Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Sunitinib

Proprietary Product Name: Sutent

Sponsor: Pfizer Australia Pty Ltd

**June 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

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

# About AusPARs

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

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# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | Extension of Indications and New Dosage |
| *Decision:* | Approved |
| *Date of Decision:* | 24 February 2011 |
| | |
| *Active ingredient(s):* | Sunitinib (as malate) |
| *Product Name(s):* | Sutent |
| *Sponsor's Name and Address:* | Pfizer Australia Pty Ltd |
| | 38-42 Wharf Road West Ryde NSW 2114 |
| *Dose form(s):* | Tablets |
| *Strength(s):* | 12.5mg, 25mg, 50mg and 37.5mg |
| *Container(s):* | Blister pack or bottle |
| *Pack size(s):* | 28 |
| *Approved Therapeutic use:* | For the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET). |
| *Route(s) of administration:* | Oral (PO) |
| *Dosage:* | 37.5 mg/day |
| *ARTG Number (s)* | 123139, 123146, 123147, 149114, 149115, 149116, 156801 and 156817 |

## Product Background

Sunitinib is a receptor tyrosine kinase (RTK) inhibitor which inhibits multiple receptors implicated in tumour growth including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and c-KIT[1]. The RTKs are important in the regulation of tumour cell growth, angiogenesis and metastases. The purported mechanism of action of sunitinib in pancreatic NET (pNET) is through inhibition of these three kinases. The drug is currently registered for use in renal cell carcinoma and gastrointestinal stromal tumour (GIST). The currently approved indications, the proposed new indication and the associated recommended starting doses are summarised below. The current Australian submission proposes a novel dosage regimen for the new indication.

*Currently approved Indications and Dosage regimen*

- Treatment of advanced renal cell carcinoma;
- Treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
- Cycles of 50 mg once daily for 4 consecutive weeks followed by a 2-week rest.
- Cycles of 50 mg once daily for 4 consecutive weeks followed by a 2-week rest.

[1] A protein-tyrosine kinase receptor that binds stem cell factor.

*Proposed Indications and Dosage regimen*

- Treatment of unresectable pancreatic neuroendocrine tumours (pNET)
- 37.5 mg once daily on a continuous dosing schedule.

Currently registered products for the treatment of neuroendocrine tumours are octreotide (Sandostatin) and lanreotide (Somatuline). However, these products are only registered for the treatment of symptoms of functioning (hormone-secreting) tumours, and only for certain tumour types (carcinoid tumours, VIPomas[2]). The proposed new indication for sunitinib encompasses both functioning and non-functioning tumours, and all tumour types arising in the pancreas.

Sunitinib has been designated as an orphan drug for the new indication.

### Regulatory Status

This indication has been approved in Switzerland (27 July 2010) and the EU (29 November 2010).

### Product Information

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

# II. Quality Findings

### Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

# III. Nonclinical Findings

### Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

# IV. Clinical Findings

### Introduction

Sunitinib (Sutent) is an orally active small molecule with anti-tumour properties that are mediated for the inhibition of multiple receptor tyrosine kinases (RTKs). Pivotal trials of sunitinib were initially conducted in metastatic renal cell carcinoma (MRCC) and gastrointestinal stromal tumours (GIST) based upon the critical role of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) signalling pathways in these tumours respectively. The results of these studies demonstrated clinical efficacy with an acceptable safety profile and sunitinib has been approved in Australia as well as 90 countries worldwide for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours.

[2] Vasoactive intestinal peptide tumours

Studies with Sunitinib have now been undertaken in pancreatic neuroendocrine tumours because of the potentially widespread importance of the VEGF and PDGF signalling pathways in other tumour types. These are a relatively rare group of tumours arising from the endocrine pancreas and they are referred to as pancreatic islet cell tumours, malignant neoplasms of Islets of Langerhans and gastroenteropancreatic tumours (GEP). In the World Health Organization (WHO) classification these tumours are further classified into three groups according to malignant potential, that is, well-differentiated neuroendocrine tumour, well-differentiated neuroendocrine carcinoma and poorly differentiated neuroendocrine carcinoma. It is the second group, 'well-differentiated neuroendocrine carcinoma', which is the disease under study for the present submission.

Data is therefore provided to support a proposed new indication for the treatment of pNET. This involves a Phase III randomised, placebo controlled trial as a pivotal study (Study A618-1111). There is one supportive Phase II trial in pNET; RTKC-0511-015.

The pivotal study A6181111 utilised administration of sunitinib in a new schedule namely 37.5mgs/day on a continuing basis. This differed from the dose schedule approved for the treatment of mRCC and GIST namely 50mg/day for four weeks followed by a two-week off-treatment period and then re-cycle. Accordingly two supportive Phase II trials utilising the 37.5 mg/day continuous regimen are provided; Study A618-1061 in RCC and Study A618-1047 in GIST.

Two pharmacokinetic (PK) studies are also provided in this submission, one related to assessment of PK in patients with renal impairment (Study A618-1106) and one PK study in patients with hepatic impairment (Study A618-1079).

All aspects of Good Clinical Practice (GCP) were observed in these studies.

## Pharmacokinetics

Previous pharmacokinetic studies have demonstrated that following oral dosing, sunitinib and its primary active equipotent metabolite SU012662 reached maximum plasma concentrations ($C_{max}$) at 6 to 12 hr post dose (median time of maximal plasma concentration; $T_{max}$) followed by exponential decline in concentrations. Terminal half-lives ($T_{1/2}$) ranged from 40-60 hr for sunitinib and from 80-110 hr for SU012662. The mean oral clearance ranged from 34-62L/hr with an inter-subject variability of 40%. The mean apparent volume of distribution for sunitinib was 2230 litres. Sunitinib is metabolised primarily by the cytochrome P450 (CYP) enzyme 3A4 to produce its primary active metabolite SU012662, which is further metabolised by CYP3A4 to an inactive metabolite. In addition to metabolism, faecal excretion is another major route of elimination of sunitinib. Renal excretion is expected to play a minor role in elimination of sunitinib. Binding of sunitinib and SU012662 to human plasma protein *in vitro* was 95% and 90%, respectively, without concentration dependence in the 100-4000ng/ml range.

The PK data in this evaluation involves an initial three multiple dose single agent studies. Also summarised is StudyA6181106 in patients with renal impairment. A fifth PK study (A6181079), involving patients with hepatic impairment, has been presented separately. The demographic characteristics of the subjects in patients enrolled in the first four studies are given in Table 2.

Table 2 **Summary Demographics for Clinical Studies with PK Evaluable Subjects or Patients**

| Protocol No. (Dose Level, if applicable) | N[a] | Age (years) | | Weight (kg) | | No. of Subjects or Patients, n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean (±SD) | Median (Min-Max) | Mean (±SD) | Median (Min-Max) | Sex | | Race | | | |
| | | | | | | M | F | W | B | A[b] | NA |
| **Multiple-Dose Single-Agent Studies in Patients with NET, GIST, MRCC** | | | | | | | | | | | |
| RTKC-0511-015 | | | | | | | | | | | |
| Carcinoid Tumor | 41 | 57.7 (11.5) | 58.0 (34.0-73.0) | 75.0 (20.1) | 73.4 (39.4-127) | 22 (53.7) | 19 (46.3) | 36 (87.8) | 3 (7.30) | 1 (2.40) | 1 (2.40) |
| Pancreatic NET | 66 | 54.2 (10.99) | 56 (32.0-81.0) | 76.3 (16.0) | 76.0 (45.0-119) | 42 (63.6) | 24 (36.4) | 59 (89.4) | 4 (6.10) | 1 (1.50) | 2 (3.00) |
| A6181047 | 60 | 58.2 (14.6) | 58.5 (24.0-84.0) | 71.7[c] (22.7) | 67.0[c] (36.0-168) | 28 (46.7) | 32 (53.3) | 48 (80.0) | 0 (0.0) | 1 (1.70) | 11 (18.3) |
| A6181061 | 107 | 58.2 (10.4) | 59.0 (28.0-80.0) | 79.0[d] (15.7) | 79.0[d] (48.0-136) | 88 (82.2) | 19 (17.8) | 64 (59.8) | 0 (0.0) | 3 (2.80) | 40 (37.4) |
| **Special Population Studies** | | | | | | | | | | | |
| A6181106 | | | | | | | | | | | |
| Normal Renal Function | 8 | 55.5 (8.90) | NC (45.0-67.0) | 74.5 (14.2) | NC (52.3-100) | 2 (25.0) | 6 (75.0) | 7 (87.5) | 1 (12.5) | 0 (0.0) | 0 (0.0) |
| Severe Renal Impairment | 8 | 56.9 (10.2) | NC (42.0-72.0) | 69.2 (10.6) | NC (53.4-87.0) | 2 (25.0) | 6 (75.0) | 4 (50.0) | 2 (25.0) | 0 (0.0) | 2 (25.0) |
| ESRD on Hemodialysis | 8 | 49.9 (9.80) | NC (35.0-64.0) | 86.3 (16.6) | NC (65.3-113) | 6 (75.0) | 2 (25.0) | 1 (12.5) | 4 (50.0) | 0 (0.0) | 3 (37.5) |

Note: % = n/N × 100; A = Asian; B = Black; F = female; GIST = gastrointestinal stromal tumor; ESRD = end-stage renal disease; M = male; Max = maximum; Min = minimum; MRCC = metastatic renal cell carcinoma; n = number of subjects or patients; N = total number of subjects or patients; NA = not available (Races other than White, Black, or Asian, or that were missing on the Case Report Form, or not allowed to ask per local regulation); NC = not calculated; NET = neuroendocrine tumor; No. = number; SD = standard deviation; W = White.

[a] Demographic characteristics calculated using number of patients included in the intent-to-treat population.

[b] Asian = Asian, Japanese, and Pacific Islander per case report form used in some studies

[c] n = 57

[d] n = 106

Plasma samples were collected in all five studies to determine trough concentrations. For the first three trials a total of 190 patients participated in multiple dose studies providing data for PK evaluations. Of these, 107 were PK evaluable patients with advanced unresectable pNET (41 with carcinoid tumour and 66 with pancreatic NET).

The Study RTKC-0511-015 was an open labelled, two cohort, two stage multicentre Phase II study to investigate the efficacy and safety of single agent sunitinib in patients with NET. Patients were enrolled independently into two cohorts, one cohort of patients with carcinoid tumour and the other cohort of patients with pNET. In this study, patients received at a starting dose of 50 mg sunitinib on Schedule 4/2 (that is, 4 weeks on treatment, 2 weeks off). During the study, pre-dose samples for determination of the $C_{trough}$ of sunitinib and SU012662 were obtained.

For Study A6181047, an open label, uncontrolled multicentre single agent multiple dose Phase II study investigating the efficacy, safety and PK of a morning (am) and evening (pm) dose[3] of sunitinib administered on a continuous daily schedule (CDD) in patients with advanced GIST. In this study patients received sunitinib at a starting dose of 37.5mg once daily on a CDD schedule. During the first 13 cycles of study (4 weeks per cycle) pre-dose blood samples for determination of $C_{trough}$ of sunitinib and SU012662 were obtained.

Study A6181061 was an open label, uncontrolled, multicentre, single agent, multiple dose, Phase II study investigating the efficacy, safety and PK of am and pm dosing of sunitinib administered on a CDD schedule in patients with mRCC. In this study, patients received sunitinib at a starting dose of 37.5mg once daily on a CDD schedule. During the first 13 cycles of the study (4 weeks/cycle) pre-dose samples for the determination of $C_{trough}$ of sunitinib and SU012662 were obtained.

The fourth study (A6181106), was an open label, single dose, parallel group, Phase I study to evaluate the PK and safety of sunitinib in patients with severe renal impairment or end-stage renal disease (ESRD) on haemodialysis. In this study, subjects received a single

[3] Patients were randomised to receive sunitinib in the morning or evening.

50mg oral dose of sunitinib. Serial plasma samples were collected to obtain a full PK profile of sunitinib and its metabolite in this population.

Plasma concentrations of analytes were determined using validated high performance liquid chromatography (HPLC) mass spectrometry.

Review of the PK data from study RTKC-0511-015 involved 107 patients, 41 with carcinoid tumour and 66 with pNET treated with sunitinib. The summary of sunitinib, SU012662 and total drug (sunitinib+SU012662) plasma $C_{trough}$ concentrations at the 50mg dose level on Days 7, 14, 21 and/or 28 of Cycles 1-4 is given in Table 3 and 4.

Table 3 **Summary of Sunitinib, SU012662, and Total Drug Plasma Trough Concentrations by Nominal Time Point Following Administration of Sunitinib 50 mg on Schedule 4/2 (Study RTKC-0511-015 – Carcinoid Tumor Cohort)**

| Day | Cycle | n | Arithmetic Mean (CV%) [Median] | | |
|---|---|---|---|---|---|
| | | | Sunitinib (ng/mL) | SU012662 (ng/mL) | Total Drug (ng/mL) |
| 7 | 1 | 9 | 46.9 (54) [39.4] | 16.8 (53) [12.3] | 63.7 (50) [54.5] |
| | 2 | 8 | 48.5 (46) [43.9] | 16.2 (42) [17.1] | 64.7 (44) [61.0] |
| | 3 | 6 | 47.8 (88) [33.4] | 16.5 (67) [14.4] | 64.3 (81) [50.6] |
| 14 | 1 | 15 | 55.6 (40) [48.8] | 22.2 (39) [22.6] | 77.8 (38) [70.6] |
| | 2 | 14 | 52.3 (38) [51.1] | 20.8 (46) [19.2] | 73.1 (39) [71.6] |
| | 3 | 12 | 49.8 (54) [53.5] | 21.3 (52) [19.5] | 71.2 (52) [70.4] |
| 21 | 1 | 15 | 46.6 (33) [44.3] | 24.6 (40) [24.4] | 71.2 (33) [77.5] |
| | 2 | 9 | 54.8 (67) [51.3] | 25.6 (62) [24.5] | 80.4 (63) [75.0] |
| | 3 | 5 | 64.9 (20) [65.5] | 25.2 (39) [26.6] | 90.2 (19) [91.9] |
| 28 | 1 | 17 | 50.6 (54) [43.1] | 24.1 (49) [20.5] | 74.7 (50) [68.8] |
| | 2 | 14 | 35.8 (58) [34.2] | 16.4 (75) [16.8] | 52.2 (61) [47.3] |
| | 3 | 13 | 41.9 (37) [47.1] | 15.3 (69) [12.4] | 57.2 (42) [58.7] |
| | 4 | 4 | 45.7 (49) [50.8] | 18.2 (109) [12.3] | 63.9 (63) [63.1] |

Source: RTKC-0511-015 CSR, Tables 13.5.1-3.
CV: coefficient of variation; n: number of observations; Total Drug: sunitinib + SU012662.

Table 4 **Summary of Sunitinib, SU012662, and Total Drug Plasma Trough Concentrations by Nominal Time Point Following Administration of Sunitinib 50 mg on Schedule 4/2 (Study RTKC-0511-015 – Pancreatic NET Cohort)**

| Day | Cycle | n | Arithmetic Mean (CV%) [Median] | | |
|---|---|---|---|---|---|
| | | | Sunitinib (ng/mL) | SU012662 (ng/mL) | Total Drug (ng/mL) |
| 7 | 1 | 11 | 47.0 (51) [43.7] | 19.7 (63) [14.3] | 66.7 (52) [62.3] |
| | 2 | 10 | 39.6 (47) [35.2] | 15.3 (26) [14.9] | 54.9 (36) [50.3] |
| | 3 | 6 | 33.6 (48) [29.6] | 18.3 (45) [19.2] | 51.8 (44) [51.3] |
| 14 | 1 | 26 | 58.2 (46) [53.6] | 24.0 (57) [21.5] | 82.2 (45) [74.8] |
| | 2 | 15 | 48.7 (49) [47.8] | 20.5 (33) [22.6] | 69.2 (41) [63.7] |
| | 3 | 24 | 41.8 (50) [40.5] | 19.6 (50) [15.5] | 61.3 (46) [55.4] |
| 21 | 1 | 8 | 37.1 (52) [30.9] | 17.2 (26) [16.9] | 54.3 (40) [50.8] |
| | 2 | 10 | 41.9 (49) [36.6] | 22.1 (44) [23.6] | 64.0 (43) [62.2] |
| | 3 | 8 | 41.9 (41) [43.2] | 21.4 (28) [22.4] | 63.3 (34) [65.0] |
| 28 | 1 | 16 | 38.0 (48) [34.3] | 16.9 (60) [15.6] | 54.8 (49) [49.2] |
| | 2 | 26 | 39.7 (43) [34.0] | 21.0 (42) [20.2] | 60.7 (35) [60.5] |
| | 3 | 19 | 33.5 (44) [29.1] | 18.8 (46) [16.8] | 52.3 (36) [50.9] |
| | 4 | 3 | 25.0 (12) [25.1] | 16.2 (48) [11.9] | 41.2 (20) [39.4] |

Source: RTKC-0511-015 CSR, Tables 13.5.1-3.
CV: coefficient of variation; n: number of observations; Total Drug: sunitinib + SU012662.

As indicated for the carcinoid tumour cohort, mean trough concentrations on Day 28 of Cycles 1-4 for sunitinib, SU012662 and the total concentration ranged from 35.8-50.6ng/ml, 15.3-24.1ng/ml and 52.2-74.7ng/ml, respectively. The inter-subject variability represented by the CV percentage ranged from 37% to 58% for sunitinib and 49%-109%

for SU012662. Additionally, pre-dose mean concentrations on Day 1 of Cycles >1 for sunitinib and SU012662 ranged from 0.38-1.20ng/ml and 0.8-1.95ng/ml, respectively. For the pNET cohort mean trough concentrations on Day 28 of Cycles 1-4 for sunitinib, SU012662 and total drug concentration ranged from 25-39.7ng/ml, 16.2-21ng/ml and 41.2-60.7ng/ml, respectively. The inter-subject variability represented by the CV percentage ranged from 12% - 48% for sunitinib and 42%-50% for SU012662. Mean pre-dose concentrations on Day 1 of Cycle >1 for sunitinib and SU012662 ranged from 0.64-2.17ng/ml and 1.8 – 6.22ng/ml respectively, indicating there was almost a complete washout between cycles.

For the carcinoid tumour cohort, review of plasma concentrations of VEGF, sVEGFR-2, sVEGFR-3 and interleukin-8 (IL-8) revealed that the plasma VEGF concentrations increased during the sunitinib four week on treatment periods with mean ratios to baseline ranging from 6.08 – 10.8 on (Day 28 of Cycles 1-4) but then returned towards baseline levels at the end of each of the two week offtreatment period (mean ratio to baseline ranging from 0.85-2.7 on Day 1 of Cycles 2-4). In contrast, plasma concentrations of both sVEGFR-2 and sVEGFR-3 decreased during the four week sunitinib treatment period, with mean ratio at the baseline ranging from 0.62–0.95 and 0.53–0.6, respectively, on Day 28 of Cycles 1-4 with a return towards baseline concentrations at the end of each two week off-treatment period (mean ratios to baseline ranging from 0.83–0.97 and 0.79–0.87, respectively, on Day 1 of Cycles 2-4). Plasma IL-8 concentrations increased above baseline during the sunitinib treatment periods with mean ratios ranging from 2.12–2.71 (Day 28 of Cycles 1-4). There was a partial return towards baseline IL-8 levels at the end of each two week off treatment period; mean ratios on Day 1 of Cycles 2-4 ranging from 1.46–1.58.

For the pNET cohort, plasma VEGF concentrations increased from baseline during the sunitinib four week on-treatment period; mean ratios to baseline ranged from 5.61-9.47 on Day 28 of Cycles 1-4. VEGF levels returned towards baseline at the end of the two week off-treatment period; mean ratios to baseline ranging from 0.96-1.29 on Days 1 of Cycles 2-4. In contrast, the plasma concentrations of both sVEGFR-2 and sVEGFR-3 decreased during the four week sunitinib treatment period; mean ratios to baseline ranged from 0.64-0.74 and 0.53-0.63, respectively, on Day 28 of Cycles 1-4. These levels returned towards baseline concentrations at the end of each two week off-treatment period; mean ratios to baseline ranged from 0.84-0.92 and 0.83-088, respectively, on Day 1 of Cycles 2-4. Plasma IL-8 concentrations increased above baseline during sunitinib treatment periods with mean ratio on Day 28 of Cycles 1-4 ranging from 1.92-2.82. There was a partial return towards baseline IL-8 concentrations at the end of each two week off-treatment period; mean ratios on Day 1 of Cycles 2-4 ranging from 1.26-1.34.

Evaluator's Comment:

These data have demonstrated that there were no clinically relevant differences observed in the steady state trough sunitinib and SU012662 concentrations in the pNET sub-population as compared to the carcinoid tumour sub-population. Steady state conditions for sunitinib and SU012662 were achieved on Day 14 of Cycle 1 in both cohorts. No disproportionate accumulation of sunitinib or SU012662 was observed in either cohort or cross-cycle. Sunitinib caused increases in VEGF and IL-8 plasma concentrations and decreases in sVEGFR-2 and sVEGFR-3 plasma concentrations in both the pNET and carcinoid tumour sub-populations.

Study A6181047 was an open labelled, uncontrolled, multicentre Phase II study investigating the efficacy, safety and PK of am and pm doses of sunitinib administered on CDD schedule in patients with advanced GIST. Patients were randomised to receive sunitinib in the morning or evening. Patients received sunitinib at a starting dose of

37.5mg every day in repeated 4 week cycles. Pre-dose blood samples on Day 1 of Cycles 1-13 were taken for determination of the trough concentrations of sunitinib and SU012662. In addition, pre-dose blood samples were obtained on Day 1 of Cycles 1-7 and Cycle 10 for the determination of plasma concentrations of VEGF, sVEGFR-2 and sVEGFR-3 and soluble fraction of KIT (sKIT). Samples were analysed using validated methods.

Sixty patients were enrolled in the study; half of these received sunitinib in the morning whereas the other half of the group received their dose in the evening. Summary of sunitinib and SU012662 and total blood plasma trough concentrations are presented in Table 5. Following continuous daily dosing with sunitinib, the mean trough plasma concentrations on Day 1 of Cycles 2-13 ranged between 26.3-41.9ng/ml, 10.7-17.7ng/ml and 37.8-59.6ng/ml for sunitinib, the metabolite and total drug, respectively. Dose corrected trough values for sunitinib, the metabolite and total drug were within 31.4-44ng/ml, 13.1-19ng/ml and 45-62.8ng/ml, respectively.

