicated a high likelihood that the study would be stopped at the time of the planned interim analysis, and 4) that the incidences of SAEs and death were higher among subjects in the placebo arm. Based on the DMC recommendation, the Sponsor notified all investigators in March 2009 and all subjects were offered sunitinib in open-label extension studies. The last subject visit occurred on 15 April 2009. The database was locked on 17 July 2009. The final PFS analysis was conducted based upon all PFS data occurring as of 15 April 2009 (81 events).

*GCP inspection findings*

The requested GCP-inspection was performed in 4 investigator sites. The inspection revealed several critical and major deviations of which the following are considered the most important for the assessment of this extension of indication:

For 12/42 trial subjects (5 sunitinib-, 7 placebo- treated patients) discrepancies between site and inspectors assessment of the primary efficacy criteria of the study were found. These discrepancies concerned:

- either the status of the disease (objective progression / censored)
- and/or the date of the objective progression or the date used to censored PFS data
- Some deviations from the in-/exclusion criteria are not reflected in the CSR,

One site has not strictly followed the objective RECIST criteria. Thus, some data reported to the Sponsor are not in line with the RECIST (e.g. 'Stable disease' was reported for 'Overall Investigator Objective Status' despite 'Progressive disease' for 'Investigator Assessment of Target Lesions').

The above discrepancies were not queried by the Sponsor and this indicates that no checks of the reported data for the tumour assessments - including calculation of the measurements - have been performed by the Sponsor. Thus the Quality Control by the Sponsor has been questioned.

The MAH acknowledged that "it may not be obvious in all cases how investigators applied RECIST in the determination of overall tumour assessments" and consequently performed an individual patient review, i.e. a derived tumour response assessment based upon algorithmic application of RECIST to investigators' tumour measurement for each subject. This analysis is discussed further below in the results section.

*Baseline data*

Baseline characteristics including age, gender, race, and ECOG performance status were generally comparable between the sunitinib and placebo arms. Approximately half of the subjects had tumours that were nonfunctioning; liver, pancreas, and lymph node were the most commonly involved sites of disease. Approximately 89% of subjects in each treatment arm had prior surgical treatment, and the majority of subjects (66.3% and 71.8% in the sunitinib and placebo arms, respectively) were previously treated with systemic therapies. Overall, the baseline disease characteristics and prior treatment history of the subjects were similar between the sunitinib arm and the placebo arm with the exception of time from diagnosis to study entry, which was 2.4 and 3.2 years in the sunitinib arm and placebo arm, respectively (table 7).

**Table 7. Summary of Baseline Characteristics in Study A6181111 (ITT Population)**

| **Variable** | **Sunitinib (N = 86)** | **Placebo (N = 85)** |
|---|---|---|
| Median Age [years] (Range) | 56 (25 – 84) | 57 (26 – 78) |
| Sex (n [%]) | | |
| Male | 42 (48.8) | 40 (47.1) |
| Female | 44 (51.2) | 45 (52.9) |
| Nonfunctioning Tumour [n (%)] | 42 (48.8) | 44 (51.8) |
| Functioning Tumour [n (%)] | 25 (29.1) | 21 (24.7) |
| Gastrinoma | 9 (10.5) | 10 (11.8) |
| Glucagonoma | 3 (3.5) | 2 (2.4) |
| Insulinoma | 2 (2.3) | 2 (2.4) |
| VIPoma | 0 | 2 (2.4) |
| Other | 11 (12.8) | 5 (5.9) |
| Unknown/missing [n (%)] | 19 (22.1) | 20 (23.5) |
| Median duration since diagnosis [years] (Range ) | 2.4 (0.1 – 25.6) | 3.2 (0.1 – 21.3) |
| Involved disease sites [n (%)] | | |
| Pancreas | 35 (40.7) | 31 (36.5) |
| Lymph node | 29 (33.7) | 41 (48.2) |
| Liver | 79 (91.9) | 78 (91.8) |
| Lung | 9 (10.5) | 15 (17.6) |
| Peritoneum | 3 (3.5) | 7 (8.2) |
| Stomach | 0 | 1 (1.2) |
| Other | 18 (20.9) | 21 (24.7) |
| Presence of distant metastatic sites [n (%)] | 82 (95.3) | 80 (94.1) |
| Prior surgery [n (%)] | 76 (88.4) | 77 (90.6) |
| Previous radiation therapy [n (%)] | 9 (10.5) | 12 (14.1) |
| Prior systemic therapies [n (%)] | 57 (66.3) | 61 (71.8) |
| Prior liver directed therapy [n (%)] | | |
| Chemoembolization | 7 (8.1) | 14 (16.5) |
| Radiofrequency ablation | 3 (3.5) | 6 (7.1) |
| Alcoholization procedure | 1 (1.2) | 2 (2.4) |
| ECOG performance status (n [%]) | | |
| 0 | 53 (61.6) | 41 (48.2) |
| 1 | 33 (38.4) | 43 (50.6) |
| 2 | 0 | 1 (1.2) |

N = total number of subjects included in the treatment population; and n = number of subjects

*Outcomes and estimation*

Primary Efficacy Endpoint - Progression-free Survival (PFS)

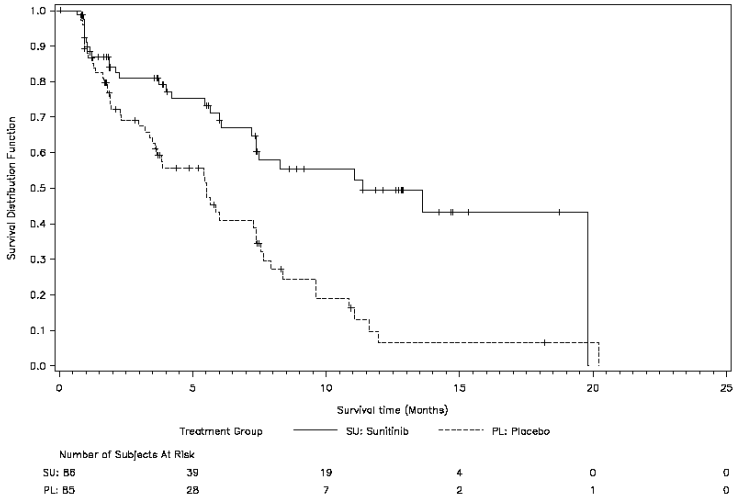
In the final analysis of PFS (based on a total of 81 events) median PFS was 11.4 and 5.5 months, respectively, in the sunitinib and placebo arms (hazard ratio [HR] 0.418, 95% confidence interval [CI] 0.263, 0.662, p=0.000118). The probability of a subject being event-free at Month 6 was 71.3% and

43.2% for sunitinib and placebo arms, respectively (table 8). A pre-specified sensitivity analysis (Analysis 1) of PFS by using uniform timing of assessments (assigning dates of disease progression according to the intended schedule of dates of assessments rather than the actual dates of the radiographic scan) has been performed (HR=0.407, 95% CI 0.257, 0.646, p=0.00070) and showed consistency compared to the primary analysis. Furthermore, a second sensitivity analysis was conducted in which subjects who discontinued treatment due to symptomatic deterioration, started anticancer treatment not specified in the protocol, or had disease progression after missing 2 or more tumour assessments were counted as PFS events. This analysis resulted in a similar hazard ratio of 0.393 (0.250, 0.620) and a p-value of 0.000027. Both sensitivity analyses confirmed the robustness of the results.

**Table 8 Analyses of Progression-Free Survival in Study A6181111 – ITT Population**

| | **Primary PFS Analysis** | | **Sensitivity Analysis of PFS** | | | |
|---|---|---|---|---|---|---|
| | | | **Analysis 1** | | **Analysis 2** | |
| | **Sunitinib (N=86)** | **Placebo (N=85)** | **Sunitinib (N=86)** | **Placebo (N=85)** | **Sunitinib (N=86)** | **Placebo (N=85)** |
| Number with Event | 30 | 51 | 30 | 51 | 30 | 55 |
| Type of Event | | | | | | |
| Objective tumour progression | 27 | 48 | 27 | 48 | 27 | 48 |
| Death without objective PD | 3 | 3 | 3 | 3 | 3 | 2 |
| Symptomatic deterioration | --- | --- | --- | --- | 0 | 5 |
| Number censored | 56 | 34 | 56 | 34 | 56 | 30 |
| Probability of being event-free at Month 6[a] (95% CI[b]) | 71.3% (60.0, 82.5) | 43.2% (30.3, 56.1) | 67.5% (55.7, 79.4) | 41.5% (28.6, 54.4) | 71.3% (60.0, 82.5) | 39.8% (27.5, 52.2) |
| Kaplan-Meier estimates of Median PFS (months) (95% CI)[c] | 11.4 (7.4, 19.8) | 5.5 (3.6, 7.4) | 11.1 (7.4, --) | 5.5 (3.6, 7.4) | 11.4 (7.4, 19.8) | 5.4 (3.6, 7.3) |
| Sunitinib vs. Placebo | | | | | | |
| Hazard ratio[d] (95% CI) | 0.418 (0.263, 0.662) | | 0.407 (0.257, 0.646) | | 0.393 (0.250, 0.620) | |
| Log-Rank test statistic[e] | 3.8506 | | 3.9751 | | 4.1945 | |
| p-value[e] | 0.000118 | | 0.000070 | | 0.000027 | |

**Figure 2. Kaplan-Meier Curve of Progression-Free Survival**

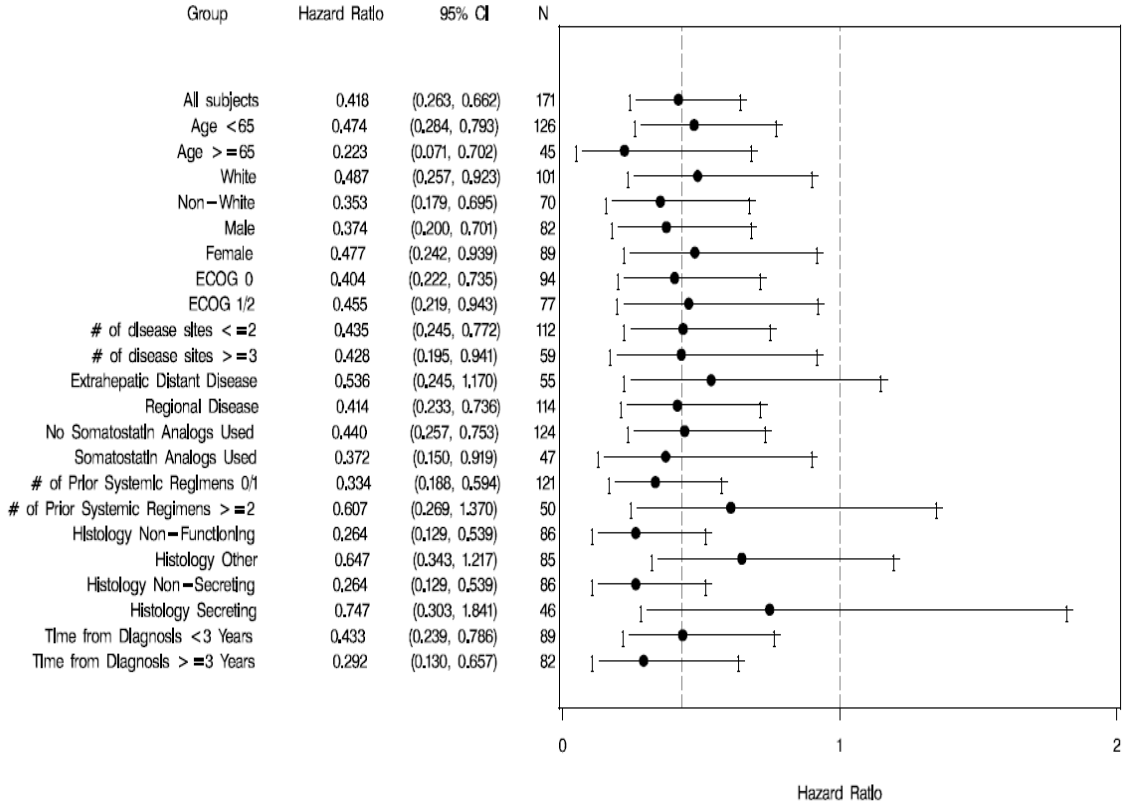


The handling of data looks of the efficacy data by the DMC was not pre-specified. An attempt to calculate the nominal critical value (Z scale) to establish statistical significance for the final analysis was calculated using the Lan-DeMets spending function both excluding and including 3 data looks by the DMC during their safety reviews. The nominal critical Z value for the final analysis with 81 events without adjusting for the 3 data looks was 3.8494; however, adjusting for 3 data looks resulted in a nominal critical Z value of 3.8809. The observed test statistic in the final analysis was 3.8506. Under the more conservative approach of adjusting for 3 data looks, the test statistic did not cross the efficacy boundary. As such, the observed difference in PFS is not statistically significantly different between treatment groups.

PFS results in subgroups

The influence of baseline characteristics on the treatment effect of PFS was analyzed using a Cox proportional hazards model including baseline factors, controlling for each factor one at a time in the ITT population; characteristics evaluated included age, race, gender, baseline ECOG performance score, number of disease sites (i.e., organ sites), disease extent (extrahepatic distant disease vs. regional disease including liver), use of a somatostatin analog, number of prior systemic regimens, histology, and time from diagnosis (Figure 2). The results showed the hazard ratio for the overall treatment effect [0.418 (95% CI: 0.263, 0.662)] was similar when controlling for each individual baseline factor.

**Figure 3. Results of Cox Proportional Hazards Analysis of Progression-Free Survival on Study A6181111 – ITT Population**




For sunitinib vs. placebo, assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favour of sunitinib arm; a hazard ratio greater than 1 indicates a reduction in hazard rate in favour of placebo.

The influence of baseline characteristic, previous therapies and time from diagnosis on the treatment effect of PFS was analysed using a Cox proportional hazard model. All the baseline factors were entered into multivariate models and only factors with p-values <0.05 following backward selection

were retained in the final model. The final model for PFS using Cox proportional hazards analysis in the ITT population revealed that treatment (sunitinib vs. placebo) and time from diagnosis (≥3 vs. <3 years) were the only factors retained, and adjusting for differences in time from diagnosis between the two treatment arms resulted in a HR for the treatment effect of 0.374 (95% CI: 0.234, 0.599).

Overall, the treatment effect in these subgroups was consistent with the result in the primary analysis regardless of demographic features, performance status, and baseline characteristics, including histology, disease burden, number and type of prior treatments.

The MAH has also performed a number of sensitivity analyses in order to address concerns due to the 1) lack of independent assessment of efficacy, 2) early stopping of the trial and 3) high censoring rate. The sensitivity analyses comprised amongst others evaluations of the effect of timing of tumour assessments, censoring for a composite of specific reasons that might result from undocumented disease progression (symptomatic deterioration, starting other anticancer therapy, missing tumour assessments at 2 or more consecutive time points) as well as censoring of additional subsets of subjects. Other analyses explored the effect of somastatin analog use (data not shown) and prior systemic therapies. Details of specific sensitivity analyses are presented below.

- Prior systemic therapies

The MAH analysed the potential influence of prior systemic therapy on the treatment effect, i.e. between subjects who were treatment-naïve and those who had received prior systemic therapy. As shown in the table below, a similar treatment effect in these two sub-groups was observed.

**Table 9**

| | **Hazard Ratio (95% CI) for PFS** |
|---|---|
| **Treatment Effect for Subjects with No Prior Treatment** | 0.365 (0.156, 0.857) |
| **Treatment Effect for Subjects with Prior Treatment** | 0.456 (0.264, 0.787) |

Source data Figure 14.6.2

- PFS result per Blinded Independent Central Review (BICR)

The MAH submitted a preliminary independent third-party radiological review for PFS, blinded for the clinical data, of 84 available radiological images. Central review of the first 84 subjects with submitted images for all study time points, which had passed the third party core lab image quality assessment as of the data cut-off date of 15 February 2010, was conducted. Further to CHMP request, the MAH has conducted a BICR of all scans received by the central imaging vendor. The set of scans reviewed by the central imaging vendor included scans from 170 subjects (99.4%) and encompassed all scans reported in the clinical database for 160 subjects (93.6%).

The results of both BICR analyses (84 subjects and 170 subjects) are shown in Table 10 and Table 11. The Kaplan Meier curve of the BICR analysis of 170 subjects is shown in Figure 4.

**Table 10 Analyses of Progression-Free Survival in Study A6181111 (ITT and subset BICR Populations)**

| | ITT Population | | BICR Population | | | |
|---|---|---|---|---|---|---|
| | Investigator-Assessed | | Investigator-Assessed | | BICR-Assessed | |
| | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=41) | Placebo (N=43) | Sunitinib (N=41) | Placebo (N=43) |
| Number with Event | 30 | 51 | 12 | 21 | 8 | 15 |
| Kaplan-Meier estimates of Median PFS (months) (95% CI)[a] | 11.4 (7.4, 19.8) | 5.5 (3.6, 7.4) | 19.8 (8.3, 19.8) | 5.8 (3.4, 11.1) | 20.6 (11.9, 20.6) | 6.2 (3.6, 14.6) |
| Sunitinib vs. Placebo Hazard ratio[b] (95% CI) p-value[c] | 0.418 (0.263, 0.662) 0.000118 | | 0.449 (0.218, 0.924) 0.024899 | | 0.289 (0.117, 0.716) 0.004183 | |

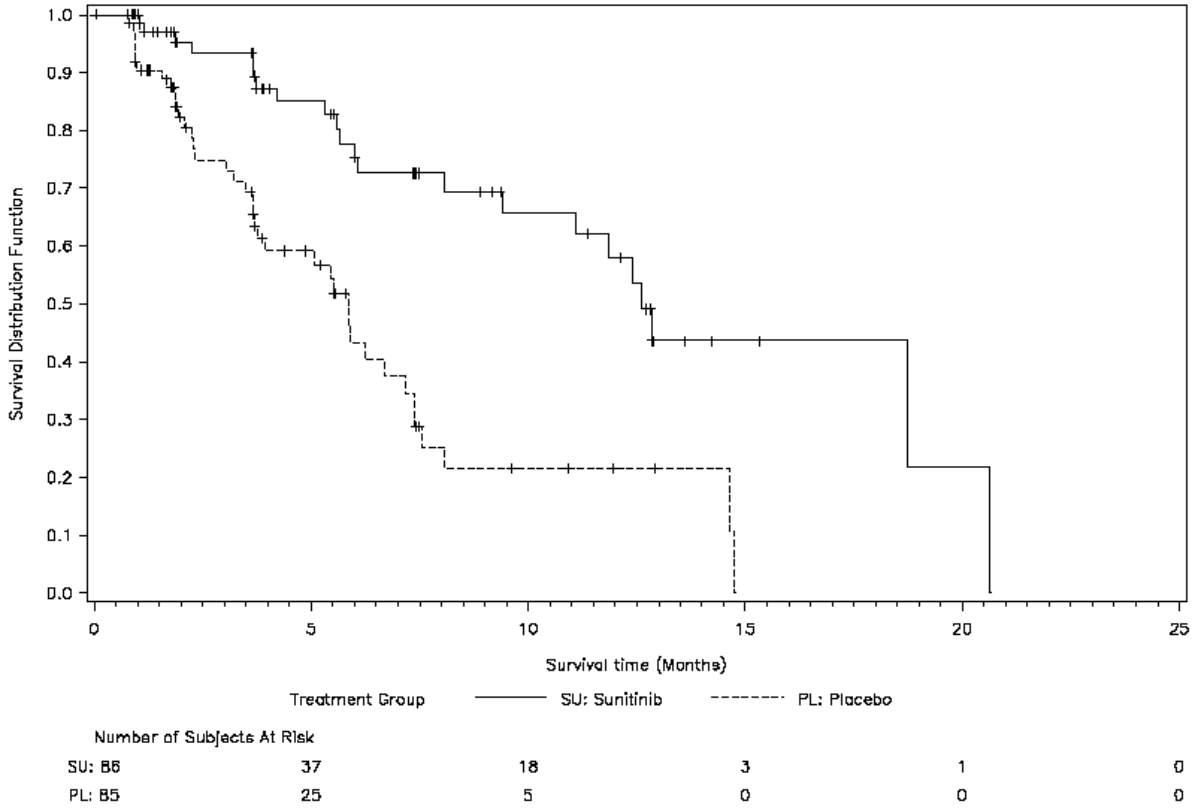
[a] Based on the Brookmeyer-Crowley method.
[b] Based on the Cox proportional hazards model.
[c] Log-rank test statistic and 2-sided p-value from the unstratified log-rank test.
N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease;
CI = confidence interval.

**Table 11 Analysis of Progression-Free Survival in Study A6181111 by BICR Assessments – Intent to Treat**

| | BICR-Assessed | |
|---|---|---|
| | Sunitinib (N=86) | Placebo (N=85) |
| Number with event | 22 | 39 |
| Objective tumour progression | 19 | 34 |
| Death without objective progression | 3 | 5 |
| Number censored | 64 | 46 |
| Kaplan-Meier estimates of Median PFS (months) (95% CI)[a] | 12.6 (11.1, 20.6) | 5.8 (3.8, 7.2) |
| Hazard ratio[b] (95% CI) p-value[c] | 0.315 (0.181, 0.546) 0.000015 | |

[a] Based on the Brookmeyer-Crowley method.
[b] Based on the Cox proportional hazards model.
[c] Log-rank test statistic and 2-sided p-value from the unstratified log-rank test.
N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease;
CI = confidence interval.

**Figure 4. Kaplan-Meier Analysis of Progression-Free Survival by BICR Assessment on an Intent-to-Treat Basis**




In addition, the MAH conducted 2 sensitivity analyses to determine the potential impact of scans unavailable for BICR review. In one sensitivity analysis, information from investigator's overall tumour assessment was imputed for missing scan data (i.e. not received by third party reviewer) in the analysis, whereas in the second sensitivity analysis, all subjects with missing scans in the placebo arm were censored while all subjects with missing scans in the sunitinib arm were treated as having an event in the PFS analysis. In both analyses there was limited impact of the missing data on the overall results. In the second, more conservative analysis, there was a HR of 0.404 (95%CI: 0.242, 0.675) with a p-value of 0.000339, and a median PFS of 5.8 months in the placebo arm and 12.4 months in the sunitinib arm.

- Derived Tumour Response assessment

An individual patient review of all imaging data by time point was performed for all subjects randomised into Study A6181111 and included review of the timing of baseline scans relative to both randomisation and on-study scans, as well as review of adherence of on-study scans at the protocol-defined time points as summarised by missing assessments. In addition, derived tumour response assessment based upon algorithmic application of RECIST to investigator tumour measurements was performed for each subject as the MAH has acknowledged that inconsistent use of RECIST had been identified during the inspection.

Method: Radiographic evidence of disease progression was established using RECIST based on an increase from the nadir Sum of the Longest Diameters (SLD) of the target lesions, the presence of new lesions, or the unequivocal progression of non-target lesions. Progressive Disease (PD) for target lesions was defined as at least a 20% increase in the SLD of target lesions, taking as reference the nadir SLD (or the baseline, if the baseline is the nadir value). PD for non-target lesions was defined as

the unequivocal progression of existing non-target lesion(s) or appearance of one or more new lesion(s).

The overall assessment of PD for each time point assessment was determined by the algorithm described in the Table 12.

**Table 12 Algorithm for Response Assessment Using Investigator Reported Target Lesion Measurements, Non-Target Lesion Assessments, and Assessments of New Lesions**

| Target Lesions | Non-Target Lesions | New Lesion | Overall Assessment |
|---|---|---|---|
| PD | Any | Any | PD |
| Any | PD | Any | PD |
| Any | Any | Yes | PD |
| Non-PD | Non-PD | No | Non-PD |
| NE | Non-PD | No | NE |

PD = Progressive disease
Non-PD = Non-Progressive disease
NE = Non Evaluable

Furthermore the MAH detailed additional conventions applied in this sensitivity analysis that are not reported in this summary.

Result: Comparison of investigator overall assessments and derived assessments demonstrated that the overall assessments of individual subjects were the same in terms of both event status (yes or no) and timing (within 10 days of the event status) for 140 of the 171 subjects (narratives provided in Appendix 1). Additionally, there were 31 subjects where the investigators' overall assessment differed from the derived response assessment with regards to either the disease status (18 subjects) or the timing of the status (13 subjects). Narratives for those subjects who were censored for reasons other than study termination were presented along with the reasons for study termination.

A sensitivity analysis using only the derived response assessment was performed for the PFS endpoint to determine whether the alternative methodology affected the observed treatment effect. As in the primary analysis, PFS was defined as the time from the date of randomization to the date of the first objective progression of disease (PD) or death on study due to any reason, whichever occurs first. The same Kaplan-Meier methodology and censoring rules were used in both the primary PFS analysis and the analysis based on derived tumour assessments.

PFS results for this sensitivity analysis are presented in Table 16; the Kaplan-Meier plot of PFS for this sensitivity analysis is shown in Figure 5 below.