Table 5 **Summary of Sunitinib, SU012662, and Total Drug Plasma Trough Concentrations on Day 1 of Cycles 2-13 Following Administration of Sunitinib at a Starting Dose of 37.5 mg on Schedule CDD (Study A6181047)**

| Cycle | Arithmetic Mean (CV%) [Median] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Observed $C_{trough}$ | | | | Dose-Corrected[a] $C_{trough}$ | | | |
| | n | Sunitinib (ng/mL) | SU012662 (ng/mL) | Total Drug (ng/mL) | n | Sunitinib (ng/mL) | SU012662 (ng/mL) | Total Drug (ng/mL) |
| 2 | 25 | 39.1 (45) [34.0] | 13.8 (44) [14.5] | 52.9 (42) [45.6] | 25 | 38.4 (49) [34.0] | 13.6 (48) [14.5] | 52.0 (46) [45.6] |
| 3 | 23 | 35.9 (51) [34.8] | 13.6 (50) [14.6] | 49.5 (48) [49.1] | 23 | 37.2 (56) [34.8] | 14.0 (52) [14.6] | 51.2 (52) [49.1] |
| 4 | 22 | 41.9 (30) [41.2] | 17.7 (42) [17.5] | 59.6 (30) [58.7] | 21 | 44.0 (38) [38.4] | 18.8 (47) [18.7] | 62.8 (38) [59.8] |
| 5 | 20 | 38.3 (46) [40.6] | 16.8 (48) [17.0] | 55.1 (44) [57.3] | 18 | 38.6 (51) [37.3] | 17.1 (47) [17.0] | 55.7 (47) [56.5] |
| 6 | 20 | 34.7 (48) [39.7] | 17.6 (51) [17.6] | 52.3 (45) [59.8] | 19 | 38.0 (43) [40.0] | 19.0 (41) [17.7] | 57.0 (37) [59.8] |
| 7 | 19 | 35.9 (44) [36.8] | 17.0 (43) [16.5] | 52.9 (40) [54.4] | 18 | 37.7 (45) [37.2] | 17.7 (39) [17.7] | 55.4 (39) [56.3] |
| 8 | 16 | 36.9 (43) [34.8] | 14.5 (56) [13.7] | 51.4 (43) [52.1] | 14 | 41.7 (47) [38.4] | 16.0 (53) [18.6] | 57.7 (45) [54.7] |
| 9 | 16 | 31.3 (46) [26.7] | 13.4 (52) [13.9] | 44.8 (44) [41.2] | 15 | 34.7 (59) [25.1] | 14.9 (48) [15.3] | 49.6 (52) [42.5] |
| 10 | 16 | 26.3 (43) [25.5] | 11.5 (46) [12.6] | 37.8 (43) [39.5] | 15 | 31.4 (61) [28.4] | 13.6 (50) [13.7] | 45.0 (57) [42.9] |
| 11 | 15 | 29.6 (49) [28.2] | 12.2 (51) [10.9] | 41.8 (46) [40.3] | 15 | 33.6 (49) [31.4] | 13.5 (45) [12.1] | 47.2 (44) [48.5] |
| 12 | 13 | 28.4 (52) [27.6] | 12.8 (58) [13.8] | 41.3 (52) [42.4] | 12 | 34.0 (59) [30.5] | 14.8 (56) [16.0] | 48.8 (56) [48.7] |
| 13 | 5 | 29.4 (25) [29.5] | 10.7 (31) [10.8] | 40.1 (21) [41.3] | 4 | 34.4 (30) [36.3] | 13.1 (34) [13.2] | 47.4 (26) [48.1] |

Source: A6181047 CSR, Tables 13.5.1–6.
CV: coefficient of variation; $C_{trough}$: trough concentration; n: number of observations; Total Drug: sunitinib + SU012662.
[a] For dose-correction, the reference dose was 37.5 mg.

VEGF plasma concentrations increased from baseline after multiple dosing with sunitinib with mean ratio to baseline of 3.19 on Day 1 of Cycle 4. In contrast sVEGFR-2 and sVEGFR-3 and sKIT plasma concentrations decreased from Day 5 after multiple dosing with sunitinib; mean ratio to baseline values of 0.6, 0.62 and 0.73, respectively.

Correlations between mean ratio to baseline of soluble proteins and trough plasma concentrations of sunitinib, its metabolite and total drug concentration were analysed by linear regression. A significant correlation was found between trough plasma sunitinib concentration and plasma VEGF mean ratio to baseline from Cycle 2 Day 1 to Cycle 5 Day 1 with a range of 0.214-0.543 with P<0.001-0.026. Linear regression analysis of the

relationship between total drug trough plasma drug concentration and VEGF mean ratio to baseline also revealed a significant correlation at Day 1 of Cycles 3-5 (P value 0.001-P 0.02). Plasma sVEGFR-2, sVEGFR-3 and sKIT regression analyses revealed little correlation between mean ratio to baseline and plasma drug concentrations.

Evaluator's Comment:

Based on the mean dose corrected trough values of sunitinib, SU012662 and total drug concentration, the PK of sunitinib and SU012662 appeared to be similar (45-62.8ng/ml versus 47.7-65ng/ml for total drug) between the CDD schedule and the Schedule 4-2 in the Phase III study of patients with GIST previously presented. No disproportionate accumulation of sunitinib and SU012662 was observed throughout the study. Sunitinib caused significant increase in VEGF and decrease in sVEGFR-2 and sVEGFR-3 and sKIT plasma concentrations. Significant correlations were observed over multiple treatment cycles between plasma VEGF mean ratios to baseline and trough concentrations of both SU012248 and total drug.

Study A6181061 was an open labelled, non randomised, multicentre Phase II efficacy and safety study of sunitinib administered on a CDD schedule in patients with cytokine refractory mRCC. The main objective of study was to determine sunitinib and SU012662 trough concentrations for evaluation of steady state PK. Patients were randomised to receive sunitinib in the morning or in the evening. Patients received sunitinib at a starting dose of 37.5mg once per day in repeated 4-week cycles. Pre-dose blood samples on Day 1 of Cycles 1-13 for the determination of trough concentrations of sunitinib and SU012662 were obtained for patients randomised to morning dosing only. These samples were analysed using validated methods.

A total 107 patients were enrolled on study, 54 to the morning dose and 53 to the evening sunitinib dose. Following continuous daily dosing of sunitinib the mean trough plasma concentrations for sunitinib, the metabolite and total drug were 30-46.2ng/ml, 11.1-18.4ng/ml and 41.6-64.6ng/ml, respectively. Dose corrected trough values for sunitinib, the metabolite and total drug were 30.7-48.2ng/ml, 11.9-18.7ng/ml and 43.7-65.6ng/ml, respectively.

VEGF plasma concentrations increased from the baseline after multiple dosing with sunitinib (mean ratio to baseline of 2.43 on Day 1 of Cycle 2). In contrast, sVEGFR-2 and sVEGFR-3 plasma concentrations decreased after multiple dosing with sunitinib; mean ratios to baseline were 0.63 and 0.57 for sVEGFR-2 and sVEGFR-3, respectively, on Day 1 of Cycle 2.

Correlations between ratios to baseline of each soluble protein and trough concentrations of sunitinib, the metabolite and total drug were analysed by linear regression and there was a significant correlation between trough plasma sunitinib concentrations and ratio to baseline of each soluble protein in Cycle 2 Day 1 (VEGFR P=0.004, sVEGFR-2 P=0.001 and sVEGFR-3 P=0.002).

Evaluator's Comment:

Following continuous daily dosing, steady state sunitinib and SU012662 concentrations were reached within the first cycle. No disproportionate accumulation of sunitinib and SU012662 were noted throughout the study. Based on the mean dose corrected trough values for sunitinib, its metabolite and total drug, the PK of sunitinib and SU012662 appeared to be similar (for example, 43.7-65.6ng/ml versus 60.6-65.4ng/ml for total drug) between this CDD schedule and Schedule 4/2 as previously discussed above (see Phase II study). Sunitinib caused significant increases in VEGF and decreases in sVEGFR-2 and sVEGFR-3 plasma concentrations. Significant correlations were observed between plasma

VEGF, sVEGFR-2 and sVEGFR-3 ratios to baseline trough concentrations of both sunitinib and total drug.

Study A6181106 was an open labelled, single-dose, parallel group, Phase I study that evaluated the PK and safety of single-dose sunitinib in subjects with severe renal impairment or ESRD on haemodialysis. The main objective of the study was to evaluate the effects of severe renal impairment and haemodialysis on the single-dose PK of sunitinib and SU012662. Three treatment groups with varying degrees of renal function determined by creatinine clearance ($CL_{cr}$) were enrolled. Group 1 were subjects with normal renal function ($CL_{cr}$ >80mls/minute), Group 2 were subjects with severe renal impairment but not requiring dialysis ($CL_{cr}$ <30mls/minute) and Group 3 were subjects with ESRD requiring haemodialysis. Patients received a single 50 mg dose of sunitinib. Serial PK blood samples were taken at specified times and analysed using a validated method for sunitinib and SU012662 concentrations.

A total of 24 patients (8 patients per group) were enrolled in the study. All patients completed the study and were included in the PK analysis. Summary of the PK parameters in each renal function group are given in Table 6. Mean PK parameters for sunitinib and SU012662 in patients with severe renal impairment were similar to those in patients with normal renal function. However, inter-subject variability in PK parameters was greater in patients with severe renal impairment (60% versus 28% for $AUC_{infinity}$[4]). The geometric mean plasma exposure to sunitinib and SU012662 was lower in subjects with ESRD requiring haemodialysis compared with subjects with normal renal function (by 30-38% for $C_{max}$ and by 31-47% for $AUC_{infinity}$). However the mean terminal $T_{1/2}$ for sunitinib and SU012662 in patients with ESRD on dialysis was similar to those with normal renal function. In subjects with ESRD the mean fraction of the dose removed by haemodialysis was 0.027% and 0.035% for sunitinib and SU012662, respectively.

Evaluator's Comment:

The PK of sunitinib and SU012662 were not affected by severe renal impairment. This finding is consistent with the fact that renal elimination is only a minor route of elimination of both compounds. The total exposure to sunitinib and its metabolite was lower in ESRD subjects on haemodialysis (by 47% and 31%, respectively), most likely due to a lower sunitinib absorption in the ESRD subjects. Haemodialysis had no effect on sunitinib and SU012662 exposure. A single 50mg oral dose of sunitinib was safe and well tolerated in all subjects irrespective of renal function. In subjects with severe renal impairment no adjustment to the starting dose of sunitinib appears to be necessary. In ESRD subjects the commonly used starting dose of sunitinib may also be used at the initiation of therapy. Any dose modification of sunitinib treatment should still be driven primarily by patients' safety and tolerability.

Study A6181079 was a Phase I study evaluating the PK of sunitinib in patients with impaired hepatic function. It was an open labelled, single dose, parallel group study. Three groups of subjects (eight subjects per group) with the following degrees of hepatic function were enrolled: Group 1 subjects had normal hepatic function, Group 2 subjects had mild hepatic impairment (Child-Pugh Classification A Score 5-6[5]) and Group 3 subjects had moderate hepatic impairment (Child-Pugh Classification B, Score 7-9). All

[4] area under the plasma concentration time curve from time zero to infinity.

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

patients received a single 50mg dose of sunitinib. Pre-dose PK blood samples were collected in each group at regular intervals for a total of seven days after dosing.

Sunitinib was detected within one hr after dosing and remained quantifiable until at least Day 15 in all subjects except one. These were quantifiable at all following time points to at least Day 17. The pharmacokinetic parameters for sunitinib, its metabolite and total drug concentration are to be found in Tables 7, 8 and 9. It was shown that the pharmacokinetics of sunitinib and metabolite were variable in both normal and hepatic impaired subjects in this study. In the case of sunitinib, inter-subject co-efficient of variation of measures of total exposure range from 12.8% - 40.3% and were measures of unbound exposure ranged from 13.8% - 40.5%. For the metabolite, inter-subjects CVs for total exposure ranged from 25.4% - 55.2% and non-measures of unbound exposure ranged from 25.9% - 52.6%.

Table 6 **Summary of Sunitinib and SU012662 Plasma PK Parameter Values Following Administration of a Single Oral 50-mg Sunitinib Dose (Study A6181106)**

| PK Parameter[a] | Arithmetic Mean (CV%) [Median] | | | GMR[b] | |
|---|---|---|---|---|---|
| | Normal Renal Function (n=8) Group 1 | Severe Renal Impairment (n=8) Group 2 | End-Stage Renal Disease (n=8) Group 3 | Group 2 vs. 1 | Group 3 vs. 1 |
| **Sunitinib** | | | | | |
| $T_{max}$ (hr) | 7.0 (6.0–12.0) | 8.0 (6.0–12.0) | 7.0 (6.0–12.0) | 0 | 0 |
| $C_{max}$ (ng/mL) | 26.1 (25) [24.4] | 24.6 (39) [23.1] | 16.1 (19) [16.8] | 0.90 | 0.62 |
| $AUC_{48}$ (ng*hr/mL) | 809 (20) [788] | 764 (42) [720] | 489 (20) [502] | NA | 0.60 |
| $AUC_{last}$ (ng*hr/mL) | 1892 (28) [1838] | 1781 (59) [1543] | 998 (29) [1018] | 0.85 | 0.53 |
| $AUC_{\infty}$ (ng*h/mL) | 1917 (28) [1858] | 1815 (60) [1561] | 1012 (28) [1033] | 0.86 | 0.53 |
| $t_{1/2}$ (hr) | 77.9 (11) [79.1] | 80.3 (20) [80.7] | 69.9 (17) [72.7] | 1.02 | 0.89 |
| CL/F (L/hr) | 28.0 (28) [26.9] | 35.5 (48) [33.5] | 53.6 (32) [48.6] | 1.17 | 1.90 |
| $V_z$/F (L) | 3106 (27) [3071] | 4002 (47) [3707] | 5172 (16) [5142] | 1.19 | 1.69 |
| $F_u$ | 0.105 (47) [0.096] | 0.116 (61) [0.086] | 0.088 (18) [0.088] | 1.07 | 0.90 |
| $C_{max,u}$ (ng/mL) | 2.72 (46) [2.69] | 2.94 (69) [2.47] | 1.39 (20) [1.25] | 0.96 | 0.56 |
| $AUC_{\infty,u}$ (ng*h/mL) | 191 (41) [163] | 230 (97) [173] | 87.5 (30) [82.0] | 0.91 | 0.48 |
| $F_d$ (%) | NA | NA | 0.027 (-107) | NA | NA |
| **SU012662** | | | | | |
| $T_{max}$ (hr) | 6.0 (6.0–12.0) | 6.0 (4.0–12.0)[b] | 6.0 (4.0–36.0) | -0.075 | 0 |
| $C_{max}$ (ng/mL) | 5.73 (23) [5.88] | 4.69 (36) [4.51] | 4.07 (29) [3.77] | 0.80 | 0.70 |
| $AUC_{48}$ (ng*hr/mL) | 196 (16) [202] | 153 (43) [150] | 135 (20) [137] | NA | 0.69 |
| $AUC_{last}$ (ng*hr/mL) | 719 (14) [734] | 580 (41) [590] | 504 (21) [518] | 0.75 | 0.69 |
| $AUC_{\infty}$ (ng*h/mL) | 770 (14) [781] | 629 (42) [622] | 535 (22) [550] | 0.76 | 0.69 |
| $t_{1/2}$ (hr) | 125 (8) [122] | 130 (21) [130] | 111 (12) [109] | 1.02 | 0.89 |
| $F_u$ | 0.221 (45) [0.187] | 0.241 (64) [0.180] | 0.144 (16) [0.148] | 1.06 | 0.70 |
| $C_{max,u}$ (ng/mL) | 1.24 (46) [1.10] | 1.03 (42) [0.949] | 0.601 (41) [0.555] | 0.84 | 0.49 |
| $AUC_{\infty,u}$ (ng*h/mL) | 169 (45) [166] | 144 (54) [124] | 77.9 (33) [68.8] | 0.80 | 0.48 |
| $F_d$ (%) | NA | NA | 0.035 (-206) | NA | NA |

Source: A6181106 CSR, Tables 13.5.2.1, 13.5.2.3, 13.5.3.1-4, 13.5.4.1-4

$AUC_{48}$: area under plasma concentration-time curve from time zero to 48 hours post-dose; $AUC_{last}$: area under plasma concentration-time curve from time zero to the last measurable sampling time point; $AUC_{\infty}$: area under plasma concentration-time curve from time zero to infinity; CL: total body clearance; $AUC_{\infty,u}$: area under unbound plasma concentration-time curve from time zero to infinity; CL/F: oral clearance; $C_{max}$: maximum concentration; $C_{max,u}$: unbound maximum concentration; CV: coefficient of variation; $F_u$: fraction unbound; $F_d$ (%): percent of the administered dose dialyzed; GMR: geometric mean ratio; n: number of subjects with observations; NA: not available or not applicable; $t_{1/2}$: apparent elimination half-life; $T_{max}$: time to maximum concentration; $V_z$/F: apparent volume of distribution

[a] Arithmetic means (coefficients of variation, %) are presented, except for $T_{max}$ (medians [ranges] are presented)

[b] Ratio of adjusted geometric means between groups, except for $T_{max}$ (median differences are presented)

Table 7

**Pharmacokinetic Parameters for Sunitinib in Plasma**

| Parameter | Geometric Mean (95% Confidence Interval) | | |
|---|---|---|---|
| | Normal N=7 | Mild N=8 | Moderate N=8 |
| SU011248 Total | | | |
| $AUC_{inf}$ (ng·h/mL) | 1368.7 (1242.7, 1507.5) | 1514.2 (1369.2, 1674.6) | 1477.2 (1431.0, 1524.8) |
| $AUC_{last}$ (ng·h/mL) | 1354.8 (1228.8, 1493.7) | 1484.6 (1344.8, 1639.0) | 1454.7 (1408.3, 1502.5) |
| $C_{max}$ (ng/mL) | 21.9 (19.9, 24.0) | 23.3 (22.2, 24.4) | 22.7 (21.4, 24.0) |
| $T_{max}$ (h)[a] | 8.1 (6.0, 16.0) | 8.0 (4.0, 12.0) | 10.0 (1.0, 16.0) |
| $T_{1/2}$ (h) | 63.8 (61.7, 65.9) | 79.5 (75.3, 83.9) | 79.2 (73.9, 84.9) |
| CL/F (L/h) | 36.5 (33.2, 40.2) | 33.0 (29.9, 36.5) | 33.8 (32.8, 34.9) |
| SU011248 Unbound | | | |
| Fu (%) | 9.8 (9.6, 10.1) | 8.0 (7.7, 8.4) | 9.0 (8.8, 9.2) |
| $AUC_{inf,u}$ (ng·h/mL) | 134.5 (124.3, 145.5) | 121.3 (111.5, 131.9) | 132.7 (128.2, 137.4) |
| $AUC_{last,u}$ (ng·h/mL) | 133.1 (122.9, 144.2) | 118.9 (109.6, 129.0) | 130.7 (126.3, 135.2) |
| $C_{max,u}$ (ng/mL) | 2.2 (2.0, 2.3) | 1.9 (1.8, 2.0) | 2.0 (1.9, 2.1) |

Data source: CSR Summary Table 13.5.2.1
Note: Data for Subject 10021030 were excluded.
[a] Median (minimum, maximum) is presented for $T_{max}$ instead of Geometric Means (95% CI).

Table 8 **Pharmacokinetic Parameters for SU012662 in Plasma**

| Parameter | Geometric Mean (95% Confidence Interval) | | |
|---|---|---|---|
| | Normal N=7 | Mild N=8 | Moderate N=8 |
| SU012662 Total | | | |
| $AUC_{inf}$ (ng·h/mL) | 559.4 (517.8, 604.4) | 491.9 (459.7, 526.3) | 505.1 (461.4, 552.9) |
| $AUC_{last}$ (ng·h/mL) | 530.7 (489.8, 575.0) | 456.4 (428.5, 486.1) | 475.0 (432.0, 522.3) |
| $C_{max}$ (ng/mL) | 4.3 (4.0, 4.7) | 4.3 (4.0, 4.7) | 4.3 (3.7, 5.0) |
| $T_{max}$ (h)[a] | 6.1 (6.0, 12.0) | 6.0 (4.0, 48.0) | 6.0 (1.0, 36.0) |
| $T_{1/2}$ (h) | 110.9 (107.1, 114.7) | 121.9 (114.4, 129.8) | 112.6 (107.4, 118.1) |
| SU012662 Unbound | | | |
| Fu (%) | 16.0 (15.5, 16.6) | 13.5 (13.0, 14.1) | 15.6 (15.4, 15.7) |
| $AUC_{inf,u}$ (ng·h/mL) | 89.7 (82.8, 97.2) | 66.6 (62.6, 70.9) | 78.6 (72.1, 85.7) |
| $AUC_{last,u}$ (ng·h/mL) | 85.1 (78.4, 92.3) | 61.8 (58.2, 65.6) | 73.9 (67.5, 81.0) |
| $C_{max,u}$ (ng/mL) | 0.7 (0.6, 0.8) | 0.6 (0.5, 0.6) | 0.7 (0.6, 0.8) |

Data source: CSR Summary Table 13.5.2.2
Note: Data for Subject 10021030 were excluded.
[a] Median (minimum, maximum) is presented for $T_{max}$ instead of Geometric Means (95% CI).

Table 9 **Pharmacokinetic Parameters for Total Drug (Sunitinib + SU012662) in Plasma**

| Parameter | Geometric Mean (95% Confidence Interval) | | |
|---|---|---|---|
| | Normal N=7 | Mild N=8 | Moderate N=8 |
| Total Drug* | | | |
| $AUC_{inf}$ (ng·h/mL) | 1937.8 (1784.4, 2104.4) | 2001.9 (1828.4, 2191.9) | 1999.1 (1940.5, 2059.4) |
| $AUC_{last}$ (ng·h/mL) | 1912.6 (1759.9, 2078.4) | 1956.1 (1794.1, 2132.7) | 1958.4 (1896.8, 2022.0) |
| $C_{max}$ (ng/mL) | 26.0 (23.8, 28.5) | 27.3 (26.0, 28.7) | 26.7 (25.0, 28.6) |
| $T_{max}$ (h)[a] | 6.1 (6.0, 12.0) | 8.0 (4.0, 12.0) | 8.0 (1.0, 16.0) |

Data source: CSR Summary Table 13.5.2.3
*As SU011248 and SU012662 have different Fu, only total (bound + unbound) PK parameters are presented.
Note: Data for Subject 10021030 were excluded.
[a] Median (minimum, maximum) is presented for $T_{max}$ instead of Geometric Means (95% CI).

Results of statistical comparisons of sunitinib, its metabolite and total drug pharmacokinetic parameters between study groups are summarised in Tables 10, 11 and 12.

Table 10 **Results of Statistical Comparisons of Plasma Pharmacokinetic Parameters Between Study Groups for Sunitinib**

| Parameter | Geometric Least Squares Mean Ratio (90% Confidence Interval) | |
|---|---|---|
| | Mild/Normal | Moderate/Normal |
| Sunitinib Total | | |
| $AUC_{inf}$ (ng·h/mL) | 1.11 (0.84, 1.47) | 1.08 (0.81, 1.43) |
| $AUC_{last}$ (ng·h/mL) | 1.10 (0.83, 1.45) | 1.07 (0.81, 1.42) |
| $C_{max}$ (ng/mL) | 1.06 (0.85, 1.34) | 1.04 (0.82, 1.30) |
| $T_{max}$ (h)[a] | 0.35 (0.73) | -0.23 (0.82) |
| $T_{1/2}$ (h) | 1.25 (1.03, 1.51) | 1.24 (1.02, 1.51) |
| CL/F (L/h) | 0.90 (0.68, 1.20) | 0.93 (0.70, 1.23) |
| Sunitinib Unbound | | |
| Fu (%) | 0.82 (0.73, 0.92) | 0.91 (0.81, 1.03) |
| $AUC_{inf,u}$ (ng·h/mL) | 0.90 (0.71, 1.14) | 0.99 (0.78, 1.25) |
| $AUC_{last,u}$ (ng·h/mL) | 0.89 (0.71, 1.13) | 0.98 (0.78, 1.24) |
| $C_{max,u}$ (ng/mL) | 0.87 (0.71, 1.07) | 0.95 (0.77, 1.17) |

Data source: CSR Summary Tables 13.5.3.1 – 13.5.3.6 and 13.5.4.1 – 13.5.4.4
Note: Data for Subject 10021030 were excluded.
[a] Wilcoxon Z-score (p-value) is presented for $T_{max}$ instead of Geometric Least Squares (LS) Mean Ratio (90% CI).