**Table 13 Comparison of the results of PFS using investigator's overall tumour assessments with tumour derived assessments**

| | ITT Population | | | |
|---|---|---|---|---|
| | Investigator's Overall Tumour Assessments | | Derived Tumour Assessments | |
| | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) |
| Number with event | 30 | 51 | 30 | 49 |
| Number censored | 56 | 34 | 56 | 36 |
| Kaplan-Meier estimates of median PFS (months) (95% CI)[a] | 11.4 (7.4, 19.8) | 5.5 (3.6, 7.4) | 12.6 (7.4, 16.9) | 5.4 (3.5, 6.0) |
| Hazard ratio[b] (95% CI) | 0.418 (0.263, 0.662) | | 0.401 (0.252, 0.640) | |
| p-value[c] | 0.000118 | | 0.000066 | |

Source: CSR A6181111, Tables 13.4.1; Appendix Tables 13.4.5.1

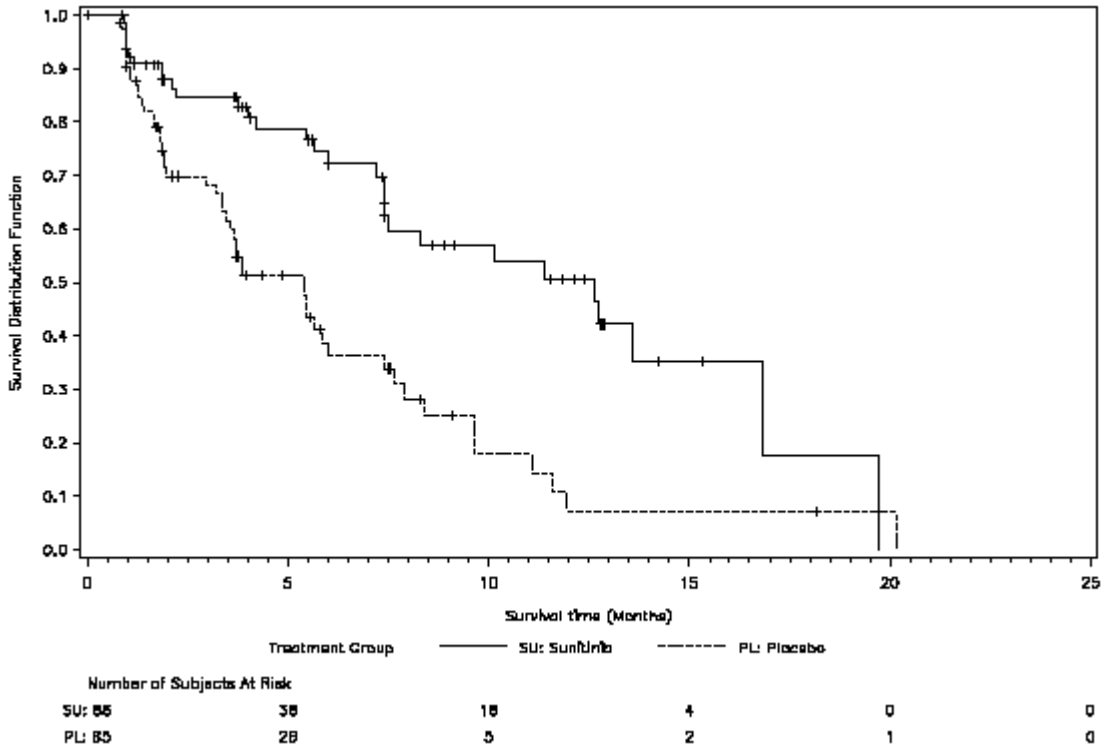
[a] Based on the Brookmeyer-Crowley method.

[b] Based on the Cox proportional hazards model.

[c] Log-rank test statistic and 2-sided p-value from the unstratified log-rank test.

N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease; CI = confidence interval.

**Figure 5. Kaplan-Meier Curves of PFS (Sensitivity Analysis) in Study A6181111 (ITT)**



- Missing scans and early censorings

Adherence to timing of baseline scans was also reviewed. Baseline scans were reported for 167 subjects, and the interval between the baseline scan and randomisation was 30 days or less for all 167 subjects with baseline scans. The median time between baseline scans and randomisation was 5 days for both the sunitinib and placebo arms, and the mean number of days between baseline scans and randomisation was 8 days in the sunitinib arm and 7 days in the placebo arm.

Similarly, adherence of on-study scans at the protocol-defined time points as summarised through missing assessments was reviewed. There were missing assessments at protocol-defined tumour imaging time points for 12 subjects in the sunitinib arm and 14 subjects in the placebo arm. Among these subjects with missing tumour imaging time point assessments, only for 3 subjects in the sunitinib arm and 4 subjects in the placebo arm did have one missing assessment immediately before a PFS event. Additionally, no patients in either arm missed 2 consecutive time point assessments; thus the censoring rules for the handling of 2 or more consecutively missing scans as described in the SAP were not applicable to any study subjects in the primary analysis.

A summary of the reasons for censoring is displayed in the Table 14 below.

**Table 14 Summary of reasons the subjects were censored in primary PFS analysis.**

| | **Sunitinib (N=86) n (%)** | **Placebo (N=85) n (%)** |
|---|---|---|
| **Number of subject censored** | 56 (65.1) | 34 (40.0) |
| **Censored for at study termination** | 38 (44.2) | 17 (20.0) |
| **Censored for reasons other than study termination** | 18 (20.9) | 17 (20.0) |
| **Adverse Events** | 12 | 4 |
| **Global Deterioration of Health** | 0 | 4 |
| **Withdrew consent** | 3 | 1 |
| **No Adequate Baseline Assessments** | 0 | 2 |
| **Other*** | 3 | 6 |

*In the sunitinib arm, one subject (10671003) was withdrawn due to a diagnosis of Rectal NET; one subject (10421002) was withdrawn due to noncompliance after 1.3 years of study drug treatment; and one subject (10031002) was withdrawn due to pregnancy. In the placebo arm, one subject (10231003) was lost to follow up; one subject (10111002) was withdrawn after a dosing error; one subject (10411010) was withdrawn after the site noted the subject did not meet the baseline serum albumin criterion; two subjects (10311006, 10401001) who died after missing the first scheduled tumour assessment were censored on day 1 because of lack of on-study assessments (rendering the time of progression unknown); and one subject (10411007) was withdrawn due to investigator's decision.

The pre-specified sensitivity analyses for PFS (see analysis 1 and 2 above) were repeated using assessments derived from tumour measurement data. The results are summarized in Table 15. Similar to the results based upon investigator overall tumour assessments, these sensitivity analyses evaluating the potential impact of differences in intended and actual timing of tumour assessments and effects of certain censored events in the primary analysis did not alter the interpretation of a clinically meaningful treatment effect for sunitinib when applied to assessments from derived tumour data.

**Table 15 – Sensitivity Analysis for PFS based on tumour derived assessments**

| | PFS Analysis Based on Derived Assessment | | Sensitivity Analysis for PFS Based on Derived Assessment | | | |
|---|---|---|---|---|---|---|
| | | | Analysis 1 | | Analysis 2 | |
| | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) |
| Number with Event | 30 | 49 | 30 | 49 | 30 | 52 |
| Number Censored | 56 | 36 | 56 | 36 | 56 | 33 |
| Kaplan-Meier Estimate of Median PFS (months) (95% CI) | 12.6 (7.4, 16.9) | 5.4 (3.5, 6.0) | 11.0 (7.4, 16.6) | 5.4 (3.6, 5.8) | 12.6 (7.4, 16.9) | 4.9 (3.5, 5.8) |
| Hazard Ratio[e] (95% CI) | 0.401 (0.252, 0.640) | | 0.401 (0.252, 0.639) | | 0.380 (0.240, 0.602) | |
| Log-Rank Test Statistic | 3.9890 | | 4.0211 | | 4.2970 | |
| p-value | 0.000066 | | 0.000058 | | 0.000017 | |

Source: Tables 13.4.5.1, 13.4.5.2.3, and 13.4.5.2.4
ITT = intent-to-treat; N = number of subjects randomized; PFS = progression-free survival;
PD = progressive disease; CI = confidence interval

- Censoring of additional subsets of subjects

The analyses regarding censoring of additional subsets of subjects included 1) an analysis where all subjects who were censored in the primary analysis were treated in the sensitivity analysis as having an event at the next scheduled visit, 2) an analysis where subjects who were censored in the primary analysis for reasons other than study termination were treated in the sensitivity analysis as having an event at the next scheduled visit, and 3) an analysis where subjects censored because of discontinuation due to Adverse Events or Global Deterioration of Health in the primary analysis were treated in the sensitivity analysis as having an event at the next scheduled visit.

These three sensitivity analyses based upon investigators' overall tumour assessments are summarised in the Table 16 below.

**Table 16 Sensitivity analyses for PFS based on investigator's overall assessments**

| | Primary PFS Analysis | | Sensitivity Analysis for PFS Based on Investigator's Overall Assessments | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | All Censored Subjects Counted as Events | | All Subjects Censored for Reasons Other Than Study Termination Counted as Events | | All Subjects Censored Due to AE or Global Deterioration as Counted as Events | |
| | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) |
| **Number with Event** | 30 | 51 | 86 | 85 | 48 | 68 | 42 | 59 |
| **Number Censored** | 56 | 34 | 0 | 0 | 38 | 17 | 44 | 26 |
| **Median PFS (months) (95% CI)** | 11.4 (7.4, 19.8) | 5.5 (3.6, 7.4) | 5.6 (4.0, 7.2) | 3.7 (1.9, 3.8) | 7.2 (5.6, 11.1) | 3.8 (3.5, 5.6) | 7.5 (5.6, 13.6) | 5.5 (3.6, 5.7) |
| **Hazard Ratio (95% CI)** | 0.418 (0.263, 0.662) | | 0.656 (0.482, 0.892) | | 0.517 (0.355, 0.754) | | 0.508 (0.339, 0.760) | |
| **p-value (log-rank test)** | 0.000118 | | 0.011236 | | 0.000412 | | 0.000694 | |

Source: Table 13.4.1, 13.4.15, 13.4.16, 13.4.17

The three additional sensitivity analyses described above were also repeated using assessments derived from algorithmic application of RECIST to investigator tumour measurement data. Results of these sensitivity analyses based upon derived tumour assessments were consistent with those based upon the investigators' overall tumour assessments and are summarised in the Table 17 below.

**Table 17 Sensitivity analyses for PFS based on <u>derived tumour assessments</u>**

| | **PFS Analysis based on derived tumour assessments** | | **Sensitivity Analysis for PFS Based on Derived Tumour Assessments** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **All Censored Subjects Counted as events** | | **All Subjects Censored for Reasons Other Than Study Termination Counted as Events** | | **All Subjects Censored Due to AE or Global Deterioration as Counted as Events** | |
| | **Sunitinib (N=86)** | **Placebo (N=85)** | **Sunitinib (N=86)** | **Placebo (N=85)** | **Sunitinib (N=86)** | **Placebo (N=85)** | **Sunitinib (N=86)** | **Placebo (N=85)** |
| **Number with Event** | 30 | 49 | 86 | 85 | 51 | 69 | 42 | 56 |
| **Number Censored** | 56 | 36 | 0 | 0 | 35 | 16 | 44 | 29 |
| **Median PFS (months) (95% CI)** | 12.6 (7.4, 16.9) | 5.4 (3.5, 6.0) | 5.6 (4.0, 7.2) | 3.7 (1.9, 3.8) | 7.4 (5.6, 9.2) | 3.7 (3.4, 5.5) | 8.3 (6.0, 12.6) | 3.9 (3.5, 5.7) |
| **Hazard Ratio (95% CI)** | 0.401 (0.252, 0.640) | | 0.642 (0.471, 0.874) | | 0.507 (0.350, 0.733) | | 0.493 (0.328, 0.742) | |
| **p-value (log-rank test)** | 0.000066 | | 0.003377 | | 0.000193 | | 0.000478 | |

Source: Table 13.4.5.1, 13.4.18, 13.4.19, 13.4.20

Secondary Efficacy Endpoints

- <u>Objective Response Rate (ORR)</u>

**Table 18 Summary of Objective Response (ITT Population)**

| | **Phase 3 Study A6181111** | | **Phase 2 Study RTKC-0511-015** |
|---|---|---|---|
| **Efficacy Parameter** | **Sunitinib (N = 86)** | **Placebo (N = 85)** | **Pancreatic NET (N = 66)** |
| Subjects with adequate baseline assessment[a] [n (%)] | 85 (98.8)[a] | 83 (97.6)[a] | 66 (100) |
| Subjects with measurable disease at baseline [n (%)] | 84 (97.7)[b] | 82 (96.5)[b] | 66 (100) |
| Best objective response [n (%)] [c] | | | |
| Complete response | 2 (2.3) | 0 | 0 (0) |
| Partial response | 6 (7.0) | 0 | 11 (16.7) |
| Stable disease | 54 (62.8) | 51 (60.0) | 45 (68.2) |
| Progressive disease | 12 (14.0) | 23 (27.1) | 5 (7.6) |
| Indeterminate/not evaluable | 12 (14.0) | 11 (12.9) | 3 (4.5) |
| Missing | | | 2 (3.0) |
| Objective response rate [% (95% exact CI)][c] | 9.3 (4.1, 17.5) | 0 (0, 4.2) | 16.7 (8.6 – 27.9) |
| Difference from placebo (95% CI)[d] | 9.3 (3.2, 15.4) | | |
| p-value[e] | 0.0066 | | |
| SD >90 days | 46 (53.5) | 44 (51.8) | |
| SD >184 days | 30 (34.9) | 21 (24.7) | 37 (56.1) |

Objective responses were reported for 8 out of 86 subjects randomized to the Sunitinib arm (ORR 9.3%) compared with no responses documented in the placebo arm (p=0.0066).

Among the 8 subjects treated with sunitinib who had an objective tumour response, only 1 subject experienced disease progression prior to termination of the study. The remaining 7 subjects continued with an ongoing tumour response 0.9+ to 15.0+ months following initial documentation of objective response until the study was terminated. With only 1 progression documented following objective response, median DR could not be estimated in this study, although the median DR exceeded 8 months based upon the durations at study completion.

- Overall Survival (OS)

The initially submitted documentation comprised a data cut-off date of 15 April 2009. During assessment up-dated long-term OS data were submitted, with cut-off date of 01 December 2009.

Information on survival status was obtained from Studies A6181111, A6181114, and A6181078 as specified in the A6181111 protocol. Subjects lacking survival data beyond randomization had their OS censored at the date of randomization.

Subsequent to the 30 deaths initially reported (9 deaths in the Sunitinib arm compared to 21 deaths in the placebo arm; the OS HR 0.409 [95% CI: 0.187, 0.894]), there were 21 additional deaths reported among the subjects who either withdrew from Study A6181111 or enrolled in one of the two open-label sunitinib extension studies during the follow-up period from 16 April 2009 through 01 December 2009. In total, 51 deaths have been reported among the 171 subjects randomized in Study A6181111 as of 01 December 2009, with fewer deaths in the sunitinib arm (21 [24.4%]) than in the placebo arm (30 [35.3%]).

Substantial percentages of subjects on the sunitinib and placebo arms (70.9% vs. 58.8%, respectively) were censored in the OS analyses, as they were still in follow-up as of the data cut-off date, and in this analysis, the median OS was not reached in either treatment arm. In a follow-up, unplanned survival analysis, the observed hazard ratio for death was 0.594 (95% CI: 0.340, 1.038; p=0.0644) in favour of the sunitinib arm. The primary cause of death was disease under study in both treatment arms. Overall survival using Kaplan-Meier methods is presented in Figure 6.

The updated probability of survival at 6 months was 91.6% (95% CI: 85.7%, 97.6%) for subjects in the sunitinib arm and 84.0% (95% CI: 76.0%, 92.0%) for subjects in the placebo arm.

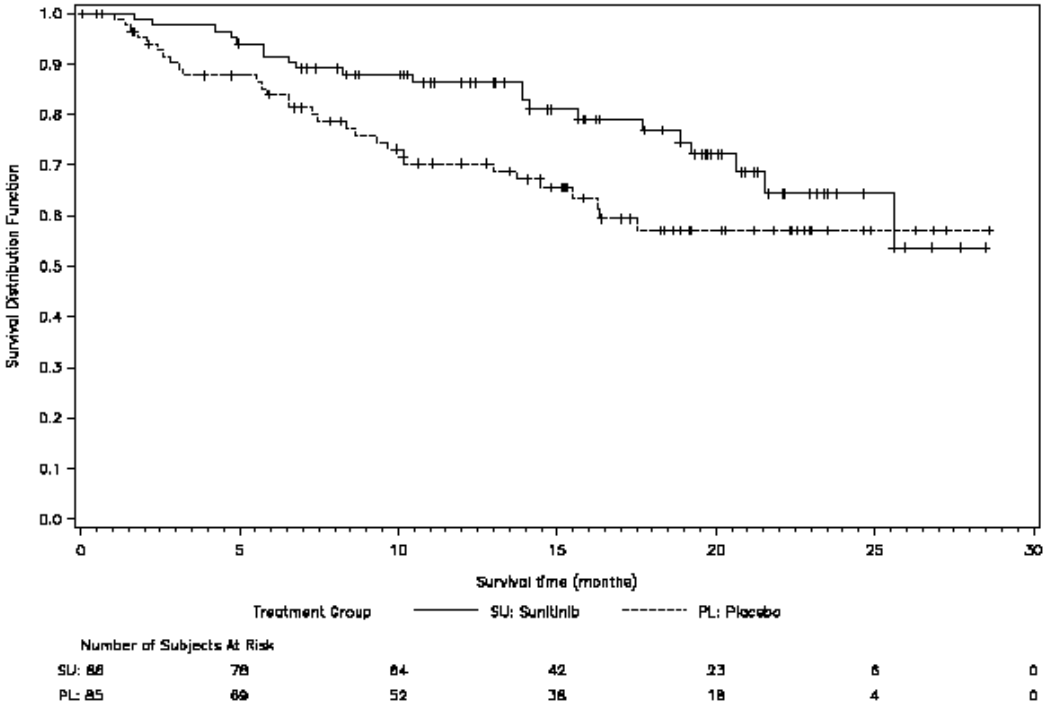
A significant number of placebo-treated patients (69%) crossed-over to receive treatment with sunitinib which has most likely confounded the results of the OS analysis, particularly in the updated analysis. This is a reasonable explanation for the narrowing of the OS K-M curves in the later updated OS analysis.

**Table 19 Summary of Overall Survival as of 01 DEC 2009 - Intent-to-Treat Population**

| | Sunitinib N = 86 | Placebo N = 85 |
|---|---|---|
| Number of deaths [n (%)] | 21 (24.4) | 30 (35.3) |
| Cause of death [n (%)] | | |
| Disease under study | 18 (20.9) | 25 (29.4) |
| Study treatment toxicity | 0 | 0 |
| Unknown | 0 | 0 |
| Other | 3 (3.5) | 5 (5.9) |
| Subjects censored [n (%)] | 65 (75.6) | 55 (64.7) |
| Reason for censorship [n (%)] | | |
| In follow-up at data cutoff | 61 (70.9) | 50 (58.8) |
| Subject withdrew consent for additional follow-up | 3 (3.5) | 2 (2.4) |
| Lost to follow-up | 1 (1.2) | 3 (3.5) |
| Survival probability at 6 months* (95% CI)[†] | 91.6 (85.7, 97.6) | 84.0 (76.0, 92.0) |
| Kaplan-Meier estimates of time to event (months) | | |
| Quartiles (95% CI)[‡] | 18.9 (13.9, -) | 9.3 (6.5, 15.5) |
| 25% | - (21.5, -) | - (16.3, -) |
| 50% | - | - |
| 75% | | |
| Hazard ratio (sunitinib vs. placebo)[§] (95% CI) | 0.594 (0.340, 1.038) | |
| p-value[#] | 0.0644 | |

All subjects who were originally randomized in Study A6181111 were included and kept under their original randomized treatment arm.
* Estimated from the Kaplan-Meier curve.
[†] Calculated from the product limit method.
[‡] Based on the Brookmeyer and Crowley method.
[§] Based on the Cox proportional hazards model.
[#] 2-sided p-value from the unstratified log-rank test.
CI = confidence interval.
Source: Update on Overall Survival in Sunitinib Study A6181111, Table 1

**Figure 6. Kaplan-Meier Curves of Overall Survival as of 01 DEC 2009 - Intent-to-Treat Population**




Source: Update on Overall Survival in Sunitinib Study A6181111, Figure 1

- Quality of Life (QoL)

Based on the responses to the EORTC QLQ-C30 questionnaire, health-related quality of life mean scores were estimated through the 10 first treatment cycles. Thereafter, only few patients remained in the study (<10 patients in each treatment arm). The overview of the number of subjects with valid QoL measurements throughout the treatment cycles was presented, however the interpretation of the results is limited by the scarce number of patients included.

The rate for all questions completed at baseline was 145 of 171 patients or 84.8% (74 of 86 patients [86.0%] for sunitinib, and 71 of 85 patients [83.5%] for placebo). At cycle 10 the completion rate for all questions answered was 22 of 25 patients (88%) for sunitinib and 10 of 12 (83.3%) for placebo. A similar high completion rate was seen through all 10 cycles why the results of this QoL analysis are considered representative of the study population but hampered by the relatively limited number of patients included.

In a repeated measures mixed effects model the use of sunitinib did not have any clinically and statistically significant negative effects compared to placebo on: patient-reported global health-related Quality of Life (QoL); all of the functioning domains (cognitive, emotional, physical, role, or social); most symptoms measured (appetite loss, dyspnoea, fatigue, nausea and vomiting, and pain); or financial difficulties. However, subjects did experience clinically and statistically significant worsening of diarrhoea at all assessment time points in the sunitinib arm. Subjects in the sunitinib arm also had a statistically significant reduction in constipation as compared with subjects in the placebo arm at Cycles 2, 3, and 4 and a statistically significant worsening of insomnia at Cycles 2 through 7. However, these changes were not clinically significant.

With respect to concomitant medications, 1 subject on the sunitinib arm and 7 subjects on the placebo arm started treatment with a somatostatin analog during the study.

#### *1.3.2.3 Supportive studies*

Supportive Study RTKC-0511-015

Study RTKC-0511-015 was an open-label, 2-cohort, 2-stage, multi-center, Phase 2 clinical trial evaluating the activity and safety of single-agent sunitinib malate in subjects with NET.

- **Methods**

Subjects with two forms of NET, carcinoid tumour and pancreatic islet cell tumours, were enrolled into separate cohorts. Subjects were to have histologically or cytologically proven diagnosis and disease not amenable to surgery, radiation, or combined modality therapy with curative intent. Evidence of measurable disease by RECIST, ECOG performance status of 0 or 1, and adequate vital organ function were also required for eligibility. Subjects with small-cell carcinoma were excluded.

Subjects received sunitinib 50 mg once daily for 4 weeks, followed by 2 weeks off treatment (Schedule 4/2) in repeated 6-week cycles. Doses could be reduced to 37.5 mg and then to 25 mg in the event of toxicity, and doses could be increased to 62.5 mg and then to 75 mg for subjects who tolerated the study medication. The primary endpoint was objective response rate (ORR), defined as the proportion of subjects with confirmed complete or partial response according to RECIST. The secondary efficacy endpoints were TTR, DR, TTP, time to treatment failure (TTF), and OS.

Safety evaluations included adverse events; clinical laboratory assessments, MUGA scans or ECHOs, ECGs, vital signs, and ECOG performance status

In Study RTKC-0511-015, the ITT population included all subjects who enrolled in the study and received at least 1 dose of study medication.

- **Results**

Study RTKC-0511-015 included 107 subjects, of whom 66 had pancreatic NET. Median age of subjects in this cohort was 56 years (range 32-81). A majority of subjects was male (42 [63.6%]) and white (59 [89.4%]). Twenty-one (31.8%) subjects completed the study, while 45 (68.2%) subjects discontinued the study; the majority of those who discontinued (28 [42.2%]) did so due to disease progression; other reasons for study discontinuation included adverse event (7 [10.6%]), protocol violation (1 [1.5%]), and consent withdrawn (9 [13.6%]).

Enrolment into the cohort of subjects with carcinoid tumour was discontinued at the end of the first stage of the study because the enrolment criteria for expansion were not met when only 1 (2.4%) of 41 subjects in the cohort had a confirmed response.

Within the pNET cohort of subjects, 7 of 38 subjects (18%) enrolled in the first stage experienced a confirmed objective response. Enrolment was expanded to Stage 2, and a total of 66 subjects were treated: 11 (16.7%) experienced a confirmed objective response, 45 (68%) had best response of SD, and 37 (56%) maintained SD for at least 6 months. Median TTP among subjects with pancreatic NET was 7.8 months.

**Table 20 Objective Response Rate in Subjects With Pancreatic NET on Study RTKC-0511-015 (ITT Population)**

| Efficacy Parameter | Number (%) of Subjects (N = 66) |
|---|---|
| Best objective response | |
| Complete response | 0 (0) |
| Partial response | 11 (16.7) |
| Stable disease | 45 (68.2) |
| Progressive disease | 5 (7.6) |
| Not evaluable | 3 (4.5) |
| Missing* | 2 (3.0) |
| Objective response rate [95% CI] | 11(16.7) [8.6-27.9] |

n = number of subjects, and CI = confidence interval.

*Includes subjects for whom on-study scans were not available due to recent entry or early withdrawal.

Among the secondary endpoints, the median TTP was 33.4 weeks (95% CI: 28.1, 54.1). While the median OS could not be estimated due to the limited number of events, the lower 95% CI of the median was estimated at 97.0 weeks (1.9 years). There did not appear to be a meaningful change in EQ-5D results, though the FACIT-Fatigue scale findings suggested a small but reversible increase in patient-reported fatigue during treatment with sunitinib. Chromogranin A (CgA) and other tumour markers including hormonal levels were also collected for exploratory analysis in Study RTKC-0511-015. Twelve (57%) of 21 subjects with available tumour marker data (and elevation at baseline) demonstrated a tumour marker response, defined as at least a 50% reduction in one or more tumour marker levels from baseline to anytime on study. Included were 8 (44%) of 18 subjects with a CgA response.

#### *1.3.2.4 Discussion on clinical efficacy*

Based on the presented PK data (See section of Clinical Pharmacology) the proposed starting dose of sunitinib (37.5 mg once daily on a CDD schedule) has been adequately justified. The observed PK of sunitinib was similar between Schedules CDD and 4/2 in both GIST and MRCC patients.

The pivotal Study A6181111 was a randomized, double-blind, placebo-controlled, Phase 3 trial of sunitinib vs. placebo in subjects with progressive advanced/metastatic well-differentiated pancreatic islet cell tumours. However, although the pivotal study was double-blind, the well-known safety profile of sunitinib may have introduced bias in the efficacy evaluations. The MAH has argued that both patients and investigators were blinded to treatment assignments and that the likelihood of effective unblinding of investigators from AEs appeared to be low based upon the high proportion of placebo-treated subjects for whom AEs were considered treatment-related (78.0%).

Primary endpoint: Based on the pivotal Study A6181111 the final analysis of PFS (based on a total of 81 events) a median PFS of 11.4 months was observed in the sunitinib arm compared to a median PFS of 5.5 months in the placebo arm which translates into a clinically relevant doubling of PFS in sunitinib-treated patients. The HR was 0.418 and the p-value 0.000118, although formally the observed difference in PFS is not statistically significantly different between treatment groups. The robustness of the result was confirmed in a number of sensitivity analyses.

The CHMP found it problematic that the study was stopped so early and that the final PFS analysis did not account for the 3 data looks performed by the DMC. It has been documented that the hazard ratios were relatively consistent through all DMC safety reviews and similar to the result in the final analysis (20 PFS events: HR 0.408, 50 PFS events: HR 0.376, 73 PFS events: HR 0.397, 81 PFS events: HR 0.418). Although this information does not preclude that the early termination of the trial has led to an overestimation of the treatment of sunitinib, it is also acknowledged that a dramatic overestimation of the true treatment effect is unlikely.