Table 11 **Results of Statistical Comparisons of Plasma Pharmacokinetic Parameters Between Study Groups for SU012662**

| Parameter | Geometric Least Squares Mean Ratio (90% Confidence Interval) | |
|---|---|---|
| | Mild/ Normal | Moderate/ Normal |
| SU012662 Total | | |
| $AUC_{inf}$ (ng·h/mL) | 0.88 (0.67, 1.16) | 0.90 (0.69, 1.19) |
| $AUC_{last}$ (ng·h/mL) | 0.86 (0.65, 1.14) | 0.90 (0.68, 1.18) |
| $C_{max}$ (ng/mL) | 1.00 (0.67, 1.48) | 0.99 (0.66, 1.46) |
| $T_{max}$ (h)[a] | 2.16 (0.03) | 0.70 (0.48) |
| $T_{1/2}$ (h) | 1.10 (0.92, 1.31) | 1.02 (0.85, 1.21) |
| SU012662 Unbound | | |
| Fu (%) | 0.84 (0.76, 0.94) | 0.97 (0.87, 1.09) |
| $AUC_{inf,u}$ (ng·h/mL) | 0.74 (0.57, 0.97) | 0.88 (0.67, 1.14) |
| $AUC_{last,u}$ (ng·h/mL) | 0.73 (0.55, 0.95) | 0.87 (0.66, 1.14) |
| $C_{max,u}$ (ng/mL) | 0.84 (0.56, 1.26) | 0.96 (0.64, 1.43) |

Data source: CSR Summary Tables 13.5.5.1 – 13.5.5.5 and 13.5.6.1 – 13.5.6.4
Note: Data for Subject 10021030 were excluded.
[a] Wilcoxon Z-score (p-value) is presented for $T_{max}$ instead of Geometric LS Mean Ratio (90%CI).

Table 12 **Results of Statistical Comparisons of Plasma Pharmacokinetic Parameters Between Study Groups for Total Drug (Sunitinib + SU012662)**

| Parameter | Geometric Least Squares Mean Ratio (90% Confidence Interval) | |
|---|---|---|
| | Mild/ Normal | Moderate/ Normal |
| Total Drug (sunitinib + SU012662) | | |
| $AUC_{inf}$ (ng·h/mL) | 1.03 (0.80, 1.33) | 1.03 (0.80, 1.32) |
| $AUC_{last}$ (ng·h/mL) | 1.02 (0.80, 1.31) | 1.02 (0.80, 1.31) |
| $C_{max}$ (ng/mL) | 1.05 (0.83, 1.33) | 1.03 (0.81, 1.30) |
| $T_{max}$ (h)[a] | -0.29 (0.77) | -0.52 (0.60) |

Data source: CSR Summary Tables 13.5.7.1 – 13.5.7.4
Note: Data for Subject 10021030 were excluded.
[a] Wilcoxon Z-score (p-value) is presented for $T_{max}$ instead of Geometric LS Mean Ratio (90% CI).

Pairwise comparisons demonstrated that the systemic exposure to sunitinib, its metabolite and total drug was not significantly different in subjects with mild and

moderate hepatic impairment compared with normal subjects. Median $T_{max}$ was not significantly different in normal subjects (median $T_{max}$ of 8.1 hr) compared to subjects with mild impairment (median $T_{max}$ of 8 hr) or moderate impairment (median $T_{max}$ of 10 hr). Median $T_{max}$ for metabolite was also similar in all three study groups (6-6.1 hr) while other ranges were wide. The mean $T_{1/2}$ for sunitinib was slightly longer in subjects with hepatic impairment (79.2-79.5 hr) compared with normal subjects (63.8 hr). Point estimates of the geometric least square mean ratio mild to normal and moderate to normal for the $T_{1/2}$ for sunitinib fell within the 80-125% range. The $T_{1/2}$ for SU012662 was similar across groups (112.6-121.9 hr in subjects with hepatic impairment and 110.9 hr in normal subjects). The oral clearance (CL-F) of sunitinib was not significantly different in subjects with hepatic impairment (33-33.8 litres/hr) compared with normal subjects (36.5 litres/hr).

The plasma unbound fractions of sunitinib and SU012662 were slightly lower in the hepatic impaired groups compared with the normal liver function group. For sunitinib, the unbound fraction in the hepatic impaired group was 8-9% compared with 9.8% in the normal group. For SU012662, the unbound fraction in the hepatic impaired groups was 13.5-15.6% which can be compared with 16% in the normal group. No significant differences between the groups in plasma protein binding can be concluded given the intrinsic variability of the protein binding assay.

Pairwise comparisons of unbound PK parameters demonstrated unbound exposure to sunitinib was not significantly changed in subjects with mild and moderate hepatic impairment compared with normal subjects. SU012662 unbound PK parameters were also similar in hepatic impaired subjects compared with normal subjects.

Evaluator's Comment:

Mean sunitinib and metabolite PK parameters were similar between patients with hepatic impairment and normal subjects. Hence, sunitinib dose adjustments are not necessary for patients with mild to moderate hepatic impairment.

## Drug Interactions

No new studies were submitted under this heading.

## Pharmacodynamics

No new studies were submitted under this heading.

## Efficacy

The clinical efficacy presented in this submission involves data to support the use of sunitinib in the treatment of patients with pNET. This involves two clinical trials with the pivotal study being A6181111.

The supportive study (RTKC-0511-015) was an open labelled two cohort two stage Phase II study of sunitinib in subjects with advanced unresectable pNET (carcinoid tumour or pancreatic islet cell tumour). The data from patients with pancreatic islet cell tumour are included in this review.

Pivotal study A6181111 was a randomised double blind Phase III study of sunitinib versus placebo in subjects with progressive advanced metastatic well-differentiated pancreatic islet cell tumour. It was a multicentre trial conducted in 42 centres worldwide. The study was initiated on 7 June 2007 and completed on 15 April 2009.

The primary objective of the pivotal trial was to compare the progression-free survival (PFS) in patients with pancreatic islet cell tumours treated with sunitinib at a starting dose of 37.5mg daily as a CDD schedule to those receiving placebo.

Secondary objectives included to compare overall survival (OS) between subjects receiving sunitinib and those receiving placebo; to compare objective response (OR) rate between subjects receiving sunitinib and those receiving placebo; to compare duration of response (DR) between subjects receiving sunitinib and those receiving placebo among those subjects achieving a response; to assess time to response (TTR) for subjects receiving sunitinib and those receiving placebo and to assess patients reported outcomes (PRO).

Patients who were randomised in a one to one fashion to receive either sunitinib 37.5mg/day on a continuous daily schedule or matching placebo. Subjects on both treatment arms received best supportive care in addition to the standard treatment. The primary endpoint of the study was PFS. Patients were to receive study treatment till documentation of objective disease progression, unacceptable toxicity or death. At the time of disease progression patients who were randomised to placebo were unblinded and offered access to sunitinib treatment in one of two separate open labelled extension studies.

The study was designed to detect a 50% improvement in median PFS with a target enrolment of 340 subjects. An interim analysis was planned when 130 events had occurred and the final analysis was to be conducted when 260 events had occurred. The conduct of the study was overseen by an independent Data Monitoring Committee (DMC).

It should be noted that after 73 PFS events had occurred, the independent DMC determined the study had met its primary endpoint early and recommended that the study be stopped and that the treatment assignments be unblinded. The sponsor subsequently offered access to open labelled sunitinib for all study subjects in one of two extension studies.

Inclusion criteria included patients with histologically or cytologically proven diagnosis of well-differentiated pancreatic islet cell tumour with disease progression within the past year. Patients had to have at least one measurable target lesion for further evaluation according to RECIST[6] and Eastern Co-operative Oncology Group performance status 0 or 1[7]. Patients were excluded if they had current treatment with any chemotherapy, chemo embolisation therapy, immunotherapy or investigational anti-cancer agent other than somatostatin analogues or prior treatment with any tyrosine kinase inhibitors or antivascular endothelial growth factor angiogenic inhibitors.

As previously indicated the primary efficacy endpoint was progression free survival. Secondary efficacy endpoints were OS, OR, TTR and DR. Tumour assessments were performed by the local study site for determination of PFS and other endpoints. Each

[6] RECIST: The Response Evaluation Criteria in Solid Tumours (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response using X-ray, CT and MRI.

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

tumour assessment of subjects were characterised as having complete response, partial response, stable disease or progressive disease.

Other evaluations included an assessment of tumour cell expression of the proliferation marker Ki-67 based on previous tumour biopsy results or previous surgical resections and this was provided at screening.

The validated EORTC of cancer quality of life questionnaire (EORTC- QLQ) C30 was selected to measure PROs. Subjects completed the questionnaire prior to administration of study drug on Day 1 and then every four weeks thereafter as well as the end of treatment or withdrawal.

Primary analysis of PFS was performed in the intent to treat population based on the investigator's assessment of tumour response. An unstratified log-rank (two-sided) was used to compare PFS time between two treatment arms with normal significance levels of 0.049 (two-sided) for the primary endpoint analysis. The Kaplan-Meier method was used to obtain the estimates of median event free time associated with each treatment arm and with the corresponding two-sided confidence intervals. The hazard ratio of 95% CI was estimated.

The number and percentage of subjects achieving OR was summarised along with corresponding exact two-sided 95% CI calculated using a method based on the F distribution. Fishers exact test was used to compare OR between the two treatment arms. DR, TTR and OS were to be summarised using Kaplan-Meier methods and displayed graphically where appropriate.

Baseline Ki-67 indices for subjects on the sunitinib and placebo arms with available Ki-67 values were analysed descriptively and the significance of the difference between treatment arms was assessed using Wilcoxon rank sum test. In each treatment arm, PFS and OS were analysed by the Kaplan-Meier method after stratification by Ki-67 index.

EORTC-QLQ-C30 data were described using summary statistics and analysed using repeated measures mixed effects model.

A total of 171 subjects were randomised to study treatment (sunitinib or placebo) and 165 of these were treated. A total of six subjects were randomised but not treated. All but one of these had completed screening but a decision to terminate the study had been made prior to the initiation of treatment.

The most common reasons for discontinuation were disease progression or relapse (22.1% of sunitinib patients and 55.3% of placebo patients), study terminated by sponsor (47.7% of sunitinib patients and 18.8% of placebo patients) and adverse events (17.4% of sunitinib patients and 8.2% of placebo patients).

Most patients (99.4%) had a primary diagnosis of pancreatic neuroendocrine tumours (malignant neoplasms of Islets of Langerhans). Approximately half of the randomised patients (54.3%) had a histological classification of non-functioning tumour that was not secreting neuropeptides while 26.9% had a functioning tumour and 22.8% had a functioning tumour of unknown histological type. The most common functioning tumour was gastrinoma involving 11.1% of patients.

Analysis of results revealed a clinically significant improvement in PFS the primary endpoint of the study observed in favour of sunitinib in subjects with progressive and well-differentiated pNET. This is summarised in Table 13 and graphically presented in Figure 1. The final analysis included a total of 81 baseline events; 30 events occurring in the sunitinib arm and 51 events occurred in the placebo arm. Seventy five events, 27 in the sunitinib arm and 48 in the placebo arm, were disease progression, while six (three in

each arm), were deaths without objective tumour progression. The median progression free survival was 11.4 months in the sunitinib arm and 5.5 months in the placebo arm (hazard ratio of 0.418 and P=0.0001).

Table 13 **Analyses of Progression-Free Survival in Study A6181111 – Intent-to-Treat Population**

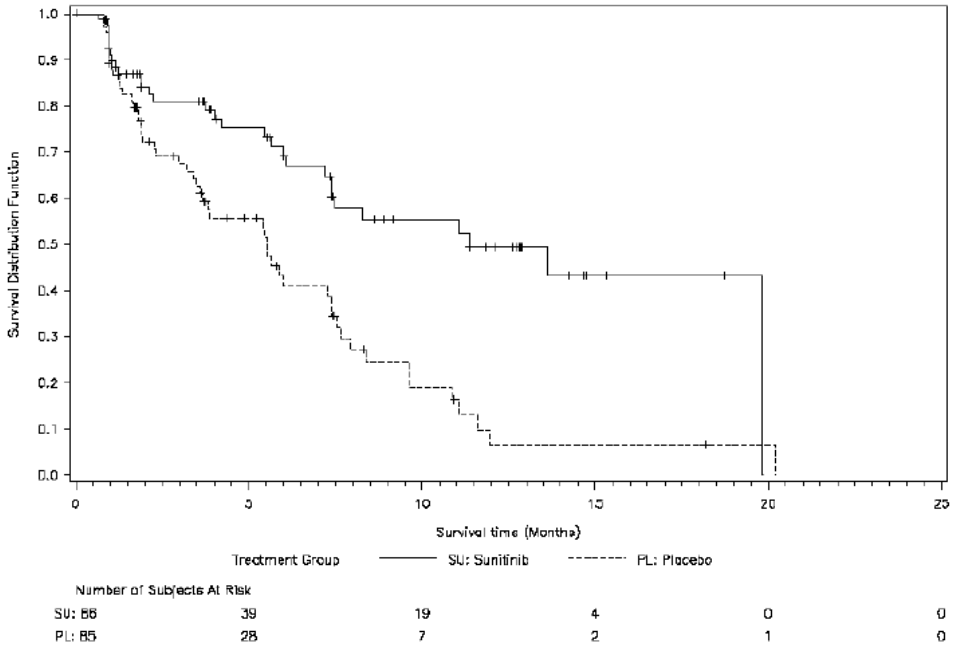
| | Primary PFS Analysis | | Sensitivity Analysis of PFS | | | |
|---|---|---|---|---|---|---|
| | | | Analysis 1 | | Analysis 2 | |
| | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) | Sunitinib (N=86) | Placebo (N=85) |
| Number with Event | 30 | 51 | 30 | 51 | 30 | 55 |
| Type of Event | | | | | | |
| Objective tumor 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 | |

Source: CSR A6181111, Tables 13.4.1, 13.4.2.1, and 13.4.2.2

[a] Estimated from the Kaplan-Meier curve.
[b] Calculated from the product-limit method.
[c] Based on the Brookmeyer-Crowley method.
[d] Based on the Cox proportional hazards model.
[e] Log-rank test statistic and 2-sided p-value from the unstratified log-rank test.

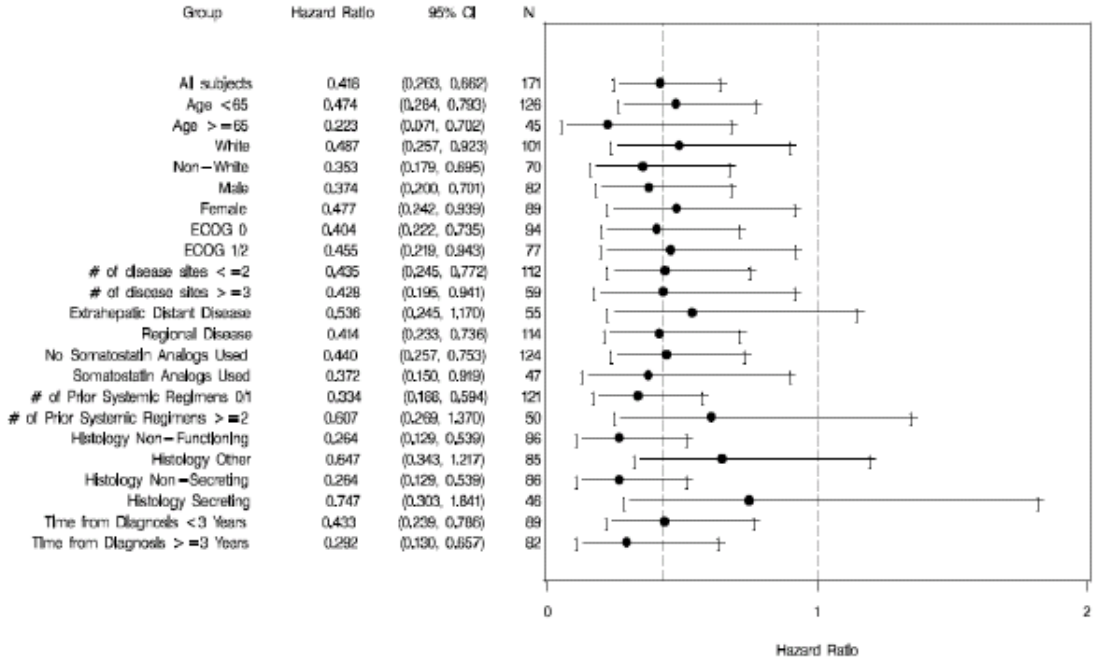
N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease; CI = confidence interval.

Figure 1 **Kaplan-Meier Curves of Progression-Free Survival in Study A6181111 (Intent-to-Treat Population)**




The influence of the various baseline characteristics on the treatment effect was analysed by Cox proportional hazard analysis (see Figure 2). These results show that the hazard ratio favours sunitinib in all sub-groups and were statistically significant in all sub-groups except in the extra-hepatic distant disease, number of prior systemic regimens being >2 and histology other than non-functioning and histology secreting sub-groups. The influence of baseline factors on treatment effect was further analysed and showed that the hazard ratio for overall treatment effect was 0.418 and was similar when controlling for each individual baseline factor.

Figure 2 **Results of Cox Proportional Hazards Analysis of Progression-Free Survival on Study A6181111 – Intent-to-Treat Population**




Source: CSR A6181111, Figure 14.6.3
Sunitinib arm vs placebo arm: assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the sunitinib arm; a hazard ratio greater than 1 indicates a reduction in hazard rate in favor of the placebo arm.
Non-White includes subjects for whom race was not recorded due to local regulations.
Regional disease includes subjects for whom disease was limited to the pancreas, lymph node (of any location), and liver.
Somatostatin analog used includes subjects treated before and/or during the study.
Nonfunctioning was reported by the investigator.
Histology other includes subjects with secreting tumor and tumor unknown secreting status.

Review of the difference in baseline Ki-67 index between the treatment arms revealed that these were not statistically significant by Wilcoxon rank-sum test. For the 72 subjects with available Ki-67 indices, the hazard ratio for treatment effect on PFS was 0.490 with a log-rank P=0.0253, which was consistent with that observed for the ITT population. This is illustrated in Table 14.

Table 14 **Comparison of PFS between Treatments in Subjects with Ki-67 Index ≤5% and Ki-67 Index >5%**

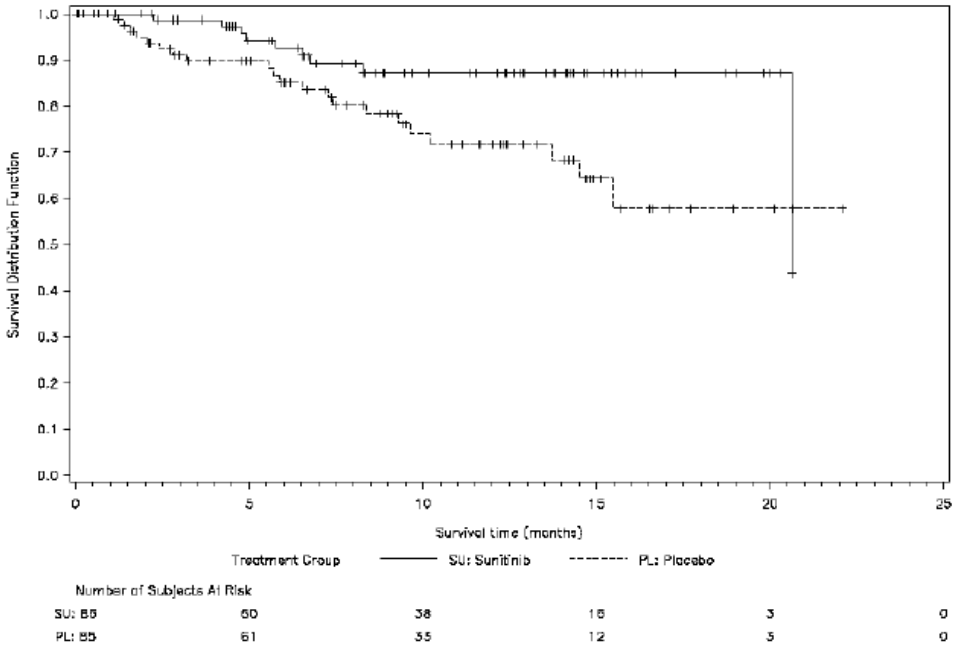
| | Ki-67 ≤ 5% | Ki-67 > 5% |
|---|---|---|
| **Sunitinib** | | |
| N | 23 | 13 |
| Median PFS[a] (weeks) (95% CI)[b] | 48.1 (17.4 – 59.1) | 9.7 (8.1 - **) |
| **Placebo** | | |
| N | 20 | 16 |
| Median PFS[a] (weeks) (95% CI)[b] | 24.0 (8.3 – 36.4) | 14.7 (5.6 – 24.6) |
| **Hazard ratio[c] (sunitinib vs placebo) (95% CI)** | 0.378 (0.155 – 0.922) | 0.634 (0.235 – 1.711) |
| P-value* | 0.0259 | 0.3638 |

Source: CSR A6181111, Table 13.12.7.
[a] Kaplan-Meier estimate.
[b]Based on the Brookmeyer-Crowley method.
[c]Based on the Cox proportional hazards model.
*2-sided p-value from the unstratified log-rank test.
**Unable to calculate.
CI = confidence interval; PFS = progression-free survival.

An exploratory analysis of subjects with Ki-67 index values =/<5% (Kaplan Meier analysis) demonstrated that PFS was significantly longer on the sunitinib arm; median PFS of 48.1 weeks compared to the placebo arm median PFS of 24 weeks (P=0.0259). Mean and median Ki-67 index values were higher for subjects with a best overall response of PD or SD =/<90 days than for subjects with SD >90 days or PR or CR. However, this difference was not statistically significant for the sunitinib or placebo arms. Using a more stringent criteria for SD in the analysis (SD >184 days) resulted in higher mean Ki-67 indices for subjects with PD or SD =/<184 days in both the sunitinib and placebo arms, with the placebo achieving statistical significance with a Wilcoxon rank-sum of P=0.0246.

Review of secondary efficacy endpoints revealed the hazard ratio for OS based on 30 events was 0.409 with 95% CI 0.187, 0.894 and P value = 0.0204 favouring sunitinib over placebo. This is illustrated in Figure 3.

Figure 3 **Kaplan-Meier Curves of Overall Survival in Study A6181111 (Intent-to-Treat Population)**




Source: CSR A6181111, Figure 14.3
Data from the open-label extension studies is included and kept under the original treatment arm.
For subjects known to be alive at the time the database was closed for analysis, survival data were censored on the date they were last known to be alive.

The overall response rate as determined by investigator' assessment was statistically significantly higher in the sunitinib arm compared to the placebo arm (9.3% versus 0%, respectively, with a 95% CI of 3.2, 15.4 and P=0.0066). This is summarised in Table 15.