This is also based on the fact that consistent results were observed in all subgroups analyzed, supporting the efficacy of sunitinib regardless of demographic features, performance status, and most baseline characteristics.

Similarly, although a GCP inspection revealed incorrect response adjudication in a number of cases, a re-analysis based on individual patient review and re-evaluation of response ("derived tumour response assessments") was consistent with the ITT results.

As the CHMP questioned the integrity of the primary analysis based on the high and uneven degree of censoring, the reasons for censoring have been re-evaluated by the MAH: 56 subjects in the sunitinib arm and 34 in placebo arm were censored. 38/56 and 17/34, respectively, were censored due to study termination. 18 subjects in the sunitinib arm and 17 in the placebo arm were censored for other reasons. Reasonable explanations have been presented for the majority of these cases and have been accepted by the CHMP.

A number of extensive and comprehensive sensitivity analyses have been performed in order to overcome the concerns due to the 1) lack of independent assessment of efficacy, 2) early stopping of the trial and 3) high censoring rate. Specifically, sensitivity analyses were conducted to evaluate the effect of timing of tumour assessments, censoring for a composite of specific reasons that might result from undocumented disease progression (symptomatic deterioration, starting other anticancer therapy, missing tumour assessments at 2 or more consecutive time points), and censoring of additional subsets of subjects (all censored subjects, subjects censored for reasons other than study termination, and subjects censored upon discontinuation due to adverse events or global deterioration of health). All of these sensitivity analyses were performed on both investigators' overall tumour assessments and tumour assessments derived from investigator measurement data.

Considering the very early termination of the study, an independent review of the PFS results would have consolidated the evaluation of the treatment effect. In addition, a certain degree of detection bias can not be excluded due to the well-known safety profile of sunitinib and the use of placebo as control

arm. The result of the IRC-based analysis of PFS was consistent with the result of the investigator-based analysis of PFS.

However, despite a possible overestimation in the primary PFS analysis, the results of the sensitivity analyses supported overall a consistent benefit in favour of sunitinib.

The CHMP raised concerns due to the limited number of treatment- naïve patients included in the pivotal study (a total of 53 patients: 29 in the sunitinib arm and 24 in the placebo arm, respectively). In view of this, the CHMP considered that the therapeutic indication should include a statement about the limited data from treatment-naïve patients as follows: *Sunitinib is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults* pointing out that *experience with Sutent as first-line treatment is limited.*

Furthermore, the committee considered that there is a need of further evidence supporting the efficacy of sunitinib in an adequate number of systemic-treatment-naïve patients to be submitted as a Follow-Up Measure. A controlled study would be preferred but feasibility and possible control arms and design should be discussed by the MAH. The MAH committed to propose and conduct a clinical study to obtain further evidence supporting the efficacy of sunitinib in an adequate number of systemic-treatment-naïve patients.

Secondary endpoints: The ORR was modest (9.3%: 2 CRs and 6 PRs) in the sunitinib arm compared to 0% in the placebo arm. The responses seem to be of a longer duration, but the median DR could not be determined (>8 months).The ORR might have been underestimated due to the early termination of the study. Of note, approximately 60% of patients in both treatment arms experienced SD.

The updated analysis of OS showed a trend towards higher chance of survival for patients treated with sunitinib. The MAH has committed to provide the final OS analysis as a Follow-Up Measure.

Overall, the analysis of the EORTC QLQ-C30 did not indicate that treatment with sunitinib lead to a significant deterioration in QoL and most symptoms measured, but these instruments are notoriously insensitive. As expected, sunitinib-treated subjects experienced worsening in diarrhoea at all time points and a worsening of insomnia at cycles 2-7.

A post-hoc analysis showed that initiation of somatostatin analog therapy was less common in sunitinib-treated subjects (1.2%) vs. in placebo-treated (7.1%).

Ki 67 is widely used in decisional algorithm, not only for pancreatic neuroendocrine tumours. It could be of potential interest to verify whether different sub-categories can be identified within the group of well-differentiated PNET, by grouping patients according to Ki 67. The role of the Ki-67 index was investigated in an exploratory analysis but definite conclusions could not be drawn as Ki-67 data were only available for 42% of the study population. It could be considered to further address the role of ki67 in the context of a prospectively designed study, where a repeated testing could be envisioned and could help to elucidate the role of this and other potential markers.

The pNET subpopulation of the supportive phase II study RTKC-0511-015 is not entirely identical with the population enrolled in the pivotal study as two different cohorts were enrolled in the study, one of which (66 patients) was represented by pNET: Whereas the pivotal study required that patients had well-differentiated tumours according to the WHO classification and that tumours had progressed during the last 12 months prior to study entry. These limitations were not imposed in the supportive phase 2 study which included both patients with pNETs and carcinoid tumours.

The ORR assessed by the investigators was higher than in the A6181111 (16.7% vs. 9.3%). Overall the results indicated that sunitinib has anti-tumour activity in pNET and support the efficacy of sunitinib treatment in patients with pNETs.

### *1.3.3 Clinical safety*

Safety analyses in this application were based on data from pivotal Study A6181111, which used a sunitinib dosing regimen of 37.5 mg on a CDD schedule, and from subjects with pNET in supportive Study RTKC-0511-015, which used a sunitinib dosing regimen of 50 mg on Schedule 4/2. In addition, results from studies A6181047 and A6181061, which used a sunitinib dosing regimen of 37.5 mg on a CDD schedule in subjects with GIST and MRCC, respectively, were included to support the evaluation of sunitinib 37.5 mg on a CDD schedule.

Additional information to support the safety of sunitinib for the treatment of patients with pNET was provided from 2 ongoing, open-label (sunitinib) extension studies, Study A6181078 and Study A6181114.

*Patient Exposure*

The initially submitted safety summary included safety data from a total of 398 subjects from 4 different clinical studies of whom 316 received at least 1 dose of sunitinib. A total of 237 subjects were on trials of pNET (of whom 152 were treated with sunitinib), and 338 subjects were treated on Schedule CDD (of whom 253 were treated with sunitinib). The pivotal study for the application was Study A6181111, a randomized, double-blind, placebo-controlled, Phase 3 study of sunitinib 37.5 mg administered on a CDD schedule in subjects with pNET, which included 83 subjects who received sunitinib and 82 subjects who received placebo. The general safety data cut-off date for the initial submission was 13 May 2009; the data cut-off date for reporting deaths was 15 April 2009. A further safety update from subjects who had been enrolled in Study A6181111 and who then enrolled in an extension study (either Study A6181114 or Study A6181078) was provided using a data cut-off date of 01 October 2009.

In Study A6181111, the median duration of treatment (defined as the number of days from first dose to last dose) was 141 (range: 13 – 602) days and 113 (range: 1 - 614) days for the sunitinib and placebo arms, respectively. The median number of 4-week cycles that subjects started was 5 (range: 1 - 20) in the sunitinib arm and 4 (range: 1 - 22) in the placebo arm. The percent of subjects starting 10 or more cycles was 28.9% in the sunitinib arm and 12.2% in the placebo arm. The number of cycles started was limited by the early termination of the study, resulting in premature discontinuation of study treatment in several subjects in the study. 31% of sunitinib-treated subjects had dose reductions vs. 11% in the placebo arm. In contrast, 10% had dose escalations in the active treatment arm vs. 24% in the control arm. Limited long-term exposure data exists due to premature termination of study.

In Study RTKC-0511-015, the median duration of treatment (i.e., the number of days from first dose to 2 weeks after the last dose of study medication) was 213 (range: 28 – 469) days, and the median number of 6-week cycles started was 5 (range: 1 - 11).

Although Study A6181111 and Study RTKC-0511-015 specified different dosing regimens (37.5 mg on a CDD schedule on Study A6181111, 50 mg on Schedule 4/2 on Study RTKC-0511-015), the overall intended (nominal) dose intensity in the two studies was similar (37.5 mg and ~33.3 mg per day, respectively). Relative dose intensity was calculated differently in these two studies in order to account for the differences in these dosing regimens. Of note, relative dose intensity for individual subjects >100% was due to intrasubject dose escalation above the starting dose depending on tolerability. The mean relative dose intensity in Study A6181111 was 91.3% and 100.6% for the sunitinib and placebo arms, respectively, and it was 91.0% in Study RTKC-0511-015. Exposure information is summarized in table 21.

**Table 21 Exposure to Treatment – As-Treated Population** Exposure Parameter

| | Phase 3 Study A6181111 | Phase 2 Study RTKC-0511-015 [f] | |
|---|---|---|---|
| | **Sunitinib (N = 83)** | **Placebo (N = 82)** | **Pancreatic NET (N = 66)** |
| Total number of cycles started, median (range) | 5 (1 – 20) | 4 (1 - 22) | 5 (1 – 11) |
| Duration of treatment<br>Days on drug, median (range)[a]<br>Days on study, median (range)[b] | <br>139 (13 – 532)<br>141 (13 – 602) | <br>113 (1 – 614)<br>113 (1 – 614) | <br>138.5 (18 – 308)<br>213.5 (28 – 469) |
| Number of subjects with dose reduction (n [%]) | 26 (31.3) | 9 (11.0) | 34 (51.5) |
| Number of subjects with dose escalation (n [%]) | 8 (9.6) | 20 (24.4) | 2 (3.0) |
| Number of subjects with dose interruption (n [%]) | 25 (30.1) | 10 (12.2) | 46 (69.7) |
| Average weekly dose administered (mg)<br>Mean (SD)<br>Median (Range) | <br>239.5 (38.7)<br>262.1 (145.1 - 330.0) | <br>264.0 (34.0)<br>262.5 (184.9 - 381.8) | <br>317.8 (44.1)<br>347.2 (198.1 – 408.1) |
| Relative dose intensity (%)[d]<br>Mean (SD)<br>Median (Range) | <br>91.3 (14.7)<br>99.8 (55.3 – 125.7) | <br>100.6 (13.0)<br>100.0 (70.4 – 145.5) | <br>91.0 (11.7)<br>94.4 (34.7 – 100.0) |

Furthermore, studies A6181078 and A6181114 included subjects from a number of previous parent sunitinib studies who were judged by the investigator to have the potential to derive clinical benefit from continuing sunitinib treatment or switching from placebo to sunitinib treatment. Only safety data from subjects with pNET (those who had previously participated in pivotal Study A6181111; 103 subjects evaluated for safety) were included in a further safety update (120-Day Safety Update) with a data cut-off of 01 October 2009. It should be noted that subjects from either treatment arm of study A6181111 could have entered the extension studies as the result of the study's early closure, or from the placebo arm due to disease progression prior to study closure. Of 44 subjects who had previously received sunitinib in study A6181111, 3 subjects entered study A6181078 and 41 subjects entered study A6181114. Of the 59 subjects who had previously received placebo in study A6181111, 5 subjects entered study A6181078, and 54 subjects entered study A6181114. Each subject received a subject identification number unique to the extension study upon enrolment. For reporting purposes in the 120-Day Safety Update, data were presented using subject identification numbers from Study A6181111.

The 103 subjects with pNET participated in the ongoing extension studies A6181078 or A6181114 for a median of 179 days (range: 5-618 days) and received sunitinib for a median duration of 162 days (range: 5-492 days). The average weekly sunitinib dose was similar between the Safety Update with cut-off 1 October 2009 and the safety summary submitted with the initial submission; 49 (47.6%) subjects had a dosing interruption of at least 1 week and 35 (34.0%) subjects had 1 dose reduction, most commonly due to AEs. No subjects had >1 dose reductions, and few subjects (7 [6.8%]) had dose escalations.

**Table 22 Exposure to Treatment – Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| | Sunitinib N=103 |
|---|---|
| Number of cycles started | 722 |
| Median (range) | 7 (1-23) |
| Duration of treatment (days)[a] | |
| Median (range) | 179.0 (5-618) |
| Number of days on drug[b] | |
| Median (range) | 162.0 (5-492) |
| Dosing interruptions [n (%)][c] | 49 (47.6) |
| Dose reductions [n (%)][d] | 35 (34.0) |
| Dose escalations [n (%)][e] | 7 (6.8) |
| Average dose (mg)[f] | |
| Mean (SD) | 224.7 (45.8) |
| Median (range) | 226.5 (104.4 – 350.0) |
| Relative dose intensity (%)[g] | |
| Mean (SD) | 85.6 (17.5) |
| Median (range) | 86.3 (39.8 – 133.3) |

[a]Duration of treatment (days) was defined as (last dose date – first dose date) + 1.
[b]Days on drug was defined as the total number of days on which study drug was actually administered.
[c]Dosing interruption was defined as an interruption of at least 7 days, or more.
[d]A single dose reduction was from 37.5 mg to 25 mg or from 50 mg to 37.5 mg. A reduction from 50 mg to 25 mg was counted as 2 dose reductions.
[e]A single dose escalation was from 25 mg to 37.5 mg or from 37.5 mg to 50 mg.
[f]Average dose was actual total dose taken expressed on a weekly basis.
[g] Relative dose intensity was [(total dose administered)/(total dose intended)] x100. Relative dose intensities for individual subjects >100% were possible given the opportunity for dose escalation above the starting dose depending on tolerability.
SD=standard deviation
Source: Tables 13.3.1.1, 13.3.1.2, 13.3.1.3, and 13.3.1.4.

Demographic and baseline characteristics of subjects with pNET included in the 120-Day Safety Update were generally consistent with those previously reported for subjects in Study A6181111 as presented, although there was a slightly higher proportion of male subjects in the 120-Day Safety Update population compared to that in the initial submission.

*Adverse Events*

The observed adverse events (AEs) were consistent with the known safety profile of sunitinib and with the diseases under study. The AE profile of sunitinib was primarily characterized by gastrointestinal, constitutional, coetaneous, and myelosuppressive events that generally were of mild to moderate severity.

The most frequent Grade 3/4 AEs were neutropenia (experienced by 12.0% of sunitinib subjects and no placebo subjects), hypertension (9.6% of sunitinib subjects and 1.2% of placebo subjects), leucopenia (6.0% of sunitinib subjects and no placebo subjects), and palmar-plantar erythrodysaesthesia syndrome (6.0% of sunitinib subjects and no placebo subjects). Grade 3/4 abdominal pain and fatigue were more frequent in the placebo arm (9.8% and 8.5%, respectively) compared to the sunitinib arm (each 4.8%).

There were 4 (4.8%) and 6 (7.3%) subjects with Grade 5 AEs in the sunitinib and placebo arms, respectively, with 3 subjects in each arm having a Grade 5 AE of disease progression.

The incidence of adverse events in the supportive studies was consistent with that in pivotal study A6181111 and consistent with the underlying disease (pNET) and known adverse effects of sunitinib in subjects with solid tumours. In study RTKC-0511-015, adverse events were most commonly associated with the Gastrointestinal Disorders SOC and the General Disorders and Administration Site Conditions SOC, and the most common adverse events were fatigue (92.4% of subjects), diarrhoea (78.8%),

nausea (60.6%), and dysgeusia (51.5%). The most frequently reported Grade 3/4 events in the pNET cohort were neutropenia, fatigue, thrombocytopenia, hypertension, and abdominal pain. Adverse events reported in studies A6181047 and A6181061 were also consistent with those in studies A6181111 and RTKC-0511-015.

The most common all-causality AEs (those reported in ≥5% of subjects) recorded on studies A6181078 and A6181114 were Diarrhoea, Neutropenia, and Asthenia, all of which were experienced by at least 35% of subjects. Most AEs were reported with a severity of Grade 1 or 2. The most frequent Grade 3/4 all-causality AEs were Neutropenia (21.4%) and Asthenia (10.7%). Abdominal pain and Diarrhoea were each reported in 7.8% of subjects, Thrombocytopenia was reported in 6.8% of subjects, and General physical health deterioration, Leucopenia, and Palmar-plantar erythrodysaesthesia syndrome were each reported in 5.8% of subjects. The other Grade 3/4 events were reported in <5% of subjects.

**Table 23. Frequency of Selected Clustered Adverse Event Preferred Terms – All Causalities - Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| | Sunitinib (N=103) | |
|---|---|---|
| **Number (%) of Subjects with Clustered Term** | **All Grades** | **Grade 3/4** |
| **All Causalities** | | |
| Fatigue/Asthenia[a] | 63 (61.2) | 15 (14.6) |
| Stomatitis, Oral discomfort and related oral syndromes[b] | 46 (44.7) | 5 (4.9) |
| Hand-foot syndrome and related skin disorders[c] | 27 (26.2) | 6 (5.8) |
| Bleeding complications[d] | 16 (15.5) | 2 (2.0) |
| Hypertension[e] | 13 (12.6) | 4 (3.9) |
| Arteriovenous thromboembolic events[f] | 1 (1.0) | 0 (0.0) |

[a] Fatigue and Asthenia.
[b] Aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, gum ulceration, mouth ulceration, oral discomfort, oral mucosal blistering, oral pain, stomatitis, swollen tongue, tongue blistering, tongue oedema, tongue ulceration, mucosal dryness, mucosal inflammation, gingival ulceration, dry mouth, oropharyngeal blistering and mouth ulceration.
[c] Palmar erythema, palmar-plantar erythrodysaesthesia syndrome, plantar erythema
[d] Haemorrhage, haemorrhage, melaena, haematochezia, bleeding, haematoma, haematemesis, metrorrhagia, and haemoptysis.
[e] Accelerated hypertension, essential hypertension, hypertensive crisis, diastolic hypertension, malignant hypertension, renovascular hypertension, systolic hypertension, labile hypertension, orthostatic hypertension, and secondary hypertension.
[f] Deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, and thrombosis.
Source: Table 13.6.2.4.4

- Treatment-Related Adverse Events

The incidence of treatment-related AEs reflected that of all-causality AEs in the studies evaluated for safety. The most common treatment-related AEs in Study A6181111 were diarrhoea and nausea, and both were reported at greater incidence in the sunitinib arm compared with the placebo arm, with 53.0% and 38.6% of sunitinib-treated subjects experiencing treatment-related diarrhoea and nausea, respectively, compared with 30.5% and 22.0% of placebo-treated subjects. Other treatment-related AEs that were reported at an incidence ≥10% greater in the sunitinib arm compared with the placebo arm included: hair colour changes, neutropenia, fatigue, hypertension, palmar-plantar erythrodysaesthesia syndrome, stomatitis, dysgeusia, epistaxis, thrombocytopenia, rash, and dyspepsia. For a detailed list of adverse drug reactions, see the SmPC (section 4.8).

None of these commonly listed AEs was reported with Grade 5 severity. Treatment-related events with a smaller, but potentially meaningful, difference in incidence between treatment arms were also listed in tabular format by the MAH.

The most frequent treatment-related Grade 3/4 AEs were neutropenia (experienced by 12.0% of sunitinib subjects but no placebo subjects), hypertension (9.6% of sunitinib but no placebo subjects), leucopenia (6.0% of sunitinib subjects but no placebo subjects), and palmar-plantar erythrodysaesthesia syndrome (6.0% of sunitinib subjects but no placebo subjects). One (1.2%) and 1 (1.2%) subjects in the sunitinib and placebo arms, respectively, experienced Grade 5 treatment-related AEs. The Grade 5 events were Cardiac failure in the sunitinib arm and Dehydration in the placebo arm.

**Table 24. Most Common Treatment-Related Treatment-Emergent Adverse Events with a Meaningful Difference* Between Treatment Arms on Study A6181111 (AT Population)**

| | **Sunitinib (N=83)** | | **Placebo (N=82)** | |
|---|---|---|---|---|
| **Number (%) of Subjects with Preferred Term Adverse Event** | **All Grades** | **Grade 3/4** | **All Grades** | **Grade 3/4** |
| Diarrhoea | 44 (53.0) | 4 (4.8) | 25 (30.5) | 1 (1.2) |
| Nausea | 32 (38.6) | 1 (1.2) | 18 (22.0) | 0 |
| Fatigue | 24 (28.9) | 4 (4.8) | 14 (17.1) | 3 (3.7) |
| Hair colour changes | 24 (28.9) | 1 (1.2) | 1 (1.2) | 0 |
| Neutropenia | 24 (28.9) | 10 (12.0) | 3 (3.7) | 0 |
| Hypertension | 19 (22.9) | 8 (9.6) | 3 (3.7) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 19 (22.9) | 5 (6.0) | 2 (2.4) | 0 |
| Stomatitis | 18 (21.7) | 3 (3.6) | 2 (2.4) | 0 |
| Dysgeusia | 16 (19.3) | 0 | 3 (3.7) | 0 |
| Epistaxis | 16 (19.3) | 1 (1.2) | 2 (2.4) | 0 |
| Thrombocytopenia | 14 (16.9) | 3 (3.6) | 4 (4.9) | 0 |
| Mucosal inflammation | 13 (15.7) | 1 (1.2) | 6 (7.3) | 0 |
| Rash | 13 (15.7) | 0 | 4 (4.9) | 0 |
| Dyspepsia | 12 (14.5) | 0 | 1 (1.2) | 0 |
| Headache | 10 (12.0) | 0 | 5 (6.1) | 1 (1.2) |
| Leucopenia | 8 (9.6) | 5 (6.0) | 1 (1.2) | 0 |
| Nail disorder | 8 (9.6) | 0 | 1 (1.2) | 0 |
| Arthralgia | 6 (7.2) | 0 | 2 (2.4) | 0 |
| Yellow skin | 6 (7.2) | 0 | 0 | 0 |
| Alopecia | 5 (6.0) | 0 | 1 (1.2) | 0 |
| Flatulence | 5 (6.0) | 0 | 1 (1.2) | 0 |
| Gingival bleeding | 5 (6.0) | 0 | 0 | 0 |
| Hypothyroidism | 5 (6.0) | 0 | 1 (1.2) | 0 |

*Meaningful difference is considered: ≥ 10% difference in incidence for events occurring at ≥ 20% incidence in at least 1 group; ≥ 2-fold difference for events occurring at ≥ 10% and < 20% in at least 1 group, and ≥ 3-fold difference for events occurring at < 10% incidence in both groups.

The relative incidence of adverse events in the supportive studies was overall consistent with that in pivotal Study A6181111 and consistent with the underlying disease (pNET) and with known adverse effects of sunitinib. In Study RTKC-0511-015, the most common treatment-related adverse events were fatigue (89.4 % of subjects), diarrhoea (65.2%), nausea (50.0%), dysgeusia (50.0%), skin discoloration (37.9%), and stomatitis (36.4%). The most frequently reported Grade 3/4 treatment-related events for the pNET cohort in Study RTKC-0511-015 were neutropenia, fatigue, and hypertension. Similarly, the adverse events reported in Studies A6181047 and A6181061 were consistent with those in studies A6181111 and RTKC-0511-015.

Most subjects (99 [96.1%]) in studies A6181078 and A6181114 experienced treatment-related AEs. The most common treatment-related AEs (those reported in ≥5% of subjects) are summarized by PT in Table 42. Observed most commonly were Diarrhoea, Neutropenia, Asthenia, Hair colour changes, and Decreased appetite, all of which were experienced by at least 30% of subjects. Most AEs were reported with a severity of Grade 1 or 2.

The most frequent Grade 3/4 treatment-related AEs in the extension studies were Neutropenia (21.4%), Diarrhoea (7.8%), Asthenia (7.8%), Palmar-plantar erythrodysaesthesia syndrome (5.8%), Thrombocytopenia (5.8%), and Leucopenia (5.8%). The other Grade 3/4 events were reported in <5% of subjects. There were no treatment-related AEs reported with a severity grade of 5.

**Table 25 Most Common (≥5% Sunitinib-Treated Subjects) Treatment-Related Adverse Events – Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| | Sunitinib (N=103) | |
|---|---|---|
| **Number (%) of Subjects with Preferred Adverse Event Term** | **All Grades** | **Grade 3/4** |
| Any AE | 99 (96.1) | 63 (61.2) |
| Diarrhoea | 54 (52.4) | 8 (7.8) |
| Neutropenia | 39 (37.9) | 22 (21.4) |
| Asthenia | 34 (33.0) | 8 (7.8) |
| Hair colour changes | 34 (33.0) | 0 (0.0) |
| Decreased appetite | 31 (30.1) | 0 (0.0) |
| Thrombocytopenia | 28 (27.2) | 6 (5.8) |
| Palmar-plantar erythrodysaesthesia syndrome | 27 (26.2) | 6 (5.8) |
| Fatigue | 25 (24.3) | 3 (2.9) |
| Mucosal inflammation | 21 (20.4) | 3 (2.9) |
| Dysgeusia | 20 (19.4) | 0 (0.0) |
| Leucopenia | 17 (16.5) | 6 (5.8) |
| Nausea | 17 (16.5) | 1 (1.0) |
| Stomatitis | 17 (16.5) | 2 (1.9) |
| Dry skin | 16 (15.5) | 0 (0.0) |
| Vomiting | 13 (12.6) | 1 (1.0) |
| Dyspepsia | 12 (11.7) | 0 (0.0) |
| Epistaxis | 12 (11.7) | 1 (1.0) |
| Oedema peripheral | 12 (11.7) | 1 (1.0) |
| Weight decreased | 12 (11.7) | 0 (0.0) |
| Abdominal pain | 11 (10.7) | 1 (1.0) |
| Erythema | 11 (10.7) | 1 (1.0) |
| Arthralgia | 10 (9.7) | 2 (1.9) |
| Back pain | 10 (9.7) | 1 (1.0) |
| Dyspnoea | 10 (9.7) | 1 (1.0) |
| Abdominal pain upper | 9 (8.7) | 0 (0.0) |
| Constipation | 9 (8.7) | 0 (0.0) |
| Headache | 9 (8.7) | 0 (0.0) |
| Insomnia | 9 (8.7) | 0 (0.0) |
| Anaemia | 8 (7.8) | 3 (2.9) |
| Hypertension | 8 (7.8) | 3 (2.9) |
| Hypoalbuminemia | 7 (6.8) | 1 (1.0) |
| Rash | 7 (6.8) | 0 (0.0) |
| Skin discoloration | 7 (6.8) | 0 (0.0) |
| Aspartate aminotransferase increased | 6 (5.8) | 2 (1.9) |
| Face oedema | 6 (5.8) | 0 (0.0) |
| Hyperkeratosis | 6 (5.8) | 1 (1.0) |
| Hypokalaemia | 6 (5.8) | 2 (1.9) |
| Lacrimation increased | 6 (5.8) | 0 (0.0) |
| Muscle spasms | 6 (5.8) | 0 (0.0) |
| Nail disorder | 6 (5.8) | 0 (0.0) |
| Pain in extremity | 6 (5.8) | 0 (0.0) |
| Pruritus | 6 (5.8) | 1 (1.0) |
| Pyrexia | 6 (5.8) | 0 (0.0) |

Source: Tables 13.6.3.2, 13.6.3.3.1, 13.6.3.3.2, and 13.6.3.4.2

The frequency of selected clustered AE PTs that were considered related to study treatment is summarized in Table 26.