Table 15 **Overview of Efficacy Endpoints - ITT Population**

| Endpoint | Median (95% CI) Sunitinib (N=86) | Placebo (N=85) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Primary** | | | | |
| PFS (months) | 11.4 (7.4, 19.8) | 5.5 (3.6, 7.4) | 0.418 (0.263, 0.662) | 0.0001 |
| **Secondary** | | | | |
| OS (months) | 20.6 (20.6, NR) | NR (15.5, NR) | 0.409 (0.187, 0.894) | 0.0204 |
| OR (ORR), number (%) of subjects[a] | 8 (9.3) | 0 | | 0.0066 |
| CR | 2 (2.3) | 0 | | |
| PR | 6 (7.0) | 0 | | |
| SD | 54 (62.8) | 51 (60.0) | | |
| PD | 12 (14.0) | 23 (27.1) | | |
| Indeterminate | 12 (14.0) | 11 (12.9) | | |
| Median (range) TTR (months)[b] | 3.1 (0.8-11.1) | NA | | |
| Median DR | NR | NA | | |

ITT = intent-to-treat; N = number of subjects randomized; CI = confidence interval; PFS = progression-free survival; OS = overall survival; OR = objective response; ORR = objective response rate; CR = complete response; DR = duration of response; PR = partial response; SD = stable disease (stable/no response); PD = progressive disease; TTR = time to tumor response; NA= not applicable; NR = not reached
Results are from the ITT population, with tumor-related endpoints based on investigator assessments according to RECIST (excluding the OS analysis).
[a] Results for OR (ORR) are given in number (%) of subjects having a confirmed CR or PR.
[b] Responders only (8 subjects on the sunitinib arm).

Median TTR in terms of Kaplan-Meier time to event for the ITT population could not be estimated due to the number of responders, however among those subjects with an objective tumour response (8 subjects in the sunitinib arm) the median TTR was 3.1 months with a range of 0.8-11.1 months. Median DR among subjects who had a response could not be estimated because seven out of eight responding subjects had ongoing responses at the time of date of cut-off.

In relation to patient reported outcomes which were assessed by the EORTC-QNQ-C30 questionnaire, there were no significant differences in global QoL for patients on sunitinib compared to patients on placebo. In all five functional domains, that is, cognitive, emotional, physical, role and social functioning, the use of sunitinib did not have any clinically significant negative effect. The analyses also showed limited negative symptomatic effects for patients on the sunitinib arm. There were no clinically significant differences noted in appetite loss, dyspnoea, fatigue, financial difficulties, nausea and vomiting and pain between the two treatment groups.

An update on overall survival data was provided in the current Australian submission; the original data cut-off of 15 April 2009 was updated to the 1 December 2009. During this period there were 21 additional deaths reported among subjects who had withdrawn from study due to disease progression or enrolled in one of the two open-labelled sunitinib extension studies. In all, 51 deaths have been reported among the 171 patients randomised in the study and there were fewer deaths in the sunitinib arm (21 patients or 24.4% versus 30 patients or 35.3% in the placebo arm; see Table 16). In this analysis the median OS was not reached for either treatment arm. The observed hazard ratio for death was 0.594 with 95% CI 0.34-1.038 with a P=0.0644 in the sunitinib arm. This is graphically presented in Figure 4.

Table 16. 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)[b] | 91.6 (85.7, 97.6) | 84.0 (76.0, 92.0) |
| Kaplan-Meier estimates of time to event (months) | | |
| Quartiles (95% CI)[c] | 18.9 (13.9, -) | 9.3 (6.5, 15.5) |
| 25% | - (21.5, -) | - (16.3, -) |
| 50% | - | - |
| 75% | | |
| Hazard ratio (Sunitinib vs. placebo)[d] (95% CI) | 0.594 (0.340, 1.038) | |
| p-value[e] | 0.0644 | |

All subjects who were originally randomized in Study A6181111 were included and were kept under the original randomized treatment arm.

[a] Estimated from the Kaplan-Meier curve.

[b] Calculated from the product limit method.

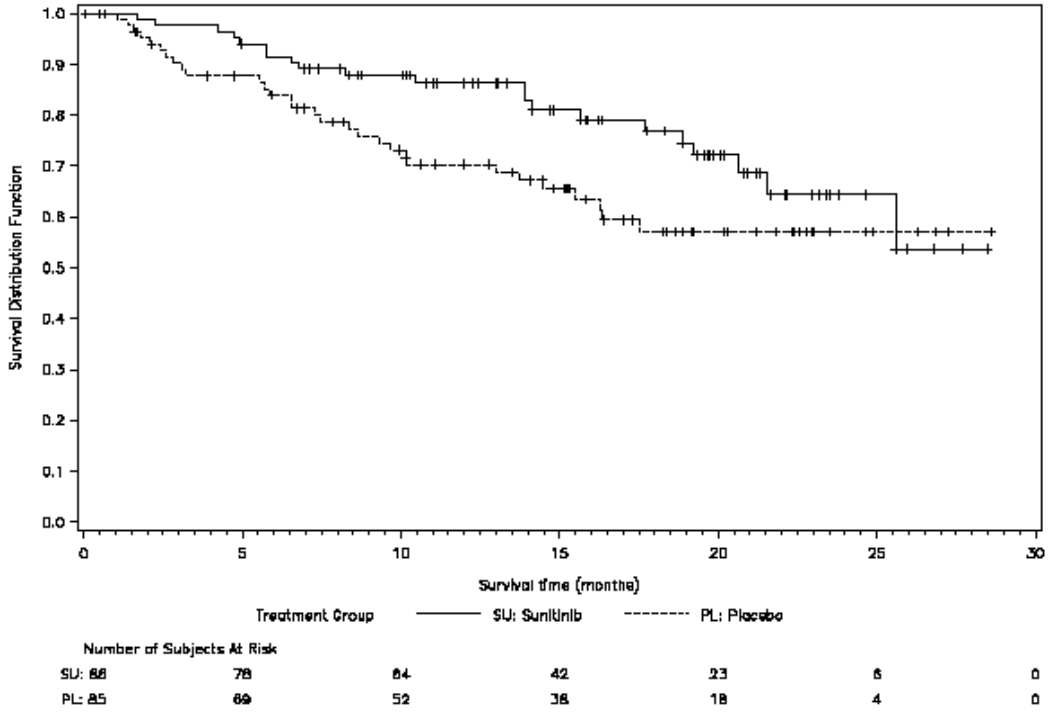
[c] Based on the Brookmeyer and Crowley method.

[d] Based on the Cox proportional hazards model.

[e] 2-sided p-value from the unstratified log-rank test.

CI = confidence interval.

Figure 4. Kaplan-Meier Curves of Overall Survival as of 01 DEC 2009 - Intent-to-Treat Population




All subjects who were originally randomized in Study A6181111 were included and were kept under the original randomized treatment arm.

The probability of survival for six months is 91.6% for patients in the sunitinib arm and 84% for patients in the placebo arm. It is worth noting that there is some potential influence on the OS analysis by the cross over from placebo to open label sunitinib treatment for a number of patients.

Evaluator's Comment:

The first study has demonstrated a level of efficacy for sunitinib in the treatment of patients with pNET. This is particularly reflected in a significant improvement in PFS which was consistent across all baseline factors. There was also a higher response rate in the sunitinib arm albeit <10% of patients treated. There was also an improvement in overall survival for patients on sunitinib but with the updated analysis this was not significant although certainly taking into account the fact that there was crossover of patients on placebo to sunitinib in a proportion which would have altered results. As this agent appears to represent the first treatment with a degree of efficacy in the treatment of pNET it seems appropriate to consider it an addition to the armamentarium for management of these patients.

There was a single supportive study (RTKC-0511-015) provided with the current Australian submission. It was an open labelled two cohort two stage Phase II study of sunitinib in patients with advanced unresectable pNET (carcinoid tumour or pancreatic islet cell tumour). Data from subjects with pancreatic islet cell tumour are included in this evaluation. The study was conducted at eight centres in the United States between 24 March 2003 and 11 November 2005.

The primary objective of the study was to determine the anti-tumour efficacy of sunitinib at a dose of 50mg orally once daily according to the 4/2 Schedule repeated every six weeks in subjects with advanced unresectable neuroendocrine tumour (pNET).

The secondary objectives included assessment of measures of duration of response and tumour control and overall survival; assessment of duration of tumour markers response to sunitinib; assessment of the safety of sunitinib and evaluation of subject assessed and investigator assessed laboratory evidence for disease and treatment related symptoms in NET subjects receiving sunitinib.

Inclusion criteria for the study were histologically or cytologically proven diagnosis of pancreatic islet cell tumour that was not amenable to surgery, radiation or combined modality therapy with a curative intent. They required evidence of uni-dimensional measurable disease per the RECIST criteria, an ECOG performance status of 0-1 and adequate vital organ function.

Treatment regimen was 50mg of sunitinib daily for four weeks followed by two weeks off-treatment in a repeated six week cycle. Doses can be reduced to 37.5mg and 25mg in the event of toxicity and doses could be increased to 62.5mg and 75mg for patients who tolerated the study medication.

The primary efficacy endpoint was overall confirmed objective response rate (ORR). ORR was defined as proportion of subjects who confirmed complete response (CR) or confirmed partial response (PR) according to RECIST. Secondary efficacy endpoints included time to tumour response (TTR), duration of objective response (DR), time to tumour progression (TTP), time to treatment failure (TTF) and overall survival (OS).

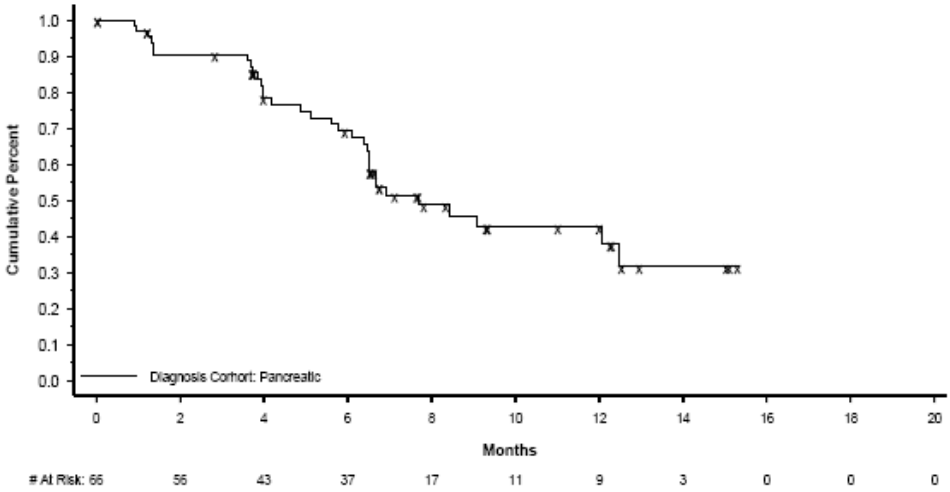
The time to event and duration analyses were performed using the Kaplan-Meier method.

A total of 66 patients with pNET were treated with sunitinib. The median age for these patients was 56 years with a range of 32-21 years. 84.8% of patients were <65 years and 63.6% male. All patients had an ECOG performance status of 0-1. Forty six of the patients had non-functioning tumours, while of the functioning tumours, the most common were those with gastrinoma (five patients or 7.6%). Some 98.5% of patients had previous surgery, 16.7% prior radiation therapy and 60.6% prior systemic treatment.

The overall response rate was 16.7%, all of which were partial responses. A further 45 patients or 68.2% of patients had stable disease. Thirty seven of patients with stable disease had the duration of this last >184 days.

Of the secondary endpoints, the median TTP was 33.4 weeks with a 95% CI of 28.1-54.1 weeks which is graphically presented in Figure 5.

Figure 5 **Kaplan-Meier Curve of Time to Tumor Progression (ITT Populaiton, Pancreatic NET Cohort) - Study RTKC-01511-015**




Evaluator's Comment:

This data has therefore confirmed a degree of activity for sunitinib in the treatment of pancreatic islet cell tumours and is consistent with that seen in the pivotal trial.

## Safety

A total of four studies are included in this evaluation of safety; Study A6181111 (the pivotal trial), Study RTKC-0511-015 (the supportive Phase II study in patients with unresectable pNET) and Studies A6181047 and A6181061 (two single arm Phase II studies of single agent sunitinib in patients with advanced GIST and RCC). A total of 398 subjects were evaluated for safety of which 316 received at least one dose of sunitinib. A total of 237 subjects were on a trial of pNET of whom 152 were treated with sunitinib. Some 338 subjects were treated on a continuous dose schedule and in this group, 253 were treated with sunitinib. In all studies, the primary populations for evaluating safety were patients who had received at least one dose of study medication. Descriptive analyses of safety data were undertaken and the data were summarised accordingly. Investigator assessment of relevant toxicities was undertaken and graded according to standard National Cancer Institute **(**NCI) Common Toxicity Criteria[8].

For haematology and blood chemistry assessments, samples were collected on a four weekly basis. History and physical examination together with vital signs were undertaken on a four weekly basis and 12-lead electrocardiogram (ECGs) were performed as screening on Day 1 of Cycles 1-4.

For the pivotal trial the median duration of treatment was 141 days for the sunitinib arm and 113 days for the placebo arm. Nineteen patients (22.9%) in the sunitinib arm and three patients (3.7%) in the placebo arm were on study for more than a year. The median

[8] A standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

number of days on which drug was administered was approximately the same as the number of days on treatment for both treatment arms. In the sunitinib arm, 25 patients (30.1%) had at least one dose interruption and 26 patients (31.3%) had a dose reduction. Eight or 9.6% of patients on the sunitinib arm and 24.4% in the placebo arm had dose escalation from 37.5mg to 50mg. The median relative dose intensity was approximately 100% in both treatment arms.

For the supportive Phase II study (in pancreatic tumour patients) the median number of days of study drug was 139 days. The median number of days on treatment was 214 days. Some 69.7% of patients had at least one dose interruption and 51.5% of patients had a dose reduction. Two patients had their dose escalated to 62.5mg.

In the other two studies (A6181047 for GIST patients and A6181061 for RCC patients), the starting dose for sunitinib was 37.5mg once daily as a single agent on a continuous daily schedule. For the 60 patients treated in Study A6181047, the median number of days on treatment was 319 and the median number of days on which drug was administered was 279. Some 76.6% of patients had at least one dose interruption and 23.3% of patients had their dose reduced to 25mg. Two patients had their dose escalated to 50mg. The median daily dose delivered was 37.5mg and the median relative dose intensity was 89%.

In the group of 107 RCC patients, the median number of days on treatment was 253 and the median number of days on which drug was administered 248. Some 64.5% of patients had at least one dose interruption and 47% had a dose reduction. Seventeen patients had their dose escalated to 50mg. The median daily dose delivered was 37.5mg and median relative dose intensity was 93%.

Review of treatment emergent all cause adverse events for the pivotal trial revealed that nearly all patients (98.8% and 95.1% of patients given sunitinib and placebo, respectively) experienced treatment emergent adverse events. Adverse events were most commonly associated with GI disorders (89.2% of sunitinib patients and 73.2% of placebo patients). This was followed by general disorders and administration site disorders (80.7% of sunitinib patients and 67.1% of placebo patients). These results are summarised in Table 17. Diarrhoea was noted in 59% of patients on sunitinib and 39% on placebo, nausea in 44.6% and 29.3%, respectively, hair colour changes in 28.9% and 1.2%, respectively, neutropenia in 28.9% and 3.7%, respectively, hypertension in 26.5% and 4.9%, respectively, hand/foot syndrome in 22.9% and 2.4%, respectively, stomatitis in 21.7% and 2.4%, respectively, dysgeusia in 20.5% and 4.9%, respectively, epistaxis in 20.5% and 4.9%, respectively, rash in 18.1% and 4.9%, respectively, and thrombocytopenia in 16.9% and 4.9%, respectively.

Table 17 **Most Common (≥5% Sunitinib-Treated Subjects) Treatment-Emergent, All-Causality Adverse Events – Study A6181111**

| | | | | |
|---|---|---|---|---|
| Chest pain | 5 (6.0) | 0 | 5 (6.1) | 0 |
| Decreased appetite | 5 (6.0) | 0 | 4 (4.9) | 0 |
| Dizziness | 5 (6.0) | 1 (1.2) | 5 (6.1) | 0 |
| Flatulence | 5 (6.0) | 0 | 2 (2.4) | 0 |
| Hemorrhoids | 5 (6.0) | 0 | 0 | 0 |
| Hypokalemia | 5 (6.0) | 1 (1.2) | 2 (2.4) | 0 |
| Muscle spasms | 5 (6.0) | 0 | 4 (4.9) | 0 |
| Edema | 5 (6.0) | 0 | 3 (3.7) | 1 (1.2) |
| Oral pain | 5 (6.0) | 1 (1.2) | 0 | 0 |

[a]None of the AEs in this table was reported with a severity of Grade 5.

Grade III/IV adverse events were more frequently experienced in sunitinib patients (49.4% of patients compared to 43.9% of the placebo group). The most frequent of these

were neutropenia (12% for sunitinib), hypertension (9.6%), leukopaenia (6%) and hand/foot syndrome (6%).

Review of treatment emergent all-cause adverse event data for the supportive Study RTKC-0511-015 showed that the most frequently reported adverse events were associated with the gastrointestinal system, followed by general disorders and administration site conditions as summarised in Table 18. The most common specific symptoms included fatigue, anorexia, headache, flushing, cough, diarrhoea, nausea, vomiting, stomatitis, skin rash, hair colour changes and hand/foot syndrome. There was also an increased incidence of neutropenia and thrombocytopenia. All of these are similar to those seen in the pivotal trial.

Grade III/IV adverse events experienced in the pNET cohort of patients amounted to 81.8%. The most frequent of these were neutropenia, fatigue, thrombocytopenia, hypertension and abdominal pain.

In the supportive Phase II Study A6181047, all (GIST) patients experienced an adverse event. The most common adverse events being of a gastrointestinal type; diarrhoea, abdominal pain, nausea, vomiting and stomatitis. This was followed by asthenia, fatigue pyrexia and cutaneous skin rash or hand/foot syndrome. There were also incidences of myelosuppression with neutropenia and thrombocytopenia as illustrated in Table 19. Grade III/IV adverse events were experienced in 48.3% of patients and included anaemia, neutropenia, diarrhoea and asthenia.

Table 18 **Most Common (≥10% Total Subjects) Treatment-Emergent, All-Causality Adverse Events by Cohort and by Maximum CTC Severity – Study RTKC-0511-015**

| | Diagnosis Cohort | | | |
|---|---|---|---|---|
| | Carcinoid Tumor N=41 | | Pancreatic NET N = 66 | |
| | Number (% of Subjects) | | | |
| Preferred Term | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Any AE | 41 (100.0) | 36 (87.8) | 66 (100.0) | 54 (81.8) |
| Fatigue | 39 (95.1) | 15 (36.6) | 61 (92.4) | 14 (21.2) |
| Diarrhea | 38 (92.7) | 4 (9.8) | 52 (78.8) | 3 (4.5) |
| Nausea | 29 (70.7) | 5 (12.2) | 40 (60.6) | 4 (6.1) |
| Dysgeusia | 19 (46.3) | 0 (0.0) | 34 (51.5) | 0 (0.0) |
| Abdominal Pain | 23 (56.1) | 5 (12.2) | 29 (43.9) | 8 (12.1) |
| Flushing | 23 (56.1) | 0 (0.0) | 26 (39.4) | 0 (0.0) |
| Anorexia | 15 (36.6) | 2 (4.9) | 27 (40.9) | 2 (3.0) |
| Headache | 18 (43.9) | 3 (7.3) | 23 (34.8) | 0 (0.0) |
| Vomiting | 17 (41.5) | 3 (7.3) | 23 (34.8) | 4 (6.1) |
| Myalgia | 14 (34.1) | 2 (4.9) | 25 (37.9) | 2 (3.0) |
| Rash | 16 (39.0) | 1 (2.4) | 23 (34.8) | 0 (0.0) |
| Skin discoloration | 14 (34.1) | 0 (0.0) | 25 (37.9) | 0 (0.0) |
| Glossodynia | 13 (31.7) | 3 (7.3) | 23 (34.8) | 0 (0.0) |
| Stomatitis | 10 (24.4) | 0 (0.0) | 26 (39.4) | 2 (3.0) |
| Constipation | 14 (34.1) | 0 (0.0) | 21 (31.8) | 0 (0.0) |
| Hair color changes | 18 (43.9) | 0 (0.0) | 16 (24.2) | 0 (0.0) |
| Dyspnea | 12 (29.3) | 2 (4.9) | 20 (30.3) | 2 (3.0) |
| Insomnia | 10 (24.4) | 0 (0.0) | 21 (31.8) | 2 (3.0) |
| Dyspepsia | 10 (24.4) | 0 (0.0) | 18 (27.3) | 1 (1.5) |
| Pain in extremity | 8 (19.5) | 1 (2.4) | 19 (28.8) | 1 (1.5) |
| Dizziness | 13 (31.7) | 0 (0.0) | 14 (21.2) | 0 (0.0) |
| Neutropenia | 8 (19.5) | 7 (17.1) | 18 (27.3) | 15 (22.7) |
| Thrombocytopenia | 7 (17.1) | 1 (2.4) | 19 (28.8) | 10 (15.2) |
| Oral pain | 11 (26.8) | 0 (0.0) | 15 (22.7) | 0 (0.0) |
| Arthralgia | 10 (24.4) | 0 (0.0) | 16 (24.2) | 1 (1.5) |
| Paresthesia | 14 (34.1) | 0 (0.0) | 12 (18.2) | 0 (0.0) |
| Edema peripheral | 7 (17.1) | 0 (0.0) | 18 (27.3) | 0 (0.0) |
| Pyrexia | 8 (19.5) | 0 (0.0) | 17 (25.8) | 2 (3.0) |
| Cough | 11 (26.8) | 0 (0.0) | 13 (19.7) | 0 (0.0) |
| Dehydration | 10 (24.4) | 4 (9.8) | 13 (19.7) | 5 (7.6) |
| Anemia | 7 (17.1) | 0 (0.0) | 16 (24.2) | 1 (1.5) |
| Back pain | 9 (22.0) | 2 (4.9) | 13 (19.7) | 1 (1.5) |
| Hypertension | 6 (14.6) | 3 (7.3) | 16 (24.2) | 9 (13.6) |

| | Diagnosis Cohort | | | |
|---|---|---|---|---|
| | Carcinoid Tumor N=41 | | Pancreatic NET N = 66 | |
| | Number (% of Subjects) | | | |
| Preferred Term | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Flatulence | 10 (24.4) | 0 (0.0) | 12 (18.2) | 0 (0.0) |
| Periorbital edema | 11 (26.8) | 0 (0.0) | 8 (12.1) | 0 (0.0) |
| Nasopharyngitis | 11 (26.8) | 0 (0.0) | 8 (12.1) | 0 (0.0) |
| Palmar-plantar erythrodysesthesia syndrome | 6 (14.6) | 0 (0.0) | 12 (18.2) | 2 (3.0) |
| Chills | 3 (7.3) | 0 (0.0) | 13 (19.7) | 0 (0.0) |
| Neutrophil count decreased | 6 (14.6) | 3 (7.3) | 9 (13.6) | 6 (9.1) |
| Upper respiratory tract infection | 5 (12.2) | 0 (0.0) | 10 (15.2) | 0 (0.0) |
| Pharyngolaryngeal pain | 6 (14.6) | 0 (0.0) | 9 (13.6) | 0 (0.0) |
| Muscle spasms | 6 (14.6) | 0 (0.0) | 8 (12.1) | 0 (0.0) |
| Abdominal distension | 7 (17.1) | 0 (0.0) | 7 (10.6) | 0 (0.0) |
| Chest pain | 6 (14.6) | 1 (2.4) | 7 (10.6) | 2 (3.0) |
| Depression | 5 (12.2) | 0 (0.0) | 8 (12.1) | 1 (1.5) |
| Mucosal inflammation | 7 (17.1) | 3 (7.3) | 5 (7.6) | 0 (0.0) |
| Leukopenia | 1 (2.4) | 1 (2.4) | 11 (16.7) | 1 (1.5) |
| Epistaxis | 5 (12.2) | 0 (0.0) | 7 (10.6) | 0 (0.0) |
| Platelet count decreased | 8 (19.5) | 2 (4.9) | 3 (4.5) | 0 (0.0) |
| Anxiety | 5 (12.2) | 0 (0.0) | 6 (9.1) | 2 (3.0) |
| Hyperhidrosis | 5 (12.2) | 0 (0.0) | 6 (9.1) | 0 (0.0) |
| Oedema | 3 (7.3) | 0 (0.0) | 8 (12.1) | 0 (0.0) |

Table 19 . **Most Common (≥10% Total Subjects) Treatment-Emergent, All-Causality Adverse Events by Maximum CTCAE Severity – Study A6181047**

| Preferred Term | Total N=60 Subjects n (%) All Grades | Grade 3/4[a] |
|---|---|---|
| Any AE | 60 (100.0) | 29 (48.3) |
| Anemia | 29 (48.3) | 9 (15.0) |
| Diarrhea | 27 (45.0) | 7 (11.7) |
| Abdominal pain | 24 (40.0) | 4 (6.7) |
| Asthenia | 23 (38.3) | 9 (15.0) |
| Fatigue | 22 (36.7) | 5 (8.3) |
| Nausea | 21 (35.0) | 3 (5.0) |
| Vomiting | 21 (35.0) | 2 (3.3) |
| Hypertension | 18 (30.0) | 5 (8.3) |
| Neutropenia | 18 (30.0) | 8 (13.3) |
| Anorexia | 15 (25.0) | 1 (1.7) |
| Palmar-plantar erythrodysesthesia syndrome | 15 (25.0) | 2 (3.3) |
| Headache | 14 (23.3) | 0 (0.0) |
| Abdominal pain upper | 13 (21.7) | 0 (0.0) |
| Back pain | 13 (21.7) | 1 (1.7) |
| Constipation | 13 (21.7) | 1 (3.3) |
| Hair color changes | 13 (21.7) | 0 (0.0) |
| Stomatitis | 13 (21.7) | 2 (3.3) |
| Thrombocytopenia | 13 (21.7) | 3 (5.0) |
| Epistaxis | 12 (20.0) | 0 (0.0) |
| Mucosal inflammation | 11 (18.3) | 0 (0.0) |
| Edema peripheral | 11 (18.3) | 2 (3.3) |
| Pain in extremity | 10 (16.7) | 2 (3.3) |
| Pyrexia | 11 (18.3) | 0 (0.0) |
| Blood TSH increased | 9 (15.0) | 0 (0.0) |
| Gastroesophageal reflux disease | 8 (13.0) | 0 (0.0) |
| Hypoalbuminemia | 8 (13.0) | 0 (0.0) |
| Hypothyroidism | 8 (13.0) | 0 (0.0) |
| Rash | 8 (13.0) | 0 (0.0) |
| Arthralgia | 7 (11.7) | 0 (0.0) |
| Chills | 7 (11.7) | 0 (0.0) |
| Dyspnea | 7 (11.7) | 1 (1.7) |
| Muscle spasms | 7 (11.7) | 0 (0.0) |
| Dry skin | 6 (10.0) | 0 (0.0) |
| Eczema | 6 (10.0) | 0 (0.0) |
| Leukopenia | 6 (10.0) | 4 (6.7) |
| Weight decreased | 6 (10.0) | 0 (0.0) |
| Yellow skin | 6 (10.0) | 0 (0.0) |

[a]None of the AEs summarized in this table was reported with a severity of Grade 5.

For the supportive Phase II study (A6181061 in RCC patients), 100% of patients experienced treatment emergent all cause adverse events. The most common of these were again gastrointestinal (diarrhoea, stomatitis, nausea and vomiting), followed by cutaneous hand/foot syndrome, skin rash and others such as hypertension and constitutional (asthenia, fatigue and pyrexia) as well as myelosuppression including neutropenia and thrombocytopenia (see Table 20). A total of 66 or 61.7% of patients experienced Grade III/IV adverse events of which the most frequent were diarrhoea, asthenia and hypertension.

Table 20 **Most Common (≥10% Total Subjects) Treatment-Emergent, All-Causality Adverse Events by Maximum CTCAE Severity – Study A6181061**

| Preferred Term | Total N=107 Subjects n (%) All Grades | Grade 3/4[a] |
|---|---|---|
| Any AE | 107 (100.0) | 66 (61.7) |
| Diarrhea | 81 (75.7) | 12 (11.2) |
| Palmar-plantar erythrodysesthesia syndrome | 51 (47.7) | 10 (9.3) |
| Hypertension | 48 (44.9) | 12 (11.2) |
| Stomatitis | 46 (43.0) | 4 (3.7) |
| Asthenia | 44 (41.1) | 13 (12.1) |
| Nausea | 44 (41.1) | 7 (6.5) |
| Anorexia | 41 (38.3) | 8 (7.5) |
| Fatigue | 41 (38.3) | 7 (6.5) |
| Hair color changes | 38 (35.5) | 1 (0.9) |
| Dyspepsia | 37 (34.6) | 0 (0.0) |
| Vomiting | 34 (31.8) | 2 (1.9) |
| Weight decreased | 32 (29.9) | 4 (3.7) |
| Dysgeusia | 28 (26.2) | 0 (0.0) |
| Epistaxis | 28 (26.2) | 1 (0.9) |
| Abdominal pain | 27 (25.2) | 2 (1.9) |
| Mucosal inflammation | 25 (23.4) | 2 (1.9) |
| Rash | 23 (21.5) | 1 (0.9) |
| Constipation | 22 (20.6) | 0 (0.0) |
| Dry skin | 22 (20.6) | 0 (0.0) |
| Pain in extremity | 22 (20.6) | 4 (3.7) |
| Abdominal pain upper | 19 (17.8) | 0 (0.0) |
| Erythema | 19 (17.8) | 0 (0.0) |
| Pyrexia | 19 (17.8) | 2 (1.9) |
| Chest pain | 18 (16.8) | 1 (0.9) |
| Arthralgia | 17 (15.9) | 1 (0.9) |
| Anemia | 16 (15.0) | 7 (6.5) |
| Cough | 16 (15.0) | 1 (0.9) |
| Back pain | 14 (13.1) | 5 (4.7) |
| Hemoptysis | 14 (13.1) | 1 (0.9) |
| Headache | 14 (13.1) | 0 (0.0) |
| Edema peripheral | 14 (13.1) | 0 (0.0) |
| Thrombocytopenia | 14 (13.1) | 5 (4.7) |
| Dizziness | 13 (12.1) | 2 (1.9) |
| Dyspnea | 13 (12.1) | 4 (3.7) |
| Insomnia | 12 (11.2) | 0 (0.0) |
| Neutropenia | 12 (11.2) | 5 (4.7) |
| Ageusia | 11 (10.3) | 0 (0.0) |
| Skin discoloration | 11 (10.3) | 0 (0.0) |

[a]None of the AEs summarized in this table was reported with a severity of missing or Grade 5

Review of treatment related adverse events for the pivotal trial revealed that gastrointestinal disorders were the most common (84.3% for sunitinib patients) followed by general disorders and administration site conditions. The most common individual events are summarised in Table 21 and include diarrhoea and nausea, hair colour changes, neutropenia, fatigue, hypertension and hand/foot syndrome, stomatitis, dysgeusia, epistaxis, thrombocytopenia and rash.

The most common treatment related Grade III/IV adverse events for sunitinib were neutropenia experienced by 12% of patients, followed by hypertension (9.6%), leukopaenia (6%) and hand/foot syndrome (6%). This is illustrated in Table 22.

Treatment related adverse events in the supportive Phase II study (RTKC-0511-015) revealed that 98% of patients experienced one of these. Again, the nature and frequency of these was similar to that observed in the pivotal study (see Table 23).

The treatment related adverse events reported for the other two supportive studies, that is, A6181047 and A6181061, were also similar (see Table 24).

The review of deaths in the pivotal trial revealed that overall there was a higher incidence of death in the placebo arm (25.6%) compared to the sunitinib arm (10.8%). The most

common cause of death was progression of disease in both arms. This is illustrated in Table 25.

Table 21 **Most Common (≥5% Sunitinib-Treated Subjects) Treatment-Related Adverse Events by Maximum CTCAE Severity – Study A6181111**

| | Sunitinib (N=83) | | Placebo (N=82) | |
|---|---|---|---|---|
| Number (%) of Subjects with Preferred Adverse Even Term | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Any AE | 81 (97.6) | 36 (43.4) | 64 (78.0) | 16 (19.5) |
| Diarrhea | 44 (53.0) | 4 (4.8) | 25 (30.5) | 1 (1.2) |
| Nausea | 32 (38.6) | 1 (1.2) | 18 (22.0) | 0 |
| Asthenia | 26 (31.3) | 3 (3.6) | 18 (22.0) | 2 (2.4) |
| Fatigue | 24 (28.9) | 4 (4.8) | 14 (17.1) | 3 (3.7) |
| Hair color changes | 24 (28.9) | 1 (1.2) | 1 (1.2) | 0 |
| Neutropenia | 24 (28.9) | 10 (12.0) | 3 (3.7) | 0 |
| Vomiting | 21 (25.3) | 0 | 14 (17.1) | 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 |
| Anorexia | 17 (20.5) | 2 (2.4) | 11 (13.4) | 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 |
| Abdominal pain | 12 (14.5) | 1 (1.2) | 10 (12.2) | 3 (3.7) |
| Dyspepsia | 12 (14.5) | 0 | 1 (1.2) | 0 |
| Weight decreased | 11 (13.3) | 1 (1.2) | 6 (7.3) | 0 |
| Dry skin | 11 (13.3) | 0 | 9 (11.0) | 0 |
| Headache | 10 (12.0) | 0 | 5 (6.1) | 1 (1.2) |
| Constipation | 8 (9.6) | 0 | 8 (9.8) | 1 (1.2) |
| Leukopenia | 8 (9.6) | 5 (6.0) | 1 (1.2) | 0 |
| Nail disorder | 8 (9.6) | 0 | 1 (1.2) | 0 |
| Dry mouth | 7 (8.4) | 0 | 4 (4.9) | 0 |
| Erythema | 7 (8.4) | 0 | 3 (3.7) | 0 |
| Insomnia | 7 (8.4) | 0 | 5 (6.1) | 0 |
| Pain in extremity | 7 (8.4) | 0 | 3 (3.7) | 0 |
| Abdominal pain upper | 6 (7.2) | 1 (1.2) | 1 (1.2) | 0 |
| Arthralgia | 6 (7.2) | 0 | 2 (2.4) | 0 |
| Dyspnea | 6 (7.2) | 1 (1.2) | 8 (9.8) | 0 |
| Yellow skin | 6 (7.2) | 0 | 0 | 0 |
| Alopecia | 5 (6.0) | 0 | 1 (1.2) | 0 |
| Apthous stomatitis | 5 (6.0) | 0 | 2 (2.4) | 0 |
| Decreased appetite | 5 (6.0) | 0 | 3 (3.7) | 0 |
| Dizziness | 5 (6.0) | 1 (1.2) | 3 (3.7) | 0 |
| Eyelid edema | 5 (6.0) | 1 (1.2) | 0 | 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 |

Table 22 **Most Common (≥10% Total Subjects) Treatment-Related Adverse Events by Cohort and Maximum CTC Severity – Study RTKC-0511-015**

| | Diagnosis Cohort | | | |
|---|---|---|---|---|
| | Carcinoid Tumor (N=41) | | Pancreatic NET (N = 66) | |
| | Number (% of Subjects) | | | |
| Preferred Term | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Any AE | 40 (97.6) | 31 (75.6) | 66 (100.0) | 43 (65.2) |
| Fatigue | 36 (87.8) | 14 (34.1) | 59 (89.4) | 12 (18.2) |
| Diarrhea | 27 (65.9) | 2 (4.9) | 43 (65.2) | 3 (4.5) |
| Nausea | 24 (58.5) | 3 (7.3) | 33 (50.0) | 3 (4.5) |
| Dysgeusia | 19 (46.3) | 0 (0.0) | 33 (50.0) | 0 (0.0) |
| Skin discoloration | 14 (34.1) | 0 (0.0) | 25 (37.9) | 0 (0.0) |
| Glossodynia | 13 (31.7) | 3 (7.3) | 23 (34.8) | 0 (0.0) |
| Myalgia | 13 (31.7) | 1 (2.4) | 22 (33.3) | 1 (1.5) |
| Stomatitis | 10 (24.4) | 0 (0.0) | 24 (36.4) | 2 (3.0) |
| Hair color changes | 18 (43.9) | 0 (0.0) | 16 (24.2) | 0 (0.0) |
| Vomiting | 13 (31.7) | 3 (7.3) | 19 (28.8) | 4 (6.1) |
| Anorexia | 9 (22.0) | 1 (2.4) | 21 (31.8) | 2 (3.0) |
| Rash | 11 (26.8) | 1 (2.4) | 17 (25.8) | 0 (0.0) |
| Oral pain | 11 (26.8) | 0 (0.0) | 15 (22.7) | 0 (0.0) |
| Neutropenia | 8 (19.5) | 7 (17.1) | 17 (25.8) | 14 (21.2) |
| Thrombocytopenia | 7 (17.1) | 1 (2.4) | 18 (27.3) | 9 (13.6) |
| Headache | 11 (26.8) | 1 (2.4) | 14 (21.2) | 0 (0.0) |
| Flushing | 10 (24.4) | 0 (0.0) | 11 (16.7) | 0 (0.0) |
| Anemia | 6 (14.6) | 0 (0.0) | 14 (21.2) | 0 (0.0) |
| Dyspepsia | 7 (17.1) | 0 (0.0) | 13 (19.7) | 0 (0.0) |
| Paresthesia | 10 (24.4) | 0 (0.0) | 9 (13.6) | 0 (0.0) |
| Palmar-plantar erythrodysesthesia syndrome | 6 (14.6) | 0 (0.0) | 12 (18.2) | 2 (3.0) |
| Hypertension | 4 (9.8) | 3 (7.3) | 13 (19.7) | 8 (12.1) |
| Periorbital edema | 11 (26.8) | 0 (0.0) | 6 (9.1) | 0 (0.0) |
| Dehydration | 5 (12.2) | 2 (4.9) | 11 (16.7) | 3 (4.5) |
| Pain in extremity | 4 (9.8) | 1 (2.4) | 11 (16.7) | 0 (0.0) |
| Arthralgia | 4 (9.8) | 0 (0.0) | 11 (16.7) | 1 (1.5) |
| Dizziness | 8 (19.5) | 0 (0.0) | 7 (10.6) | 0 (0.0) |
| Neutrophil count decreased | 5 (12.2) | 3 (7.3) | 9 (13.6) | 6 (9.1) |
| Leukopenia | 1 (2.4) | 1 (2.4) | 11 (16.7) | 1 (1.5) |
| Mucosal inflammation | 6 (14.6) | 3 (7.3) | 5 (7.6) | 0 (0.0) |
| Platelet count decreased | 8 (19.5) | 2 (4.9) | 3 (4.5) | 0 (0.0) |
| Insomnia | 2 (4.9) | 0 (0.0) | 9 (13.6) | 0 (0.0) |

Table 23 **Most Common (≥10% Total Subjects) Treatment-Related Adverse Events by Maximum CTCAE Severity – Study A6181047**

| Preferred Term | Total N=60 Subjects n (%) All Grades | Grade 3/4[a] |
|---|---|---|
| Any AE | 59 (98.3) | 30 (50.0) |
| Anemia | 25 (41.7) | 5 (8.3) |
| Diarrhea | 24 (40.0) | 5 (8.3) |
| Asthenia | 22 (36.7) | 6 (10.0) |
| Fatigue | 20 (33.3) | 4 (6.7) |
| Neutropenia | 18 (30.0) | 8 (13.3) |
| Hypertension | 17 (28.3) | 5 (8.3) |
| Nausea | 16 (26.7) | 1 (1.7) |
| Palmar-plantar erythrodysesthesia syndrome | 15 (25.0) | 2 (3.3) |
| Vomiting | 14 (23.3) | 0 (0.0) |
| Hair color changes | 13 (21.7) | 0 (0.0) |
| Stomatitis | 13 (21.7) | 2 (3.3) |
| Thrombocytopenia | 13 (21.7) | 3 (5.0) |
| Anorexia | 12 (20.0) | 1 (1.7) |
| Abdominal pain upper | 11 (18.3) | 0 (0.0) |
| Mucosal inflammation | 11 (18.3) | 0 (0.0) |
| Blood TSH increased | 9 (15.0) | 0 (0.0) |
| Abdominal pain | 8 (13.3) | 1 (1.7) |
| Epistaxis | 8 (13.3) | 0 (0.0) |
| Headache | 8 (13.3) | 0 (0.0) |
| Hypothyroidism | 7 (11.7) | 0 (0.0) |
| Muscle spasms | 7 (11.7) | 0 (0.0) |
| Pain in extremity | 6 (10.0) | 1 (1.7) |
| Eczema | 6 (10.0) | 0 (0.0) |
| Leukopenia | 6 (10.0) | 4 (6.7) |
| Edema peripheral | 6 (10.0) | 1 (1.7) |
| Rash | 6 (10.0) | 0 (0.0) |
| Yellow skin | 6 (10.0) | 0 (0.0) |

[a]None of the AEs summarized in this table was reported with a severity of Grade 5

Table 24 **Most Common (≥10% Total Subjects) Treatment-Related Adverse Events by Maximum CTCAE Severity – Study A6181061**

| Preferred Term | Total N=107 All Grades | Grade 3/4[a] |
|---|---|---|
| Any AE | 106 (99.1) | 63 (58.9) |
| Diarrhea | 80 (74.8) | 12 (11.2) |
| Palmar—plantar erythrodysesthesia syndrome | 51 (47.7) | 10 (9.3) |
| Hypertension | 47 (43.9) | 12 (11.2) |
| Stomatitis | 46 (43.0) | 4 (3.7) |
| Asthenia | 44 (41.1) | 12 (11.2) |
| Anorexia | 40 (37.4) | 8 (7.5) |
| Nausea | 40 (37.4) | 6 (5.6) |
| Fatigue | 39 (36.4) | 5 (4.7) |
| Hair color changes | 38 (35.5) | 1 (0.9) |
| Dyspepsia | 34 (31.8) | 0 (0.0) |
| Vomiting | 29 (27.1) | 1 (0.9) |
| Dysgeusia | 28 (26.2) | 0 (0.0) |
| Epistaxis | 28 (26.2) | 1 (0.9) |
| Weight decreased | 28 (26.2) | 4 (3.7) |
| Mucosal inflammation | 25 (23.4) | 2 (1.9) |
| Rash | 22 (20.6) | 1 (0.9) |
| Dry skin | 19 (17.8) | 0 (0.0) |
| Erythema | 18 (16.8) | 0 (0.0) |
| Thrombocytopenia | 14 (13.1) | 5 (4.7) |
| Abdominal pain | 13 (12.1) | 1 (0.9) |
| Abdominal pain upper | 12 (11.2) | 0 (0.0) |
| Neutropenia | 12 (11.2) | 5 (4.7) |
| Pain in extremity | 12 (11.2) | 1 (0.9) |
| Ageusia | 11 (10.3) | 0 (0.0) |

[a]None of the AEs summarized in this table was reported with a severity of Grade 5

Table 25 **Summary of Deaths - Study A6181111**

| Cause of Death | Sunitinib N = 83 | Placebo N = 82 |
|---|---|---|
| Deaths | 9 (10.8) | 21 (25.6) |
| Subjects who Died while On Study[a] | 5 (6.0) | 9 (11.0 |
| Disease under study | 4 (4.8) | 7 (8.5) |
| Study treatment toxicity | 1 (1.2)[bc] | 1 (1.2)[cd] |
| Other | 0 | 1 (1.2)[e] |
| Subjects who Died during Follow-up[f] | 4 (4.8) | 12 (14.6) |
| Disease under study | 3 (3.6) | 12 (14.6) |
| Study treatment toxicity | 0 | 0 |
| Other | 1 (1.2)[g] | 0 |

Deaths of subjects during extension Studies A6181078 and A6181114 are also included.
[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]Heart failure (Subject 10061002).
[c]Reason for death was presented as 'other' in Study A6181111 CSR Table 13.6.7.2 and Appendix B6.4.
[d]Dehydration (Subject 10311006).
[e]Hepatic failure (Subject 10351002).
[f]Follow-up deaths are those that occurred more than 28 days after the last dose of study medication.
[g]Cardiac insufficiency (Subject 10491001).

There was one death in each arm of study which was considered treatment related; heart failure in one sunitinib patient and dehydration in one placebo patient.

For the supportive Phase II study (RTKC-0511-015), one study death was attributed to sunitinib treatment due to gastrointestinal haemorrhage.

In the two supportive Phase II studies (A6181047 for GIST patients and A6181061 for RCC patients), one patient in the GIST study died of Grade V septic shock considered to be possibly related to study treatment. The only other death that may possibly be related to study treatment was in Study A6181061 in which one patient, during the follow up period, developed and died of acute myeloid leukaemia. This was considered potentially related to sunitinib therapy.

Review of serious adverse events (SAE) revealed that in the pivotal trial a total of 22 or 26.5% of subjects receiving sunitinib experienced at least one SAE. This is summarised in Table 26. The nature of these symptoms was similar to those observed in the overall adverse event profile. The most frequent serious adverse events in the supportive studies (RTKC-0511-015, A6181047 and A6181061) reflect those seen in the overall incidence of adverse events.

Table 26 **Most Common (≥2% Sunitinib-Treated Subjects) Treatment-Emergent, All-Causality Serious Adverse Events – Study A6181111**

| | Subjects n (%) | |
|---|---|---|
| Preferred Term | Sunitinib (N=83) | Placebo (N=82) |
| Any serious adverse event | 22 (26.5) | 34 (41.5) |
| Disease progression | 3 (3.6) | 2 (2.4) |
| Abdominal pain | 2 (2.4) | 4 (4.9) |
| Abdominal pain upper | 2 (2.4) | 0 |
| Cardiac failure | 2 (2.4) | 0 |
| Nausea | 2 (2.4) | 1 (1.2) |
| Renal failure | 2 (2.4) | 0 |
| Vomiting | 2 (2.4) | 3 (3.7) |

Summaries of serious treatment related adverse events again reflected the same profiles.

Review of adverse events associated with discontinuation of treatment in the pivotal trial revealed that 18 patients (21.7%) in the sunitinib arm and 14 patients (17.1%) in the placebo arm withdrew from treatment. These are listed Table 27. It is noteworthy that 10 of these were related to the study drug including one death from cardiac failure, two

patients with fatigue, others with individual problems, that is, mucositis, diarrhoea, biliary duct obstruction and neutropenia.

Review of treatment withdrawals in the Phase II study RTKC-0511-015 revealed that this occurred in 12 patients in the carcinoid tumour cohort and eight in the pancreatic NET cohort. Five of these were related to study drug including one episode of fatal GI haemorrhage, one grade III mucositis, one grade III nausea, one grade III elevation of liver enzymes and one grade II decrease in ejection fraction.

Table 27. Discontinuation due to Adverse Events-Study A6181111

| Preferred Term | Start/Stop Day | Grade | Causality |
|---|---|---|---|
| Disease progression[a] | 603/>603 | 5 | Disease under study |
| Spinal compression fracture[a] | 141/146 | NRr | Other illness |
| Hyperbilirubinemia | 141/>141 | 2 | Disease under study |
| Fatigue | 10/29 | 1 | Study drug |
| Mucosal inflammation[a] | 31/46 | 3 | Study drug |
| Diarrhea[a] | 17/22 | 2 | Study drug |
| Bile duct obstruction[a] | 16/31 | 2 | Study drug |
| Catheter related infection[a] | 15/23 | 1 | Unknown |
| Hepatic encephalopathy[a] | 250/>250 | 4 | Disease under study |
| Asthenia | 21/25 | 3 | Study drug |
| Cardiomyopathy | 41/>41 | 2 | Study drug |
| Hypertension | 29/125 | 3 | Study drug |
| Disease progression[a] | 122/>145 | 5 | Disease under study |
| Leukoencephalopathy[a] | 28/224 | 3 | Study drug |
| Cardiac failure[a] | 77/>77 | 3 | Valvular aortic stenosis |
| Ascites[a] | 89/>115 | 5 | Disease under study |
| Disease progression[a] | 89/127 | 5 | Disease under study |
| Fatigue | 204/219 | 2 | Disease under study |
| Cardiac failure[a] | 68/68 | 5 | Study drug |
| Diarrhea | 225/239 | 2 | Study drug |
| Fatigue | 100/133 | 4 | Study drug |
| Neutropenia | 124/139 | 3 | Study drug |
| Abdominal pain[a] | 82/>85 | 3 | Disease under study |
| Tremor | 280/>288 | 1 | Disease under study |
| Malignant pleural effusion[a] | 4/>4 | 2 | Disease under study |
| General physical health deterioration | 144/>144 | 2 | Disease under study |
| Convulsion[a] | 137/>143 | 3 | Disease under study |
| Disease progression[a] | 41/63 | 5 | Disease under study |
| Dehydration[a] | 29/>29 | 5 | Study drug |
| Disease progression[a] | 48/>48 | 5 | Disease under study |
| Hepatic failure[a] | 173/175 | 5 | Disease under study |
| Hepatic failure[a] | 39/>39 | 5 | Disease under study |
| Disease progression | 233/>233 | 5 | Disease under study |
| Cerebrovascular accident[a] | 49/52 | 3 | Diabetes |
| Abdominal pain | 242/252 | 3 | Study drug |
| Fatigue | 30/>37 | 3 | Disease under study |
| Nausea[a] | 73/81 | 3 | Disease under study |
| Vomiting[a] | 73/81 | 3 | Disease under study |

In the supportive Phase II studies (A6181047 and A6181061), 13 patients withdrew in the former and 19 in the latter. A total of 13 of these were considered related to the study treatment and included episodes of diarrhoea, stomatitis, vomiting, thrombocytopenia, congestive cardiac failure, pyrexia and gastrointestinal (GI) haemorrhage.

Review of adverse events associated with temporary discontinuation or dose reductions of treatment revealed that in the pivotal study this occurred in 47% of patients on sunitinib,

68% of patients in the supportive Phase II study (RTKC-0511-015), 56.7% of patients in the Phase II Study A6181047 and 64.5% of patients in Study A6181061 all of which are consistent to the adverse events that were recognised as associated with sunitinib therapy.

Cardiac failure was reported as an adverse event in two patients on sunitinib in the pivotal study. There was one episode of cardiomyopathy. All three adverse events were considered related to the study treatment.

In the supportive Phase II study (RTKC-0511-015), one patient experienced congestive cardiac failure which was considered related to study treatment. Three patients experienced episodes of ventricular dysfunction. A total of nine patients experienced decreased ejection fraction in this study, six with a maximum intensity of Grade I and three of a Grade II.

In the other two Phase II studies, one patient experienced congestive cardiac failure (in Study A6181061) which was considered related to study treatment.

Six subjects developed hypothyroidism while receiving sunitinib in the pivotal study. All of these were considered treatment related and were Grade I-II in severity.

In the supportive Phase II study (RTKC-0511-015), two patients experienced hypothyroidism of Grade I severity which was considered related to treatment. A further patient experienced thyroiditis while receiving sunitinib. This event was Grade II in severity.

In the supportive Phase II study (A6181047), two patients experienced hyperthyroidism and eight experienced hypothyroidism. Both cases of hyperthyroidism were considered as Grade I and related to the study treatment. All eight cases of hypothyroidism were Grade I or II and seven out of the eight patients were considered to be related to the study treatment. In the supportive Phase II study (A6181061), two patients experienced hypothyroidism related to study treatment. Both were Grade II in severity.

Bleeding experienced in 16 or 19.3% of patients receiving sunitinib in the pivotal trial was considered to be a treatment related adverse event. All were Grade I or II in severity with epitaxis being the most common occurring in 20.5% of patients. One of these was Grade III in severity.

In the supportive Phase II study (RTKC-0511-015), two patients experienced Grade III/IV bleeding events, both gastrointestinal haemorrhage with one leading to death, which were considered related to treatment.. A further 12 patients experienced epistaxis of Grade I or II in severity which were considered related to treatment.

In the other two Phase II studies, one patient experienced a Grade III/IV rectal haemorrhage in Study A6181047 which was considered related to treatment. Epistaxis of Grade I or II severity experience in twelve patients in this study was considered related to study treatment. One patient who experienced a Grade V abdominal wall haemorrhage was not considered related to treatment.

In Study A6181061, two patients experienced treatment related bleeding, one a Grade IV gastric haemorrhage and one an undesignated Grade III haemorrhage. Twenty eight patients experienced epistaxis which was considered related to treatment (all were Grade I-II except for one Grade III event).

No patients in the pivotal trial receiving sunitinib experienced thromboembolic events. In the supportive Phase II study (RTKC-0511-015), two of three patients who experienced pulmonary embolism were considered related to treatment. In the supportive Phase II study (A6181047), a single patient experienced a pulmonary embolism of Grade I severity

that was considered related to study treatment. In Study A6181061 three patients experienced pulmonary embolism; one was Grade I and two were Grade IV. None were considered related to treatment.

Grade III or IV haematologic abnormalities, principally neutropenia and to a lesser extent thrombocytopenia, were more common in the sunitinib arm than the placebo arm of the pivotal trial.

Abnormalities of blood chemistry in the pivotal trial were infrequent and essentially equally represented in the patients receiving sunitinib versus placebo as illustrated Table 28.

Table 28 **Summary of Selected CTCAE Grade 3 and 4 Chemistry Abnormalities and Shifts from Grade ≤2 to Grade ≥3 (All Cycles) – As-Treated Population – Study A6181111**

| | Number (%) of Subjects with Highest CTCAE Grade of Abnormality | | Number (%) of Subjects with Shift from CTCAE Grade ≤2 | |
|---|---|---|---|---|
| Parameter | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| **Sunitinib (N=82)** | | | | |
| Alkaline phosphatase | 8 (9.8) | 0 | 4 (4.9) | 0 |
| Creatinine | 1 (1.2) | 3 (3.7) | 1 (1.2)[a] | 2 (2.4)[a,b] |
| Hyperglycemia | 8 (9.8) | 2 (2.4) | 6 (7.3)[b] | 1 (1.2)[a] |
| Hypophosphatemia | 6 (7.4) | 0 | 3 (3.8)[a,c] | 0 |
| **Placebo (N=80)** | | | | |
| Alkaline phosphatase | 8 (10.0) | 1 (1.3) | 2 (2.5)[b] | 1 (1.3)[b] |
| Creatinine | 2 (2.5) | 2 (2.5) | 1 (1.3)[a] | 1 (1.3)[a] |
| Hyperglycemia | 13 (16.3) | 1 (1.3) | 9 (11.3)[a,b,c] | 0 |
| Hypophosphatemia | 4 (5.2) | 0 | 2 (2.6)[a] | 0 |

Table presents CTCAE Grade 3 and 4 chemistry abnormalities reported in at least 8 subjects
[a] Includes at least 1 subject with a shift from CTCAE Grade 0
[b] Includes at least 1 subject with a shift from CTCAE Grade 1
[c] At least 1 additional subject had a missing/not reported CTCAE grade at baseline and a maximum CTCAE Grade 3

In the pivotal trial, post-baseline TSH levels above the upper limit of normal were reported in 26 patients (31.3%) in the sunitinib arm and 12 patients (14.6%) in the placebo arm. Conversely post-baseline TSH levels below normal were recorded in three patients in the sunitinib arm and seven in the placebo arm.

Review of laboratory abnormalities in supportive study RTKC-0511-015 are summarised in Table 29. Again these are principally related to the disturbances of neutrophils and platelets. Similar results were noted in the other two supportive Phase II trials.

Table 29 **Summary of Subjects with Grade 3 or 4 Chemistry Abnormalities (All Cycles) – Study RTKC-0511-015**

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Carcinoid (N=41) | | Pancreatic (N=66) | |
| | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| Hematology | | | | |
| ANC | 9 (22.0) | 2 (4.9) | 22 (33.3) | 3 (4.5) |
| Hemoglobin | 2 (4.9) | 0 (0.0) | 1 (1.5) | 0 (0.0) |
| Lymphocytes | 5 (12.2) | 0 (0.0) | 23 (34.8) | 0 (0.0) |
| Platelets | 3 (7.3) | 0 (0.0) | 6 (9.1) | 0 (0.0) |
| WBC | 3 (7.3) | 0 (0.0) | 12 (18.2) | 0 (0.0) |
| Chemistry | | | | |
| ALT | 1 (2.4) | 0 (0.0) | 3 (4.5) | 0 (0.0) |
| AST | 1 (2.4) | 0 (0.0) | 3 (4.5) | 0 (0.0) |
| Albumin | 0 (0.0) | 0 (0.0) | 1 (1.5) | 0 (0.0) |
| Alkaline phosphatase | 2 (4.9) | 0 (0.0) | 5 (7.6) | 0 (0.0) |
| Amylase | 0 (0.0) | 0 (0.0) | 1 (1.5) | 0 (0.0) |
| Indirect bilirubin | 0 (0.0) | 0 (0.0) | 1 (1.5) | 0 (0.0) |
| Hypocalcemia | 0 (0.0) | 1 (2.4) | 2 (3.0) | 0 (0.0) |
| Creatine kinase | 0 (0.0) | 0 (0.0) | 2 (3.0) | 0 (0.0) |
| Hyperglycemia | 2 (4.9) | 0 (0.0) | 9 (13.6) | 0 (0.0) |
| Lipase | 4 (9.8) | 1 (2.4) | 10 (15.2) | 1 (1.5) |
| Hypophosphatemia | 3 (7.3) | 0 (0.0) | 5 (7.6) | 0 (0.0) |
| Hypokalemia | 1 (2.4) | 0 (0.0) | 1 (1.5) | 0 (0.0) |
| Hyponatremia | 1 (2.4) | 0 (0.0) | 2 (3.0) | 1 (1.5) |
| Total bilirubin | 0 (0.0) | 0 (0.0) | 2 (3.0) | 0 (0.0) |
| Uric acid | 0 (0.0) | 6 (14.6) | 0 (0.0) | 3 (4.5) |
| Coagulation | | | | |
| Prothrombin | 1 (2.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Review of vital signs and ECG data revealed that across the four studies there was no evidence of a significant adverse effect of sunitinib on vital signs, physical examination findings or ECG results.

An increase in blood pressure occurred in 43.8% of patients receiving sunitinib in the pivotal trial, one was a Grade III event but none required discontinuation of treatment. In the supportive Phase II study RTKC-0511-015, 49.5% of patients experienced hypertension and four of these were Grade III/IV. In supportive Study A6181047, 43.3% of patients experienced hypertension, six of which were considered severe. In supportive Study A6181061, 21 patients experienced hypertension but none were considered severe.

A 120 day safety update was provided from 103 patients with pNET previously involved in study A6181111 who went on to receive sunitinib in extension studies. All of these patients experienced adverse events. The most commonly associated events were of a general systemic nature, the most common being diarrhoea, neutropenia and asthenia, all of which were experienced by at least 35% of patients, and those associated with the site of administration followed by gastrointestinal disorders, skin and subcutaneous disorders.. The most frequent Grade III/IV adverse events were neutropenia and asthenia followed by abdominal pain, diarrhoea and thrombocytopenia. These appear to be generally consistent with those reported from the original pivotal study. Treatment related adverse events occurred in 96.1% of patients in the extension studies and were similar in incidence and severity of those reported overall. The most frequent Grade III/IV treatment related adverse events were neutropenia, diarrhoea, asthenia, hand/foot syndrome, thrombocytopenia and leukopaenia.

Review of deaths in this extension period revealed that 18 patients died while on treatment or during follow up. None of these were considered to be related to study treatment. While review of treatment related serious adverse events revealed that 11

patients receiving sunitinib experienced an SAE. The events are summarised in Table 30 and are again consistent with results previously reported in pivotal trial.

Table 30 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)** | | | | | |
| **1** | Haematemesis | 3/7 | 2 | Resolved | |
| | Nausea | 77/>77 | 3 | Still present | |
| | Vomiting | 77/>77 | 3 | Still present | |
| **2** | Palmar-plantar erythrodysaesthesia syndrome | 189/189 | 3 | Resolved | |
| **3** | Metabolic encephalopathy | 12/>12 | 3 | Still present | |
| **4** | Diarrhoea | 76/82 | 3 | Resolved | |
| | Diarrhoea | 138/173 | 3 | Resolved | |
| **5** | Lung disorder | 92/114 | 3 | Resolved | |
| **6** | Respiratory failure | 33/38 | 2 | Resolved | |
| **7** | Arthralgia | 16/22 | 3 | Resolved | |
| | Arthralgia | 23/27 | 3 | Resolved | |
| **8** | Abdominal pain | 26/36 | 3 | Resolved | |
| **9** | Pneumatosis intestinalis | 47/73 | 2 | Resolved | |
| **10** | Neutropenia | 183/190 | 3 | Resolved | |
| | Neutropenia | 198/203 | 3 | Resolved | |
| | General physical health deterioration | 227/>227 | 3 | Resolved | |
| | Anorexia | 244/>258 | 1 | Unknown | |
| **11** | Diarrhoea | 124/>158 | 3 | Still present | |

F=female, M=male
Use of '>' represents imputed data

During the extension studies, 23.6% of patients experienced adverse events requiring treatment withdrawal. In eight patients this was related to treatment and included single episodes of diarrhoea, two episodes of thrombocytopenia, two of neutropenia and deterioration of general physical health. Specific adverse events of note included five reports of hypothyroidism in the extension studies, four of which were Grade I and one Grade II. There were 16 episodes of epistaxis; 14 of which were Grade I and II, one Grade III and one Grade IV in severity.

Review of laboratory data in the extension studies highlighted the incidence of neutropenia and thrombocytopenia while there were few abnormalities related to changes in blood chemistry.

Ten patients experienced hypertension during the extension studies, three of which were considered severe but none required discontinuation of treatment.

Evaluator's Comment:

The toxicity profile demonstrated in the pivotal trial and the three supportive studies is is well recognised in patients treated with sunitinib. The most frequent toxicities were constitutional in character or associated with gastrointestinal, cutaneous and haematopoietic systems. These were most often mild to moderate in severity. Nevertheless, there were a small number of severe toxicities including those leading to death which involved cardiac failure, gastrointestinal haemorrhage, septic shock and one later death which was associated with acute myeloid leukaemia.

Other severe adverse events included cardiac failure in four patients, cardiomyopathy in one and haemorrhagic events including epistaxis. This all indicates a need for careful monitoring in the management of patients receiving sunitinib. These adverse events have all been reported previously and are clearly outlined in the relevant Product Information. The single episode of acute myeloid leukaemia is a note of caution for the ongoing follow up for these patients.

## List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

The clinical evaluator stated that there were no outstanding clinical questions in this submission.

## Clinical Summary and Conclusions:

Three Phase II studies (RTKC-0511-015, A6181047 and A6181061) assessed pharmacokinetic data in multiple dose single agent studies. In addition two other studies, namely A6181106 and A6181079 evaluated single dose PK data in relation to renal impairment and hepatic dysfunction respectively.

The pharmacokinetic studies showed that the steady state trough plasma exposure to sunitinib and its active metabolite SU012662 in the pNET sub-population appeared to be similar to that in the GIST and MRCC patient populations, indicating that the PK of sunitinib and metabolite were not tumour type dependent.

In addition, the PK of sunitinib and the metabolite appeared to be similar between the continuous dose schedule and the 4/2 schedule in GIST and metastatic RCC patients. Therefore it would be expected that the total plasma exposures to sunitinib and metabolite following treatment with sunitinib 37.5mg on a continuous daily schedule would be similar to that following treatment with sunitinib 50mg in the cyclical 4/2. The PK of sunitinib and metabolite was not affected by either severe renal impairment or hepatic dysfunctions. This would indicate that in subjects with either renal impairment or hepatic impairment no adjustment to the starting dose for sunitinib appears to be necessary. It should be noted that in ESRD patients on dialysis the commonly used starting dose of sunitinib may need to be assessed for possible subsequent dose modification based on patients' safety and tolerability.

In relation to efficacy data, the principal evidence provided in this submission are derived from two studies (A6181111 and RTKC-0511-015)

A total of 171 subjects were randomised to study treatment of which 165 patients were treated in the pivotal study. A clinically significant improvement in PFS was observed in favour of sunitinib in patients with progressive well-differentiated pNET. A median PFS of 11.4 months was observed in the sunitinib arm and a median PFS of 5.5 months observed in the placebo arm with a hazard ratio of 0.418 and P value 0.0001 based on a total of 81 events.

Of the secondary efficacy endpoints, the overall response determined by investigator assessment was statistically significantly higher on the sunitinib arm than the placebo arm being 9.3% versus 0% with a P value 0.0066. All responses were partial in nature. The median TTR in terms of Kaplan-Meier estimate of time to event for the ITT population is only estimated due to the number of responders, however among those patients with objective response the median TTR was 3.1 month. The median DR among patients could not be estimated as 7 of 8 responding patients had ongoing responses at the time of data cut-off.

An updated overall survival analysis through to 1 December 2009 showed fewer deaths in the sunitinib arm (n=21 versus n=30 in the placebo arm). Sub-group analysis of PFS according to baseline characteristics continued to indicate significant benefit for patients receiving sunitinib.

Patient reported outcomes show no significant differences between the subjects in the sunitinib and placebo arms during treatment within most domains and symptoms as assessed against the questionnaire EORTC-QNQ-C30.

In the supportive Phase II trial RTKC-0511-015, a total of 66 patients with pNET were treated with sunitinib. The overall response rate for this group was seven of the first 38 patients treated, all of whom had partial responses. A subsequent total of 66 patients were enrolled with the overall response rate of 11 partial responses (16.7%). The median TTP was 33.4 weeks with a 95% CI of 28.1-54.1 weeks.

A total of four studies comprised the safety data presented in this evaluation (A6181111, RTKC-0511-015, A6181047 and A6181061). A total 398 patients in these studies were evaluated for safety, of these 316 received at least one dose of sunitinib. A total of 237 subjects were on a trial of pNET of whom 152 were treated with sunitinib. Some 338 patients were treated on a continuous daily schedule and 253 of these were treated with sunitinib.

Based on the results of the pivotal Phase III study, sunitinib 37.5mg on a continuous daily schedule has an acceptable safety profile in subjects with pNET.

The most common sunitinib related adverse events included diarrhoea, nausea, asthenia, vomiting and fatigue. Most of these were Grade I/II in severity. Nevertheless it is important to note that there were severe adverse events which included cardiac dysfunction, thyroid dysfunction, haemorrhagic events and thromboembolic events but are of relatively low incidence and have been previously reported.

Temporary discontinuation or dose reductions due to adverse events occurred more frequently on the sunitinib arm (54.2% compared to 32.9% in the placebo arm). Deaths were reported more frequently in the placebo arm (25.6% compared to 10.8% in the sunitinib arm) although only one death on the sunitinib arm was considered related to treatment (due to cardiac failure).

The most common clinical laboratory disturbances were the haematological effects of neutropenia and thrombocytopenia and a modest incidence of hypoglycaemia and disturbed thyroid function tests. All of these have previously been reported for sunitinib.

Similarly there was a moderate incidence of hypertension including relatively severe hypertension, again generally previously reported and reversible on temporary discontinuation of treatment. One unusual late adverse event, acute myeloid leukaemia, was considered related to sunitinib therapy and requires further evaluation and potential monitoring of patients after long-term administration of sunitinib.

***Benefits and Risk Assessment***

These studies have demonstrated that in pNET tumours administration of sunitinib is associated with a significant improvement of progression free survival compared with placebo. The data show a benefit and sub-group analyses confirm this benefit. The only proviso relates to evidence of improvement in overall survival which on an updated review of data does not reach significance. Nevertheless this may at least in part be related to the crossover effect of patients on placebo subsequently receiving sunitinib in extension studies. Certainly the supportive study tends to confirm evidence of beneficial effect of sunitinib in the treatment of this relatively rare tumour group.

The pharmacokinetic comparisons of intermittent versus continuous dose schedules confirm the pharmacokinetic equivalence of continuous daily dose schedule. The safety evaluation confirms essentially a similar safety profile. The two Phase I studies assessing the influence of renal and hepatic dysfunction in volunteers confirm the lack of influence of these organ dysfunctions on pharmacokinetics and therefore indicate that dose adjustments are not routinely required in the presence of either renal or hepatic dysfunction.

The safety profile demonstrated in these studies, are in essence, in line with that previously reported for sunitinib. Certainly it has an incidence of significant adverse effects including gastrointestinal, haemorrhagic, cardiac and haematologic events, all of which require appropriate monitoring and relevant management. The only new area of concern is the one patient with acute myeloid leukaemia raising the issue of long term effects of sunitinib which will require appropriate monitoring.

In summary the clinical evaluator considers that the benefit risk balance favours the approval of sunitinib for the treatment of unresectable pancreatic neuroendocrine tumours (pNET).

# V. Pharmacovigilance Findings

## Risk Management Plan

The following Risk Managment Plan (RMP) was included with the current Australian submission (see Table 31).

Table 31. Risk Managment Plan

| Safety Concern | Routine risk minimisation activities sufficient? | Description of routine activity and justification |
|---|---|---|
| **Identified Risks** | | |
| Hypertension | Yes | PV monitoring as described in Section 2.1 and product information and labeling as described in Section 2.3 are expected to be sufficient for risk minimization. |
| Hemorrhagic events | Yes | " |
| Cytopenic events | Yes | " |
| QTc interval prolongation | Yes | " |
| Fatigue and asthenia | Yes | " |
| Thyroid dysfunction | Yes | " |
| Left ventricular dysfunction / Heart Failure | Yes | " |
| Serious infection | Yes | " |
| Thrombotic microangiopathy | Yes | " |
| Proteinuria / Nephrotic syndrome | Yes | " |
| Reversible Posterior Leukoencephalopathy Syndrome | Yes | " |
| Fistula formation | Yes | " |
| **Potential risks** | | |
| Thromboembolic events | Yes | " |
| Gastrointestinal perforations | Yes | " |
| Adrenal gland dysfunction | Yes | " |
| Carcinogenicity | yes | Routine Pharmacovigilance and periodic review of Targeted Medical Events are considered adequate to collect, collate, analyze, and monitor these potential risks. |
| Pancreatic dysfunction | Yes | Product information and labeling as described in Section 2.3 is expected to be sufficient for risk minimization. |
| Drug interaction with CYP3A4 inhibitor or inducer | Yes | " |
| Myopathy | Yes | " |
| Cardiotoxicity | Yes | Routine Pharmacovigilance and periodic review of Targeted Medical Events are considered adequate to collect, collate, analyze, and monitor these potential risks. |
| **Important missing information** | | |
| Pediatric subjects | Yes | "PV monitoring as described in Section 2.1 and product information and labeling as described in Section 2.3 are expected to be sufficient for risk minimization. |
| Pregnancy | Yes | " |
| Severe Hepatic impairment | Yes | " |

In summary, routine pharmacovigilance[9] and risk minimisation[10] activities, including ongoing clinical trials, are proposed by the sponsor and considered sufficient to monitor the safety concerns presented by sunitinib (Sutent).

Recommendations to the Delegate to changes to the current RMP are:

- Addition of the important potential risk OsteoNecrosis of the Jaw (ONJ) and prior or concomitant treatment with IV bisphosphonates' to the pharmacovigilance and risk management plans. This should include the sponsor proposing appropriate pharmacovigilance and risk management activities and updating the relevant sections of the PI to reflect the changes made to the Summary of Product Characteristics (SPC).
- Update section *Summary of safety concerns and planned pharmacovigilance actions* table to include the following studies listed in the *Detailed action plan for specific safety concerns*:
    - A Phase I Study of Sunitinib in Children with Refractory Solid Tumours is a study not sponsored by Pfizer in the United States.
    - A Phase 1 Study To Evaluate The Pharmacokinetics Of SU011248 In Subjects with Impaired Hepatic Function
- The *Overview of study protocols for pharmacovigilance plan* states that "The pharmacovigilance plan does not include any study protocols". This text should be updated as the pharmacovigilance plan does include study protocols.
- The *Summary of outstanding actions, including milestones* states that "There are no outstanding actions". This text should be updated to include information such as the estimated/actual completion date of the studies included in the pharmacovigilance plan.

It is recommended that the sponsor be required to include osteonecrosis of the jaw and concomitant or previous administration with IV bisphosphonates into the relevant sections of the Australian PI. It is important prescribers be alerted to this serious adverse event, especially because bisphosphonates are commonly prescribed. It is also recommended the sponsor be required to notify the Office of Product Review at TGA if the Risk Managment Plan that was updated 19th October 2010 has any additional safety concerns to the current Risk Managment Plan (Version, 7.0 11th November) that was reviewed.

# VI. Overall Conclusion and Risk/Benefit Assessment

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

[9] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[10] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

## Quality

No quality data were submitted with the current Australian application.

## Nonclinical

No nonclinical data were submitted with the current Australian application.

## Clinical[11]

The clinical evaluator has recommended approval of the application.

**Pharmacodynamics (PD)**

In a phase II study in patients with pNET or carcinoid tumour (**RTCK 0511-015**), sunitinib administration was associated with reductions in circulating soluble VEGFR (an endogenous inhibitor of VEGF) and increases in circulating VEGF, suggesting inhibition of the VEGF pathway.

**Pharmacokinetics (PK)**

The submission included two studies which used the proposed new dosage regimen (A618-1061 in RCC and A618-1047) in GIST). Both studies measured trough levels of sunitinib and its active metabolite. There was no accumulation of drug or metabolite after 4 weeks of continuous daily dosing. Trough levels observed were similar to those seen in previous studies at the end of 4 weeks using the currently approved 4/2 cycle regimen.

The submission also included a study on the effect of renal impairment on the PK of sunitinib (A618-1106). Severe renal impairment (CrCL <30 mL/min) had no clinically significant effect on the PK of sunitinib. Patients with end stage renal disease on haemodialysis had an approximate 50% reduction in AUC. However, analysis of dialysate samples indicate that only a very small fraction of circulating sunitinib or its active metabolite is removed by dialysis, suggesting that reduced systemic exposure in dialysis patients may have been due to reduced absorption.

Sunitinib and its main metabolite are known to be metabolised by CYP3A4. The submission included a study on the effect of mild or moderate hepatic impairment on the PK of sunitinib (A618-1079). Mild or moderate hepatic impairment was not associated with a clinically significant effect on the PK of sunitinib or its primary metabolite. The effect of severe hepatic impairment has not been studied.

[11] Studies RTCK-0511-015, A6181061, A6181061 and A6181047 7 are incorrectly referred to as RTKC-0511-015, AS18-1111, AS18-1061 and AS18-104 in the text under the heading *Clinical*.

## Efficacy

Evidence for efficacy comes primarily from a single double-blind, randomised, controlled trial (**AS18-1111**) which compared sunitinib with placebo. At the time of writing the trial had not yet been published but the sponsor has indicated that it has been accepted for publication in the New England Journal of Medicine. Subjects included had *well-differentiated*, advanced or metastatic pNETs, that had shown evidence of progression within the preceding 12 months and which were not amenable to curative therapy.

The primary endpoint was progression-free survival (PFS). Patients on the placebo arm who experienced progression were permitted to crossover to sunitinib treatment. The study was planned to enrol 340 subjects, with an interim analysis to be done after 130 PFS events and a final analysis after 260 PFS events. The study had a data monitoring committee (DMC) which had access to PFS data. The DMC determined that the study had met its primary endpoint after only 73 PFS events had been observed. The study was therefore closed early (after 171 subjects had been randomised) and the PFS analysis presented in the submission is based on a total of 81 PFS events. After closure of the study, all subjects were able to receive sunitinib.

Sunitinib treatment was associated with a significant reduction in the risk of progression or death-hazard ratio of 0.418 (95% CI: 0.263-0.662): p=0.000118. Median PFS was doubled (11.5 versus 5.5 months).

Overall survival was a secondary endpoint. Although there was a trend towards improved survival, this was not statistically significant. The survival data are not mature with only 51 of 171 subjects having died. However, given that all patients enrolled in the placebo arm were able to cross-over to sunitinib, it would seem unlikely that a survival benefit will be demonstrated.

Sunitinib treatment was associated with a statistically significantly higher response rate (9.3% vs 0%). There were no differences between treatment arms in quality of life measures.

There was one supportive study - **RTCK 0511-015**. This was an open uncontrolled Phase II study which enrolled 66 subjects with pNETs which were not amenable to curative therapy. Subjects were treated with the 50 mg/day, 4 weeks on, 2 weeks off regimen. The primary endpoint was response rate. The observed response rate was 16.7 % with all responses being partial responses.

**Safety**

A total of 149 pNET subjects were treated with sunitinib in the submitted studies. A further 167 RCC and GIST patients were treated with the proposed new dosage regimen in two phase II studies (**AS18-1061** in RCC and **AS18-1047** in GIST).

In the pivotal, double-blind, placebo-controlled phase III study, the pattern of toxicity observed was generally consistent with that previously documented for sunitinib. The overall toxicity is summarised in the following table:

| Table 32 | Sunitinib (n = 83) | Placebo (n=82) | CER |
|---|---|---|---|
| Adverse events (AEs) | 98.8 % | 95.1 % | p 58 |
| Treatment related AEs | 97.6 % | 78.0 % | p 64 |
| Grade III or IV AEs | 49.4 % | 43.9 % | p 58 |
| Treatment related Grade III or IV AEs | 43.4% | 19.5 % | p 64 |
| Serious AEs (SAEs) | 26.5 % | 41.5 % | p 68 |
| Treatment related SAEs | 13.2 % | 7.3 % | p 71 |
| Discontinuations due to AEs | 18 | 14 | p 73 |
| Deaths due to study drug | 1 | 1 | p 68 |

Sunitinib was associated with an increased incidence of:

- Gastrointestinal events (diarrhoea, nausea, vomiting, stomatitis, anorexia, dysgeusia, dyspepsia, abdominal pain, etc);
- Asthenia and fatigue;
- Skin toxicity (discolouration, rash, palmar-plantar erythrodysesthesia syndrome, hair colour change
- Marrow toxicity (neutropaenia, thrombocytopaenia);
- Hypertension;
- Bleeding events (epistaxis, gingival bleeding);
- Hypothyroidism.

These toxicities have previously been documented for sunitinib and are described in the current product information. Most toxicities were grade I or II in severity.

The toxicities observed in the phase II studies were consistent with those seen in the pivotal study.

## Risk Management Plan

A risk management plan (RMP) dated 11 November 2009 was included with the submission and was evaluated by the TGA's Office of Product Review. The RMP was considered generally acceptable. Cases of osteonecrosis of the jaw (ONJ) have recently been reported and the RMP evaluator has recommended information regarding this adverse event be included in the Product Information.

## Risk-Benefit Analysis

### *Delegate Considerations*

Overall risk benefit

The pivotal study has demonstrated a clinically significant benefit for sunitinib in terms of delaying disease progression, with a doubling of progression-free survival (11.5 vs 5.5 months). Currently therapies for pNET (octreotide, lanreotide) are only registered for symptomatic treatment and only for *functioning* tumours. There are therefore no currently registered therapies for patients with non-functioning tumours, who make up approximately 50% of this patient group. No new safety issues have been identified. Overall I consider that the benefits of sunitinib in pNET patients outweigh its risks and I propose to approve the application.

Indication

The indication proposed by the sponsor is:

> *"... for the treatment of unresectable pancreatic neuroendocrine tumours (pNET)."*

The inclusion criteria for the pivotal study restricted enrolment to patients with "well differentiated neuroendocrine tumour" according to the WHO classification system shown below. Patients with poorly differentiated pNETs were specifically excluded.

Table 33. Classification of neuroendocrine tumours of the gastroenteropancreatic system (GEP-NET)

| | |
|---|---|
| 1a | Well-differentiated neuroendocrine tumor |
| 1b | Well-differentiated neuroendocrine carcinoma |
| 2 | Poorly differentiated neuroendocrine carcinoma |

The Delegate therefore proposed to restrict the indication to the following:

> *"... for the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pNET)."*

Hepatotoxicity

Sunitinib is known to be associated with liver toxicity. In May 2010 the FDA required the sponsor to include a boxed warning in the US prescribing information, concerning the potential for severe, sometimes fatal hepatotoxicity.

As part of the current application, the sponsor has revised the text concerning hepatic toxicity in the Precautions section of the PI. However, the Committee's advice is sought as to whether a boxed warning should be included in the Australian PI. Another agent in the same class (pazopanib) also currently has a boxed warning regarding hepatotoxicity.

***Proposed action***

The Delegate proposed to approve the application. The advice of the ACPM was requested, both in relation to approval of the new indication and the need for a boxed warning regarding hepatotoxicity.

## Sponsor's Response

Excerpt from the sponsor's response to the questions raised by the Delegate:

> Currently there is no standard, effective therapy for patients with pNET. The pivotal study investigating the efficacy and safety of SUTENT in the treatment of pNET was terminated early at the recommendation of an independent Data Monitoring Committee due to its determination that the study had met its primary objective and out of concern for the rates of disease progression, serious adverse events and deaths in patients randomised to placebo. Patients in both arms of the study were then offered open-label SUTENT in extension studies. This pivotal study demonstrated a substantial improvement in PFS for the SUTENT treatment arm with a median PFS of 11.4 months compared to 5.5 months in the placebo arm (HR 0.418, 95% CI 0.263, 0.662, p=0.0001). Even though the magnitude of the effect of sunitinib on survival is likely to have been confounded by a large proportion of subjects in the placebo arm receiving sunitinib upon crossover, the updated survival analysis included in the application continued to favour treatment with sunitinib with a hazard ratio of 0.594 (95% CI: 0.340 – 1.038; p=0.0644).
>
> SUTENT administered at a daily dose of 37.5 mg in the pivotal study displayed a manageable safety profile and the observed adverse events were consistent with the disease under study and with the known safety profile of SUTENT. No new hepatic safety concerns were identified in this application; hepatic failure was reported in the placebo arm but not the sunitinib arm of the pivotal study and hepatic adverse events were considered to be related to the disease under study rather than to treatment with SUTENT. As stated above, Pfizer does not consider a boxed warning concerning hepatotoxicity is warranted in the Australian PI for SUTENT.
>
> Both the clinical evaluator and TGA Delegate consider the benefits of SUTENT in pNET patients outweigh its risks and recommend the approval of this application. SUTENT fulfils an unmet medical need in the treatment options for patients with unresectable, well-differentiated pNET.

## Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommends approval of the submission from Pfizer Australia Pty Ltd to register sunitinib (as malate) (Sutent) capsules 12.5 mg, 25 mg, 37.5 mg and 50 mg to change the dose regimen and include the indication:

> *For the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pNET).*

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include:

Amendments to the *Precautions* and *Contraindications* sections to strengthen the statements on hepatotoxicity. * A boxed warning was not considered necessary.

* Following discussion with the Delegate, the *Precautions* text provided in the pre-ACPM response was considered acceptable and changes to the *Contraindications* section were not required.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sutent Capsules containing sunitinib (as malate) for the new indication:

> *"For the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET). "*

The full indications are now:

- For the treatment of advanced renal cell carcinoma;
- For the treatment gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance;
- For the treatment of unresectable, well-differentiated, pancreatic neuroendocrine tumours (pancreatic NET).

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

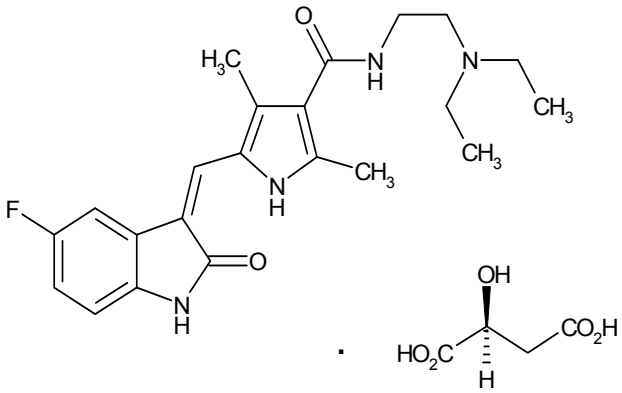
# PRODUCT INFORMATION

## SUTENT® (sunitinib malate)

## NAME OF THE MEDICINE

Sunitinib malate is designated chemically as (*Z*)-*N*-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (*S*)-2-hydroxysuccinate.

The molecular formula of sunitinib malate is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and its molecular weight is 532.57. The CAS Registry Number is 341031-54-7. The structural formula of sunitinib malate is shown below.




## DESCRIPTION

Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL.

SUTENT is supplied as a hard gelatin capsule for oral administration. Each capsule contains sunitinib malate equivalent to sunitinib 12.5, 25, 37.5 or 50 mg. The capsules also contain the following inactive ingredients: mannitol, croscarmellose sodium, povidone and magnesium stearate.

The capsules are differentiated by size, colour and printing. The hard gelatin capsules consist of Swedish Orange cap and body (12.5 mg), Swedish Orange body and caramel cap (25 mg), yellow cap and body (37.5 mg) and caramel cap and body (50 mg) and are printed with white printing ink (12.5 mg, 25 mg and 50 mg) or black printing ink (37.5 mg). The orange capsule shells contain gelatin, titanium dioxide and red iron oxide CI77491. The caramel capsule shells contain gelatin, titanium dioxide, red iron oxide CI77491, yellow iron oxide CI77492 and black iron oxide CI77499. The yellow capsule shells contain gelatin, titanium dioxide and yellow iron oxide CI77492.

## PHARMACOLOGY

### Mechanism of action

Sunitinib is a small molecule that simultaneously inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis and metastatic progression

of cancer. Sunitinib was evaluated for its inhibitory activity against a wide range of kinases and was identified as a potent inhibitor of platelet-derived growth factor receptor β (PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R) and the glial cell-line derived neurotrophic factor receptor (RET).

Inhibition of the tyrosine kinase activity of these RTKs by sunitinib has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays in which the activity of PDGFRα was inhibited. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays for inhibition of PDGFRβ, VEGFR2 and KIT tyrosine kinase activities.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumour xenografts expressing RTK targets in vivo and demonstrated inhibition of tumour growth or tumour regression, and/or inhibited metastases in some experimental models of cancer. Consistent with its multi-targeted profile, sunitinib demonstrated the ability to directly inhibit growth of tumour cells expressing dysregulated RTK targets (PDGFR, RET, FLT3 or KIT) and to inhibit tumour angiogenesis.

**Pharmacokinetics**

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and 266 patients with solid tumours.

***Absorption***

Absolute bioavailability has not been determined.

Maximum plasma concentrations ($C_{max}$) are generally observed between 6 - 12 hours ($T_{max}$) following oral administration. In multiple dose studies in the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and $C_{max}$ increase proportionately with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and its active metabolite are 62.9-101 ng/mL which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumour stasis/growth reduction *in vivo*.

Food has no effect on the bioavailability of sunitinib.

***Distribution***

Binding of sunitinib and its primary active metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no apparent concentration dependence in the range of 100-4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was large, 2230 L, indicating distribution into the tissues.

***Metabolism***

Sunitinib is metabolised primarily by the cytochrome P450 enzyme, CYP3A4, which produces its primary active metabolite, which is also metabolised by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure.

### *Elimination*

Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active metabolite are approximately 40-60 hours and 80-110 hours, respectively.

Excretion is primarily via faeces (61%) with renal elimination of drug and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine and faeces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (Cl/F) was 34-62 L/hr with an inter-patient variability of 40%.

No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite are observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

### *Special Populations*

The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

### *Hepatic impairment

Sunitinib and its primary metabolite are mainly metabolised by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment.

### *Renal impairment

Systemic exposures after a single dose of SUTENT were similar in subjects with severe renal impairment (CLcr<30 mL/min) compared to subjects with normal renal function (CLcr>80 mL/min). Although sunitinib and its primary metabolite were not eliminated through haemodialysis in subjects with end-stage renal disease (ESRD), the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

### *Population Pharmacokinetics*

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, gender, race or Eastern Cooperative Oncology Group (ECOG) performance status on the pharmacokinetics of sunitinib or the primary active metabolite.

There are no pharmacokinetic data available in paediatric patients.

## CLINICAL TRIALS

### Advanced Renal Cell Carcinoma (RCC)

A 1:1 randomised, multi-centre, Phase 3 study comparing SUTENT with interferon-α is ongoing in over 700 treatment-naïve patients with metastatic RCC (mRCC). The starting dose of SUTENT is sunitinib 50 mg orally once daily as a single agent for 4 consecutive weeks followed by 2 weeks off (Schedule 4/2) and the dosage of interferon-α2a (IFN-α) administered subcutaneously is 9 MIU three times weekly.

The primary endpoint is Progression Free Survival (PFS) and the study is also powered to detect an improvement in Overall Survival (OS). The statistical plan includes an interim analysis of Objective Response Rate (ORR) between the two treatments after 250 patients have completed at least 3 cycles. The results of the planned interim analysis, with ORR as the primary endpoint, are provided in Table 1.

**Table 1. SUTENT versus IFN-α in First-Line Treatment of mRCC Objective Response Rate and Progression Interim Results**

| **Core Imaging Laboratory Measurements (N= 235)** | | |
|---|---|---|
| | **SUTENT N=129 (%)** | **IFN-α N=124 (%)** |
| Patients with baseline assessment, n (%) | 115 (89.1) | 106 (85.5) |
| Best Overall Response | | |
| Complete Response | 0 (0.0) | 0 (0.0) |
| Partial Response | 33 (25.6) | 9 (7.3) |
| Stable Disease | 53 (41.1) | 54 (43.5) |
| Progressive Disease | 25 (19.4) | 29 (23.4) |
| Not evaluable (< 6 weeks on study) | 4 (3.1) | 14 (11.3) |
| Scans still to assess | 14 (10.9) | 18 (14.5) |
| Overall Response Rate (CR+PR), n (%)<br>(95% CI) | 33 (25.6)<br>(18.3 – 34.0) | 9 (7.3)<br>(3.4 – 13.3) |
| Patients with progression or death due to any cause while on study[1], n (%) | 32 (24.8) | 51 (41.1) |
| Median Progression Free Survival (PFS) in weeks, (95% CI) | NA (NA, NA) | 23.0 (16.7, NA) |

[1] On study includes a 28-day follow up period after the last dose of study drug.

NA = Could not be calculated because the data were not mature.

The use of single agent SUTENT in the treatment of advanced cytokine-refractory RCC was investigated in two studies, a pivotal Phase 2 study and a supportive Phase 2 study. Both studies were single-arm, non-randomised, multi-centre, open-label studies in patients with mRCC who were refractory to prior cytokine treatment (interferon-α, interleukin-2, or interferon-α plus interleukin-2). The primary endpoint for both studies was ORR. Secondary endpoints included assessment of Time to Tumour Progression (TTP), PFS, Duration of Response (DR) and OS.

The pivotal study enrolled 106 patients and the supportive study enrolled 63 patients. The starting dose in both studies was sunitinib 50 mg daily on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race, ECOG performance status, baseline malignancy and prior treatment history of the patients were comparable between the two studies. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in the pivotal study. All patients had received one previous cytokine regimen, to which 9.5% (n=16) had experienced an objective disease response. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in the pivotal study (27% vs. 16% in the supportive study) and bone metastases were more common in the supportive study (51% vs. 25% in the pivotal study); 52% of patients in the pooled population had at least 3 metastatic sites.

The results of the two studies are provided in Table 2.

**Table 2. Efficacy Results in second-line treatment of mRCC**

| Efficacy Parameter | Pivotal Study N = 106 | Supportive Study N = 63 |
|---|---|---|
| Objective Response Rate: CR + PR [% (95% CI)] | 35.8 (26.8, 45.7)[a] | 25.4 (15.3, 37.9) [a] |
| Median Time to Progression [weeks (95% CI)] | 38.0 (34.0, *)[a] | 37.7 (24.0, 46.4)[b] |
| Median Progression Free Survival [weeks (95% CI)] | 36.0 (33.9, 62.6)[a] | 37.7 (24.0, 46.4) [b] |
| Median Duration of Response [weeks (95% CI)] | ** (42.0, *) | 54 (34.3, 70.1) |

CI=Confidence interval, CR=Complete response, PR=Partial response

[a] Assessed by blinded core radiology laboratory

[b] Assessed by investigator; TTP and PFS were not measured by the core laboratory in the supportive study.

* Data not mature enough to determine upper confidence limit

** Median DR has not yet been reached.

The primary endpoint for both studies was ORR. The core imaging laboratory reported 38 partial responses (PRs) in the pivotal study resulting in an ORR of 35.8% (95% CI: 26.8, 45.7). Consistent results were observed in the supportive study where an ORR of 25.4% was demonstrated. The majority of objective disease responses were observed during Cycles 2 to 4; responses were observed as late as Cycle 11. Duration of tumour response (DR) data from the pivotal study is premature as only a relatively small number of patients responding to treatment had experienced disease progression (Median DR not yet reached [95% CI: 42.0 weeks,*] using core-laboratory assessment). The median DR in the supportive study, based on investigator assessment, was 54 weeks (95% CI: 34.3, 70.1). These results indicate that disease responses induced by SUTENT in patients with cytokine-refractory RCC were durable.

**Gastrointestinal Stromal Tumours (GIST)**

An initial open-label, dose-escalation study was conducted in patients with GIST after failure of imatinib (median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven patients were enrolled at various doses and schedules; 55 patients received a dose of 50 mg daily at the recommended treatment schedule of 4 weeks on followed by 2 weeks off (Schedule 4/2). In this study the investigator-assessed median TTP was 34.0 weeks (95% CI = 22.0–46.0 weeks).

A randomised, double-blind, placebo-controlled Phase 3 study of SUTENT was conducted in patients with GIST who were intolerant to, or had experienced disease progression during or following treatment with, imatinib (median maximum daily dose 800 mg). In this study, 312 patients were randomised (2:1) to receive either SUTENT 50 mg or placebo orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received SUTENT and 105 patients received placebo).

The results of the dose escalating and Phase 3 studies are provided in Table 3.

**Table 3. GIST Efficacy Results[a]**

| Efficacy Parameter | Phase 3 Study[b] | | Dose escalating study[c] |
|---|---|---|---|
| | SUTENT N = 207 | Placebo N = 105 | SUTENT N = 55 |
| Median Time to Progression [weeks (95% CI)] | 27.3[d] (16.0, 32.1) | 6.4[d] (4.4, 10.0) | 34.0 (22.0, 46.0) |

| Efficacy Parameter | Phase 3 Study[b] | | Dose escalating study[c] |
|---|---|---|---|
| | SUTENT N = 207 | Placebo N = 105 | SUTENT N = 55 |
| Median Progression Free Survival [weeks (95% CI)] | 24.6[e] (12.1, 28.3) | 6.4[e] (4.4, 10.0) | 34.0 (22.0, 46.0) |
| Median Overall Survival [weeks (95% CI)] | *[f] (43.7, *) | * (30.0, *) | Not measured |
| Objective Response Rate (ORR): CR+PR [n (%)] | 14 (6.8[g]) | 0 | 5 (9.1) |
| Duration of SD ≥ 22 weeks [n (%)] | 36 (17.4) | 2 (1.9) | 28 (50.9) |
| Clinical benefit rate: SD ≥22 weeks + CR + PR [n (%)] | 50 (24.2) | 2 (1.9) | 33 (60.0) |

CI=Confidence interval, CR=Complete response, PR=Partial response, SD=Stable disease

a Data based on cutoff date of 1 January 2005 for the phase 3 study and 1 December 2004 for the dose-escalating study.

b Core Imaging Laboratory Assessment

c Investigator Assessment (Core Imaging not conducted for secondary endpoints)

d Hazard Ratio 0.329, 95% CI 0.223, 0.466, p-value <0.001.

e Hazard Ratio 0.333, 95% CI 0.238, 0.467, p-value <0.001.

f Hazard Ratio 0.491, 95% CI 0.290, 0.831, p-value = 0.007.

g 95% CI = 3.7, 11.1.

* Unable to calculate due to the low number of deaths in the ongoing study.

In the Phase 3 study, a statistically significant prolongation in the primary endpoint, TTP, was observed between the treatment arms and was considered clinically significant (Figure 1). The median TTP by core imaging laboratory assessment was 27.3 vs. 6.4 weeks for the SUTENT and placebo arms, respectively (Hazard Ratio 0.329, 95% CI 0.222, 0.466, p-value <0.00001). The risk of experiencing progression was 3 times higher for patients in the placebo arm compared to the SUTENT arm (representing a 72% reduction in the risk of developing progressive disease for patients receiving SUTENT). Median TTP for the group of patients treated with SUTENT was more than 4 times longer than that for patients receiving placebo. Results of the dose escalating study with median TTP of 34.0 weeks by investigator assessment are consistent with the results of the Phase 3 study.

In the Phase 3 study, 14 PRs (6.8% ORR), as determined by response evaluation criteria in solid tumours (RECIST) using core laboratory assessment were observed in patients treated with SUTENT, while none was observed in the placebo arm. Results of the dose escalating study were consistent, with 5 PRs reported (9.1% ORR) by investigator assessment.

When evaluated for clinical benefit response (percentage of patients experiencing CR, PR or stable disease [SD] ≥22 weeks), 50 (24.2%) of patients treated with SUTENT in the Phase 3 study experienced clinical benefit, while only 2 (1.9%) placebo-treated patients experienced clinical benefit. In the dose escalating study, the clinical benefit rate was 60%. The difference in clinical benefit response rates between studies is the result of the longer follow-up period in the dose escalating study, resulting in more patients treated for at least 22 weeks compared to the Phase 3 study. These results demonstrate the ability of SUTENT to achieve and maintain disease control in patients with GIST after failure of imatinib.

**Figure 1. Kaplan-Meier Curve of TTP in Phase 3 GIST Study (Intent-to-Treat Population)**

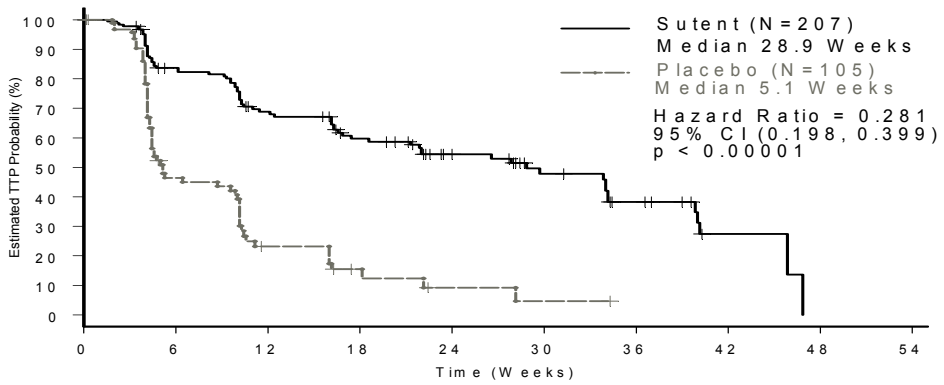
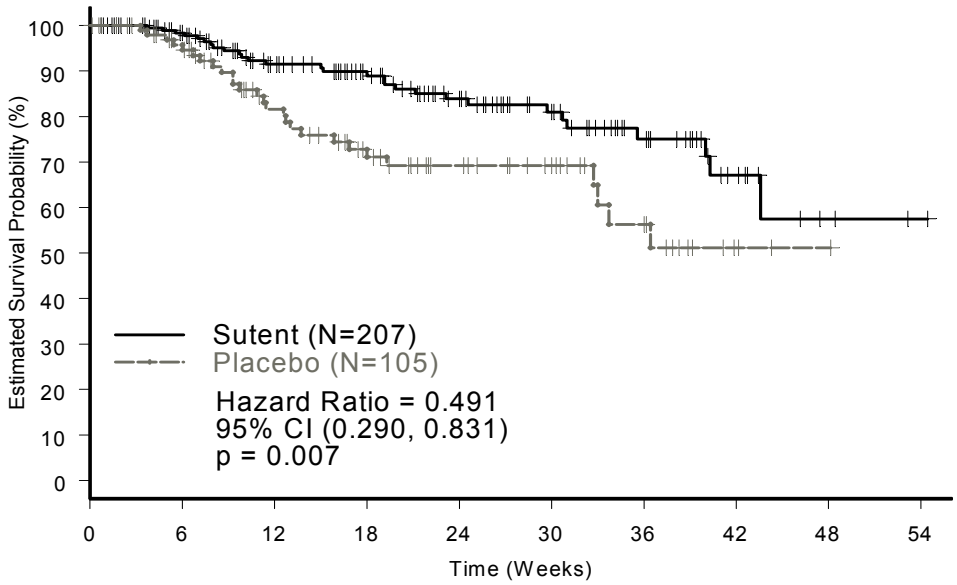



**Figure 2. Kaplan-Meier Curve of OS (Intent-to-Treat Population)**




The difference in OS was statistically significant (Hazard Ratio 0.491; 95% CI: 0.290, 0.831, p = 0.007) in the Phase 3 study (Figure 2). The risk of death was twice as high in patients in the placebo arm of the study compared to the SUTENT arm. Median OS had not yet been reached in either treatment arm at the time of the analysis. The percentages of deaths were 14% for SUTENT vs 25% for placebo.

*** Pancreatic Neuroendocrine Tumours (pancreatic NET)**

A supportive phase 2, open-label, multi-centre study evaluated the efficacy and safety of single-agent SUTENT 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pancreatic NET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%. All were partial responses.

A pivotal phase 3, multi-centre, international, randomised, double-blind placebo-controlled study of single-agent SUTENT was conducted in patients with unresectable, well-differentiated pancreatic NET. Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomised (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n=86) or placebo (n=85). The primary objective was to compare PFS in patients receiving sunitinib versus patients receiving placebo. Other endpoints included OS, ORR, Patient-reported Outcomes (PRO) and safety. Use of somatostatin analogs was allowed in the study.

Demographics were comparable between the SUTENT and placebo groups. Additionally, 49% of SUTENT patients had non-functioning tumours versus 52% of placebo patients and 92% of patients in both arms had liver metastases. A total of 66% of SUTENT patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of SUTENT patients had received somatostatin analogs compared with 22% of placebo patients.

A clinically significant advantage in PFS for SUTENT over placebo was seen. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI 0.263, 0.662) p-value =0.0001]. A hazard ratio favouring SUTENT was observed in all subgroups of baseline characteristics evaluated. The results are provided in Table 4.

This study was terminated early at the recommendation of an independent Drug Monitoring Committee and patients offered open-label SUTENT in extension studies.

**Table 4. Pancreatic NET Efficacy Results from the Phase 3 Study**

| Efficacy Parameter | SUTENT (n = 86) | Placebo (n = 85) | P-Value | HR (95% CI) |
|---|---|---|---|---|
| Progression-Free Survival [median, months] (95% CI) | 11.4 (7.4, 19.8) | 5.5 (3.6, 7.4) | 0.0001[a] | 0.418 (0.263, 0.662) |
| Overall Survival [median, months][a] (95% CI) | NR (21.5, NR) | NR (16.3, NR) | 0.0644[b] | 0.594 (0,340, 1.038) |
| Objective Response Rate [%] (95% CI) | 9.3 (3.2, 15.4) | 0 | 0.0066[c] | NA |

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached

[a] All subjects originally randomised were included and analysed under the original randomised treatment arm.

[b] 2-sided unstratified log-rank test

[c] Fisher's Exact test

**Figure 3. Kaplan-Meier Curve of PFS in the Phase 3 Pancreatic NET Study**

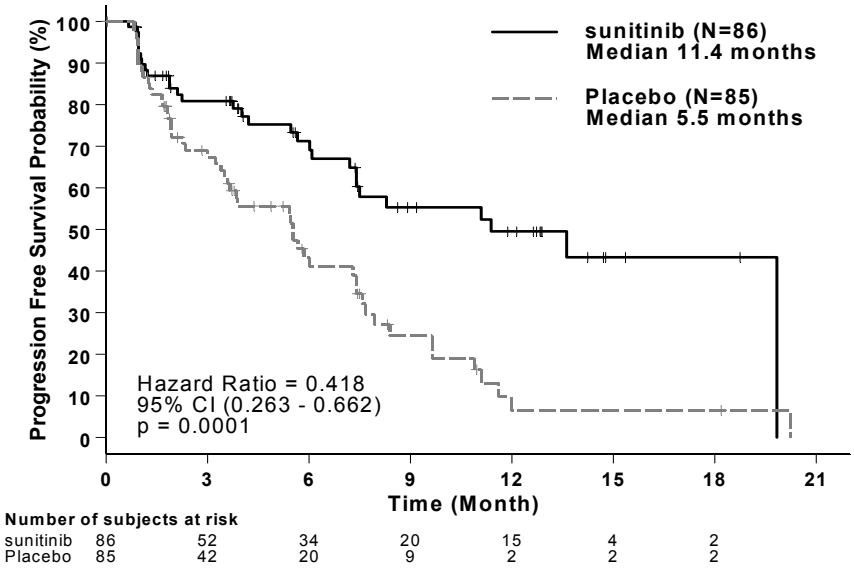
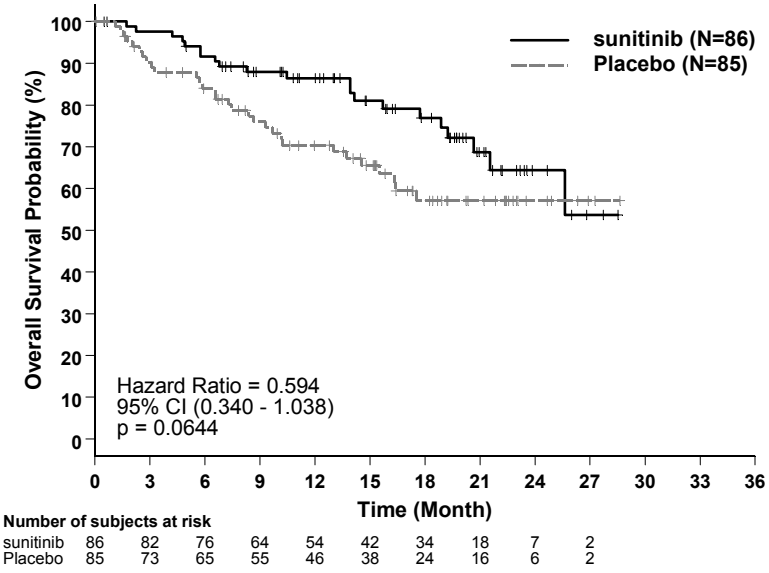



**Figure 4. Kaplan-Meier Curve of OS in the Phase 3 Pancreatic NET Study**




OS data were not mature at the time of the analysis. There were 21 deaths in the SUTENT arm and 30 deaths in the placebo arm. Patients in the placebo arm were able to receive SUTENT after disease progression, possibly confounding the survival analysis. A statistically significant difference in ORR favouring SUTENT over placebo was observed.

Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) demonstrated that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

# INDICATIONS

SUTENT is indicated for the treatment of advanced renal cell carcinoma.

SUTENT is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

*SUTENT is indicated for the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET).

# CONTRAINDICATIONS

Use of SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT capsules.

# PRECAUTIONS

***Skin and Tissues***

Skin discolouration possibly due to the colour of the active drug substance (yellow) is a common treatment-related adverse event occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters or occasional rash on the palms of the hands and soles of the feet.

The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.

***Haemorrhagic Events***

Haemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumour, urinary tract and brain haemorrhages. In clinical trials, treatment-related tumour haemorrhage occurred in approximately 2% of patients with GIST. These events may occur suddenly and, in the case of pulmonary tumours, may present as severe and life-threatening haemoptysis or pulmonary haemorrhage. Fatal pulmonary haemorrhage occurred in 2 patients receiving SUTENT in a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC.

Bleeding events occurred in 18% of patients receiving sunitinib in a Phase 3 GIST study compared to 17% of patients receiving placebo. In patients receiving sunitinib for treatment-naïve mRCC, 28% of patients had bleeding events compared with 7% of patients receiving interferon-α. (IFN-α). Seven (1.9%) patients on sunitinib versus 0% of patients on IFN-α experienced Grade 3 or greater treatment-related bleeding events. Of patients receiving sunitinib for cytokine-refractory mRCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in 19% of patients receiving sunitinib in the phase 3 pancreatic NET study compared to

4% of patients receiving placebo. Epistaxis was reported in 21% of patients receiving SUTENT for pancreatic NET and 5% of patients receiving placebo.*

Routine assessment of haemorrhagic events should include complete blood counts and physical examination.

Epistaxis was the most common treatment-related haemorrhagic adverse event reported. Less common bleeding events in mRCC,GIST and pancreatic NET patients included rectal, gingival, upper GI, genital and wound bleeding.

***Haematological***

Decreased absolute neutrophil counts of Grade 3 and 4 severity respectively were reported in 10% and 1.7% of patients on the phase 3 GIST study, in 16% and 1.6% of patients on the phase 3 mRCC study and in 13% and 2.4% of patients on the phase 3 pancreatic NET study. Decreased platelet counts of Grade 3 and 4 severity respectively were reported in 3.7% and 0.4% of patients on the phase 3 GIST study, in 8.2% and 1.1% of patients on the phase 3 mRCC study and in 3.7% and 1.2% of patients on the phase 3 pancreatic NET study. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. None of these events in the phase 3 studies were fatal, but rare fatal haematological events have been reported through post-marketing experience.*

Complete blood counts should be performed at the beginning of each treatment cycle or every 4 weeks during continuous therapy for patients receiving treatment with SUTENT.

***Cardiovascular***

Cardiovascular events, including heart failure, cardiomyopathy and myocardial disorders, some of which were fatal, have been reported through post-marketing experience. In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥20% and below the lower limit of normal occurred in approximately 2% of SUTENT-treated GIST patients, 4% of cytokine-refractory mRCC patients and 2% of placebo-treated patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued.

In the treatment-naïve mRCC study, 21% and 12% of patients on sunitinib and IFN-α, respectively, had an LVEF value below the LLN. One (<1%) patient who received sunitinib was diagnosed with congestive heart failure (CHF).

In GIST patients, treatment-related adverse events of 'cardiac failure', 'cardiac failure congestive' or 'left ventricular failure' were reported in 0.7% of patients treated with sunitinib and 1% of patients treated with placebo. In the phase 3 GIST study, treatment-related fatal cardiac reactions occurred in 1% of patients on each of the sunitinib and placebo arms of the study. In the phase 2 study in cytokine-refractory mRCC patients, 0.9% of patients experienced treatment-related fatal myocardial infarction and in the phase 3 study in treatment-naïve mRCC patients, 0.6% of patients on the IFN-α arm and 0% patients on the sunitinib arm experienced fatal cardiac events. In the phase 3 pancreatic NET study, one (1%) patient who received sunitinib had treatment-related fatal cardiac failure.* The relationship, if any, between receptor tyrosine kinase (RTK) inhibition and cardiac function remains unclear.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischaemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is

unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. 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.

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.

***QT Interval Prolongation***

The effect of sunitinib on QT interval was investigated in an open, positive control (moxifloxacin 400 mg) trial of 24 patients, aged 20-87 years with advanced malignancies. At plasma concentrations seen with normal recommended doses, the maximum QTcF (Fridericia's correction) mean change from baseline was 9.6 msec (upper 95% CI 15.1 msec). At plasma concentrations approximately twice those seen with recommended doses, the maximum QTcF mean change from baseline was 15.4 msec (upper 95% CI 22.4 msec). The positive control (moxifloxacin 400 mg) showed a maximum QTcF mean change from baseline of 5.6 msec.

One case of Torsades de Pointes has been reported in a patient receiving sunitinib 50 mg per day. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking other drugs known to prolong the QT interval (e.g. antiarrhythmics), or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of sunitinib reduced (see Interactions with other medicines and DOSAGE AND ADMINISTRATION).

***Hypertension***

Treatment-related hypertension was reported in approximately 16% of patients with solid tumours. SUTENT dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these patients was discontinued from treatment with SUTENT. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. Treatment-related hypertension was reported in approximately 24% of patients receiving sunitinib for treatment-naïve mRCC compared to 1% of patients receiving IFN-α . Severe hypertension occurred in 5% of treatment-naïve patients on sunitinib and 1% of patients on IFN-α. Treatment-related hypertension was reported in 23% of patients receiving sunitinib in a phase 3 pancreatic NET study, compared to 4% of patients receiving placebo. Severe hypertension occurred in 10% of pancreatic NET patients on sunitinib and 3% of patients on placebo.* 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.

***Venous Thromboembolic Events***

Treatment-related venous thromboembolic events were reported in approximately 1% of patients with solid tumours who received sunitinib on clinical trials, including GIST and mRCC.

Seven patients (3%) on SUTENT and none on placebo in a phase 3 GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT) and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Seven patients (2%) receiving sunitinib in the phase 3 treatment-naïve mRCC study and four patients (2%) on the two cytokine-refractory mRCC studies had treatment-related venous thromboembolic events reported. Six of these patients had pulmonary embolisms, one was Grade 3 and five were Grade 4, and five of these patients had DVT, one each with Grade 1 and 4, and three with Grade 3. Dose interruption occurred in one of these cases.

In treatment-naïve mRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolisms, one with Grade 1 and four with Grade 4.

*No treatment-related venous thromboembolic events were reported for patients receiving sunitinib and one Grade 2 DVT was reported for a patient receiving placebo in the phase 3 pancreatic NET study. No cases with fatal outcome were reported in GIST, mRCC and pancreatic NET registration studies. Cases with fatal outcome have been reported in the post-marketing setting.

***Thyroid Dysfunction***

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. 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.

Treatment-emergent acquired hypothyroidism was noted in 4% of GIST patients on SUTENT versus 1% on placebo. Hypothyroidism was reported as an adverse event in 2% of patients on sunitinib in the treatment-naïve mRCC study and one patient (<1%) in the IFN-α arm, and in 4% of patients across the two cytokine-refractory mRCC studies. Additionally, TSH elevations were reported in 2% of cytokine-refractory mRCC patients. Overall, 7% of the cytokine-refractory mRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the phase 3 pancreatic NET study treatment-related hypothyroidism was reported in 5 patients (6%) receiving sunitinib and in one patient (1%) on placebo.*

Rare cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

***Gastrointestinal Events***

Nausea, diarrhoea, stomatitis, dyspepsia and vomiting were the most commonly reported treatment-related gastrointestinal events. Supportive care for gastrointestinal adverse events requiring treatment may include medication with an anti-emetic or anti-diarrhoeal medication.

***Gastrointestinal Tract***

Serious, sometimes fatal, gastrointestinal complications, including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

***Pancreatitis***

Increases in serum lipase and amylase were observed in patients with various solid tumours who received SUTENT. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours. Pancreatitis has been observed uncommonly (<1%) in patients receiving sunitinib for GIST or mRCC. Cases of serious pancreatic events, some with fatal outcome, have been reported.

No treatment-related pancreatitis was reported in the phase 3 pancreatic NET study.*

If symptoms of pancreatitis are present, SUTENT should be discontinued and patients provided with appropriate supportive care.

***Hepatotoxicity***

Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumour patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment and as clinically indicated. Sunitinib should be interrupted for Grade 3 or 4 hepatic-related adverse events and discontinued if there is no resolution.

***Seizures***

In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. 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.

***Surgical Procedures***

Cases of impaired wound healing have been reported during sunitinib therapy. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

***Osteonecrosis of the Jaw (ONJ)***

Cases of ONJ have been reported in patients treated with SUTENT. The majority of cases occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and i.v. bisphosphonates are used either simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving i.v. bisphosphonates, invasive dental procedures should be avoided if possible.

**Carcinogenicity, mutagenicity and impairment of fertility**

***Genotoxicity***

Sunitinib was not genotoxic in in vitro tests for bacterial gene mutation and human lymphocyte structural chromosomal aberrations, or in an in vivo micronucleus test in rats. Polyploidy (numerical chromosome aberrations) was induced by high sunitinib concentrations in human lymphocytes in vitro. The major active metabolite was indirectly evaluated in these tests.

***Carcinogenicity***

Carcinogenicity studies with sunitinib have not been performed.

***