**Table 26 Frequency of Selected Clustered Adverse Event Preferred Terms** – Treatment-Related - **Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| | Sunitinib (N=103) | |
|---|---|---|
| **Number (%) of Subjects with Clustered Term** | **All Grades** | **Grade 3/4** |
| **Treatment-Related** | | |
| Fatigue/Asthenia[a] | 56 (54.4) | 11 (10.7) |
| Stomatitis, Oral discomfort and related oral syndromes[b] | 46 (44.7) | 5 (4.9) |
| Hand-foot syndrome and related skin disorders[c] | 27 (26.2) | 6 (5.8) |
| Bleeding complications[d] | 9 (8.7) | 0 (0.0) |
| Hypertension[e] | 8 (7.8) | 3 (2.9) |
| Arteriovenous thromboembolic events[f] | 0 (0.0) | 0 (0.0) |

[a] Fatigue and Asthenia.
[b] Aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, gum ulceration, mouth ulceration, oral discomfort, oral mucosal blistering, oral pain, stomatitis, swollen tongue, tongue blistering, tongue oedema, tongue ulceration, mucosal dryness, mucosal inflammation, gingival ulceration, dry mouth, oropharyngeal blistering and mouth ulceration.
[c] Palmar erythema, palmar-plantar erythrodysaesthesia syndrome, and plantar erythema.
[d] Haemorrhage, haemorrhage, melaena, haematochezia, bleeding, haematoma, haematemesis, metrorrhagia, and haemoptysis.
[e] Accelerated hypertension, essential hypertension, hypertensive crisis, diastolic hypertension, malignant hypertension, renovascular hypertension, systolic hypertension, labile hypertension, orthostatic hypertension, and secondary hypertension.
[f] Deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, and thrombosis.
Source: Table 13.6.3.4.4

In summary, the types, frequencies, and severities of all-causality AEs in subjects with pNET continuing in the extension studies were generally consistent with those in sunitinib-treated subjects in the parent pivotal Study A6181111; although Grade 3/4 Neutropenia was reported with higher frequency in the safety update (cut-off 1 October 2009) than initially safety summary (21.4% vs. 12.0%). No new safety concerns emerged from this evaluation, when viewed in the context of a low discontinuation rate due to Neutropenia and only 1 neutropenia-associated SAE reported.

*Serious adverse event/deaths/other significant events*

- Deaths

In Study A6181111, there were fewer deaths among sunitinib-treated subjects (9 [10.8%]) compared with placebo-treated subjects (21 [25.6%]).

The most common cause of death in both treatment arms was "Disease under Study." Two deaths were attributed to treatment with study drug. One subject in the sunitinib arm died of cardiac failure, and 1 subject in the placebo arm died of dehydration. Both were considered by the investigator to be related to study treatment.

The results of the supportive studies are consistent with results from Study A6181111, and the most common reason for death was "Progression of the Disease under Study." Two of 26 on-study deaths in the supportive studies were considered related to treatment with sunitinib (Study RTKC-0511-015 – gastrointestinal haemorrhage, and Study A6181047 – septic shock), and 1 of 96 deaths during the follow up period (Study A6101061 – acute myeloid leukaemia) was considered related to treatment.

Eighteen (17.5%) deaths were reported for subjects with pNET in studies A6181078 and A6181114 (Table 46). Eleven deaths occurred during the on-study period, and 7 deaths occurred during the follow-up period. Eight of the 11 deaths that occurred during the on-study period were due to "Disease under Study". Of the remaining 3 on-study deaths, 2 occurred as the result of AEs (Renal failure and Hepatic encephalopathy) that were not considered related to study treatment but due to the disease

under study, and 1 death was a sudden death of unknown origin. All deaths that occurred during the follow-up period were due to "Disease under Study".

**Table 27 Summary of Deaths - Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| Cause of Death | Sunitinib (N = 103) |
|---|---|
| Deaths | 18 (17.5) |
| | |
| Subjects who Died while On Study[a] | 11 (10.7) |
| Disease under study | 8 (7.8) |
| Study treatment toxicity | 0 (0.0) |
| Other | 3 (2.9)[b] |
| Unknown | 0 (0.0) |
| | |
| Subjects who Died during Follow-Up[c] | 7 (6.8) |
| Disease under study | 7 (6.8) |
| Study treatment toxicity | 0 (0.0) |
| Other | 0 (0.0) |
| Unknown | 0 (0.0) |

[a]On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
[b]Subject 10021001 Renal failure; Subject 10331004 Sudden death from unknown origin; Subject 10411013 Hepatic encephalopathy.
[c]Follow-up period deaths are those that occurred more than 28 days after the last dose of study medication.
Data source: Table 13.6.7 and B6.4.

Of the 18 deaths summarized in Table 27, 10 were initially reported in the safety summary (Study A6181111). Of the 8 deaths not previously reported, 5 occurred during the on-study period and 3 occurred during the follow-up period. Four of the 5 deaths that occurred during the on-study period were due to "Disease under Study, and 1 death was a sudden death of unknown origin. All 3 deaths that occurred during the follow-up period were due to "Disease under Study".

- Serious Adverse Events

Subjects with pancreatic NET who experienced a Grade 5 AE during Study A6181078 or A6181114 are presented in Table 28. These AEs were generally considered to be due to the disease under study, and all were reported as SAEs. The deaths of 4 subjects were previously reported.

**Table 28 Subjects with Grade 5 Adverse Events – Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| Subject Number | Sex/Age (years) | Preferred Term | Start/Stop Day | Causality |
|---|---|---|---|---|
| **Sunitinib (N=103)** | | | | |
| 10021001[a] | F/61 | Renal failure acute | 389/395 | Disease under study |
| 10091005 | F/73 | Dyspnoea | 29/29 | Disease under study |
| 10131002[a] | M/51 | General physical health deterioration | 148/>148 | Disease under study |
| 10291002 | F/74 | Disease progression | 88/88 | Disease under study |
| 10331004 | M/84 | Sudden death | 37/37 | Unknown origin |
| 10421010[a] | M/63 | Disease progression | 114/157 | Disease under study |
| 10421011[a] | M/40 | Acidosis | 9/11 | Disease under study |
| 10711001 | F/62 | Hepatic failure | 134/>134 | Disease under study |

[a]Death of subject previously reported in Study A6181111 CSR B6.4.
F=female, M=male
Use of '>' represents imputed data.
Source: B6.1, B6.2.

- Treatment-Related Serious Adverse Events

In pivotal Study A6181111, treatment-related SAEs were experienced by a greater proportion of sunitinib-treated subjects (11 [13.3%]) than placebo-treated subjects (6 [7.3%]). Among subjects who received sunitinib, the most commonly reported events were abdominal pain upper, nausea, and renal failure. Among placebo-treated subjects, treatment-related SAEs were limited to single occurrences of abdominal pain, pyrexia, pneumonia, dehydration, back pain, pleurisy, pulmonary embolism, and deep vein thrombosis.

In the supportive studies, the incidences of treatment-related SAEs (13.3%-25.8%) were similar to those observed among sunitinib-treated subjects in pivotal Study A6181111. In Study RTKC-0511-015, treatment-related SAEs were reported in 17 subjects (25.8%) in the pancreatic NET cohort. The most common events for subjects with pancreatic NET were vomiting (5 subjects, 7.6%), dehydration, fatigue, and nausea (each 3 subjects, 4.5%). Vomiting appeared to be the only event common among Study A6181111 and all 3 supportive studies. Treatment-related SAEs for all 4 studies are shown in table 14.

Eleven (10.7%) subjects who received sunitinib experienced at least 1 treatment-related SAE. Five (4.9%) subjects experienced treatment-related SAEs reported for the Gastrointestinal Disorders SOC, and 2 (1.9%) subjects experienced treatment-related SAEs reported for the Respiratory, Thoracic and Mediastinal Disorders SOC. Other SAE SOCs were limited to single occurrences.

Treatment-related SAEs are listed in table below.

**Table 29 Treatment-Related Serious Adverse Events – Ongoing Studies A6181078 and A6181114 – Subjects with Pancreatic NET**

| Subject Number | Sex/ Age (years) | Preferred Term | Start/Stop Day | Grade | Outcome |
|---|---|---|---|---|---|
| **Sunitinib (N=103)** | | | | | |
| 10021003 | M/32 | Haematemesis | 3/7 | 2 | Resolved |
| | | Nausea | 77/>77 | 3 | Still present |
| | | Vomiting | 77/>77 | 3 | Still present |
| 10241005 | F/46 | Palmar-plantar erythrodysaesthesia syndrome | 189/189 | 3 | Resolved |
| 10331004 | M/84 | Metabolic encephalopathy | 12/>12 | 3 | Still present |
| 10481002 | F/69 | Diarrhoea | 76/82 | 3 | Resolved |
| | | Diarrhoea | 138/173 | 3 | Resolved |
| 10481007 | M/60 | Lung disorder | 92/114 | 3 | Resolved |
| 10491002 | M/71 | Respiratory failure | 33/38 | 2 | Resolved |
| 10531005 | F/59 | Arthralgia | 16/22 | 3 | Resolved |
| | | Arthralgia | 23/27 | 3 | Resolved |
| 10541002 | F/58 | Abdominal pain | 26/36 | 3 | Resolved |
| 10601003 | M/74 | Pneumatosis intestinalis | 47/73 | 2 | Resolved |
| 10701002 | M/77 | Neutropenia | 183/190 | 3 | Resolved |
| | | Neutropenia | 198/203 | 3 | Resolved |
| | | General physical health deterioration | 227/>227 | 3 | Resolved |
| | | Anorexia | 244/>258 | 1 | Unknown |
| 10711001 | F/62 | Diarrhoea | 124/>158 | 3 | Still present |

F=female, M=male
Use of '>' represents imputed data
Source: Table B6.2

*Adverse Events of special interest*

Selected safety topics of special interest to sunitinib were chosen based on their clinical significance and association with other in-class RTK inhibitors and/or antiangiogenic agents, and/or because they were the focus of previous inquiries by regulatory bodies. These topics included cardiac dysfunction,

thyroid dysfunction, hemorrhagic events, and thromboembolic events. Hypoglycaemia was also included for the pancreatic NET population which included subjects who had undergone pancreatic resection, carried a diagnosis of insulinoma, or received treatment for disease-related diabetes. Although adverse events were reported in each of these categories, there were only two subjects with a Grade 4 adverse event (both Grade 4 hypoglycaemia in two subjects treated with sunitinib on Study A6181111) and one subject with a Grade 5 adverse event (cardiac failure in one subject treated with sunitinib on Study A6181111). Thus, severe significant adverse events were reported at a relatively low rate in these studies.

*Discontinuation due to adverse events*

Eighteen subjects (21.7%) and 14 subjects (17.1%) on the sunitinib and placebo arms, respectively, were permanently discontinued from the study due to treatment-emergent, all-causality AEs. The most common events associated with permanent discontinuation in the sunitinib arm were Disease progression (3 cases), Fatigue (3 cases), Diarrhoea and Cardiac failure (2 cases each) The most common events associated with permanent discontinuation in the placebo arm were Disease progression (3 cases), Abdominal pain and Hepatic failure (2 cases each). In 20 subjects (10 [12%] subjects in both arms), the AE leading to discontinuation was serious ; however only 4 subjects on the sunitinib arm and 1 subject on the placebo arm discontinued due to an SAE that was considered to be treatment-related.

*Safety in special populations*

There was no evidence of an effect of age, race, or gender on the overall incidence of all-causality adverse events among sunitinib- or placebo-treated subjects.

*Post marketing experience*

Upon review of the safety data involving cases for which the indication was neuroendocrine tumour, there was no suggestion that this population was at a greater risk for experiencing any particular adverse event with sunitinib, and there were no new safety concerns identified.

- **Discussion on clinical safety**

The most common sunitinib-related AEs were generally tolerable and consistent with the known safety profile of sunitinib and/or signs and symptoms of pancreatic NET and included Diarrhoea, Neutropenia, and Asthenia. Most of these AEs were Grade 1 or 2 in severity.

In the pivotal study the most common AEs of all-causality in the sunitinib arm were diarrhoea (59%) and nausea (45%) compared with 39.0% and 29.3%, respectively, in placebo-treated subjects. Other AEs that were reported at a higher incidence in the sunitinib arm than in the placebo arm included hair colour changes, neutropenia, hypertension, palmar-plantar erythrodysaesthesia syndrome, stomatitis, dysgeusia, epistaxis, rash, and thrombocytopenia. The most frequent Grade 3/4 AEs in the sunitinib arm of the pivotal study were neutropenia (12.0%), hypertension (9.6%), leucopenia (6.0%), and palmar-plantar erythrodysaesthesia syndrome (6.0%).

The types and incidences of sunitinib-related AEs in the follow-up period were mostly Grade 1 or 2 in severity and similar to those reported initially for sunitinib-treated subjects with pancreatic NET.

Most subjects in the extension studies experienced treatment-related AEs (96.1%). The most common treatment-related AEs were diarrhoea (52.4%), neutropenia (37.9%), asthenia (33.0%), hair colour changes (33.0%) and decreased appetite (30.1%). Most of these AEs were of mild to moderate severity. The most frequent Grade 3 / 4 treatment-related AEs were neutropenia (21.4%), diarrhoea (7.8%), asthenia (7.8%).

Grade 3/4 Neutropenia was reported in the extension studies with higher frequency (21.4%) than in the pivotal study (12%) and in other indications (GIST: 10.0%, mRCC: 9.4%).However, the reported discontinuation and SAE rates associated with neutropenia were low and similar to those reported initially.

AEs were generally manageable through the use of dosing interruptions and dose reductions, and/or standard medical management. Temporary discontinuations due to AEs occurred fairly commonly; whereas, the incidence of permanent discontinuations (and deaths) was low.

The frequency of discontinuations due to adverse events for subjects who received sunitinib was generally comparable among the studies which employed CDD (Study A6181111, 21.7%; Study A6181047, 21.7%; Study A6181061, 17.8%).

The types of AEs resulting in permanent discontinuation and the rates of discontinuation presented from the extension studies were generally consistent with those for sunitinib-treated subjects in the pivotal study.

Treatment-related SAEs were reported at a relatively low incidence and were most commonly associated with the Gastrointestinal disorders SOC. The results of clinical laboratory investigations, vital signs, and ECG results did not reveal evidence of a clinically meaningful adverse effect of sunitinib.

Other significant AEs of particular interest, including severe AEs of cardiac dysfunction, thyroid dysfunction, hemorrhagic events, thromboembolic events, and hypoglycaemia, occurred with relatively low incidence and did not reveal any new safety risks.

The results of clinical laboratory evaluations for the safety update with 1 October 2009 cut-off did not reveal any new safety risks of sunitinib treatment, consistent with what was previously reported in the pivotal study. In summary, the safety profile of sunitinib 37.5 mg CDD in subjects with pancreatic NET in the extension studies was generally consistent with that previously reported in the safety summary for the pivotal study. The AE profile of sunitinib was primarily characterized by gastrointestinal, constitutional, cutaneous, and myelosuppressive events that were generally of mild to moderate severity. Investigation of other significant AEs of interest did not reveal any new safety risks. Deaths were most commonly due to disease progression. Treatment-related SAEs were reported at a relatively low incidence and were most commonly associated with the Gastrointestinal disorders SOC. The results of clinical laboratory investigations, vital signs, and ECG results did not reveal evidence of a clinically meaningful adverse effect of sunitinib.

#### *1.3.4 Risk Management Plan*

The MAH submitted an updated risk management plan comprising the indications GIST, MRCC, and Pancreatic NET (version 7.0 for, dated 11 November 2009) with the application for review. However, subsequently in parallel to the ongoing extension of indication procedure a Risk Management Plan version 7.0, dated 25 March 2010 was agreed by CHMP concerning an updated for the GIST and MRCC indications only.

Therefore, the MAH provided a final consolidated updated RMP for this new indication, i.e. version 8.0, dated 19 October 2010.

**SUMMARY OF THE EU RISK MANAGEMENT PLAN for Sutent**

**Summary of Activities for Each Safety Concern**

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities |
|---|---|---|
| **Identified Risks** | | |
| Hypertension | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled. |
| Haemorrhage (including tumour) | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. SUTENT is not approved for use in patients with non-small cell lung cancer (NSCLC) |
| Cytopenias (including anaemia, neutropenia, and thrombocytopenia) | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT. |
| QT interval prolongation | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. SUTENT should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmic, 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 (see Section 4.2 and Section 4.5 of the SmPC) |
| Fatigue / Asthenia | Routine pharmacovigilance | Labelled in Section 4.8 (undesirable effects) of the SmPC |
| Thyroid dysfunction | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice. |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities |
|---|---|---|
| Left ventricular dysfunction / Heart Failure | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. Close monitoring for clinical signs and symptoms of CHF should be performed, especially in patients with cardiac risk factors and/or history of coronary artery disease.<br><br>Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.<br><br>In the presence of clinical manifestations of CHF, discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline. |
| Serious infection | Routine pharmacovigilance | Labelled in Section 4.8 (undesirable effects) of the SmPC |
| Thrombotic microangiopathy | Routine pharmacovigilance | Labelled in Section 4.8 (undesirable effects) of the SmPC |
| Proteinuria / Nephrotic syndrome | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue SUTENT in patients with nephrotic syndrome. |
| Reversible posterior leukoencephalopathy | Routine pharmacovigilance<br>Data Capture Aid | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician. |
| Fistula formation | Routine pharmacoviglance | Labelled in Section 4.8 (undesirable effects) of the SmPC. |
| **Potential Risks** | | |
| Thromboembolic events | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities |
|---|---|---|
| Gastrointestinal perforation | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. |
| Drug-drug interaction caused by inhibition/induction of CYP3A4 | Routine pharmacovigilance | Labelled in Section 4.5 of the SmPC (Interaction with other medicinal products and other forms of interaction),<br><br>Drugs that may increase sunitinib plasma concentrations: Administration of SUTENT with potent inhibitors of the CYP3A4 family (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations<br><br>Combination with inhibitors should therefore be avoided, or the selection of an alternate concomitant medication with no, or minimal potential to inhibit CYP3A4 should be considered.<br><br>If this is not possible, the dosage of SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability.<br>Drugs that may decrease sunitinib plasma concentrations:<br><br>Administration of SUTENT with potent inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or Hypericum perforatum known also as St. John's Wort) may decrease sunitinib concentrations. Combination with inducers should therefore be avoided, or selection of an alternate concomitant medication with no, or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of SUTENT may need to be increased in 12.5 mg increments (up to 87, 5 mg per day) based on careful monitoring of tolerability. |
| Adrenal gland dysfunction | Routine pharmacovigilance<br>Data Capture Aid | Labelled in Section 4.8 (undesirable effects) of the SmPC. Labelled in Section 5.3 (Preclinical safety data). |
| Carcinogenicity | Routine pharmacovigilance | A rat carcinogenicity study with sunitinib malate remains ongoing. |
| Pancreatic dysfunction | Routine pharmacovigilance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC.<br><br>If symptoms of pancreatitis are present, patients should have SUTENT discontinued and be provided with appropriate supportive care |
| Myopathy | Routine pharmacovigilance | Labelled in Section 4.8 (undesirable effects) of the SmPC. |
| Cardiotoxicity | Routine pharnacoviglance | Labelled in Section 4.8 (undesirable effects) of the SmPC. |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation Activities |
|---|---|---|
| Hepatic failure | Routine pharnacoviglance | Listed in the Special warnings and precautions for use (Section 4.4) of the SmPC. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided. |
| Renal failure | Routine pharnacoviglance | Labelled in Section 4.8 (undesirable effects) of the SmPC. |
| **Missing Information** | | |
| Paediatric | Routine pharmacovigilance | The safety and efficacy of SUTENT in paediatric patients have not been established. SUTENT should not be used in paediatric population until further data become available. (Section 4.2 of the SmPC) |
| Pregnancy | Routine pharmacovigilance | There are no studies in pregnant women using SUTENT. Studies in animals have shown reproductive toxicity including foetal malformations (see Section 5.3 of the SmPC). SUTENT should not be used during pregnancy or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus.<br><br>Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.<br><br>Based on non-clinical findings, male and female fertility may be compromised by treatment with SUTENT |

#### *1.2.5 User consultation*

With the application the MAH provided a justification for not performing a Consultation with Target Patient Groups for addition of a new indication to the Sutent Package leaflet which was considered acceptable by the CHMP.

# 2. BENEFITS AND RISKS CONCLUSIONS

## Benefits

The primary objective of the study was PFS. Sunitinib 37.5 mg on a CDD schedule resulted in a median PFS of 11.4 months vs. 5.5 months in the placebo arm (hazard ratio 0.418, p=0.0001, 81 PFS events), thus translating into more than a 2-fold reduction in the relative risk of disease progression or death in subjects with pNET.

PFS improvement was observed independently of baseline histology, Ki-67 index (exploratory analysis only), disease burden, amount of prior therapy, and time from diagnosis.

Improvements in the secondary efficacy endpoints of ORR (9.3% vs 0%, p=0.0066) and OS (HR 0.409, 95% CI 0.187, 0.894, p=0.0204, 30 OS events) in the sunitinib arm was also observed.

Additionally fewer subjects treated with sunitinib than placebo started the use of disease-specific concomitant medications such as somatostatin analogs while on study.

## Uncertainty in the knowledge about the beneficial effects

In general, all supportive analyses submitted by the MAH showed consistency of the results with the primary analysis. The robustness was further corroborated by the complimentary PFS analysis based on derived tumour assessments and in the IRC-based PFS analysis. Data on efficacy of sunitinib in the treatment of pancreatic NET from both pivotal Study A6181111 and supportive Study RTKC-0511-015 are supporting of the substantial clinical benefit to patients with this relatively rare form of pancreatic cancer for whom approved or effective treatment options are currently unavailable.

Although the study was designed with an interim analysis at 130 PFS events and a final analysis at 260 events, the DMC recommended in February 2009 that the study be closed based on their review of safety and efficacy data after 73 events had been recorded.

A major issue has been the robustness of the efficacy results because the DMC was supplied with efficacy data during the 3 safety reviews when only 1 interim analysis was planned (after 130 events) and why these 3 "safety reviews" were not considered as interim analyses.

The CHMP found it problematic that the study had been stopped so early and that the final PFS analysis did not account for the 3 data looks by the DMC. Only one (later) interim analysis was pre-specified. When accounting for these additional "safety reviews", the p-value did not cross the efficacy boundary (p-value: 0.000104). The observed medians and the HR were estimated based on data from a study that was terminated at a very early stage. It is well-known that such estimates may overestimate the true treatment effect.

However, it has been documented that the hazard ratios were relatively consistent through all DMC safety reviews and similar to the result in the final analysis. It was also acknowledged that a dramatic overestimation of the true treatment effect was highly unlikely.

Updated OS data as of 01 December 2009 demonstrate a persistent advantage for sunitinib on OS, with a HR for OS of 0.594 (95% CI: 0.340, 1.038; p=0.0644, 51 OS events), despite the greater potential for confounding of the OS analysis due to treatment crossover. Mature OS data will be submitted as a FUM, agreed by the MAH, by 31 December 2014, 5 years after LSFV in the pivotal study.

The CHMP considered reasonably well documented that sunitinib has a clinically relevant treatment effect in the proposed indication, although the true benefit may be slightly more modest than in the early presented estimate.

There were concerns due to the limited number of treatment- naïve patients included in the study. The MAH committed to propose and conduct a clinical study to obtain further evidence supporting the efficacy of sunitinib in an adequate number of systemic-treatment-naïve patients as FUM.

## Risks

In the pivotal Study A6181111, the following AEs were more commonly reported in subjects on the sunitinib arm as compared to the placebo: diarrhoea, nausea, hair colour changes, neutropenia, hypertension, palmar-plantar erythrodysaesthesia syndrome, stomatitis, dysgeusia, epistaxis, rash, and thrombocytopenia.

Grade 3/4 AEs and treatment-related SAEs, particularly gastrointestinal disorders, were also more commonly reported in subjects receiving sunitinib compared to placebo, although at a modestly increased rate.

Eighteen subjects (21.7%) on the sunitinib arm and 14 (17.1%) subject on the placebo arm were permanently discontinued from Study A6181111 due to a treatment-related SAE, and only 1 subject on each treatment arm had a Grade 5 SAE (cardiac failure on sunitinib; dehydration on placebo) that was considered to be treatment-related, as the majority of SAEs and deaths were related to underlying disease.

Overall, the observed pattern of adverse events was consistent across all 4 studies and with the known safety profile for sunitinib.

Data are consistent with those that have previously been reported with sunitinib, and no new or increased safety risks were identified. Therefore, we can conclude that sunitinib 37.5 mg on a CDD schedule has an acceptable safety profile for the treatment of pancreatic NET.

## Uncertainty in the knowledge about the unfavourable effects

Long-term safety data are not available in the proposed indication due to the premature termination of the pivotal. However, it does not seem to be a major concern as the safety profile of sunitinib has been well-described in other indications and as no new safety signals have been identified.

Safety update from the two open-label extension studies have been provided and also included more mature OS data and AEs of special interest for this type of medicinal product and this indication. No major concerns have been raised on the basis of this safety update.

## Benefit-risk balance

Treatment with sunitinib as a 37.5 mg CDD in patients with well-differentiated neuroendocrine carcinoma of the pancreas was associated with a positive effect on PFS without important deterioration in the QoL of patients. These are important clinical benefits in the context of the existing unmet need for this patient population.

Although the early termination of the pivotal study complicated the interpretation of the study results looking at the totality of the data, an important overestimation of the beneficial effects seems unlikely. The safety profile of sunitinib is well-described and common AEs are considered manageable. No new safety signals have been identified. The benefit of sunitinib in the above mentioned indication is considered to overcome the risk associated with the safety profile of the medicinal product.

In conclusion, the CHMP considered that the benefit/risk balance of sunitinib is positive in the following therapeutic indication

*"SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.*
*Experience with SUTENT as first-line treatment is limited (see section 5.1)."*

# 3. Conclusion

On 21 October 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet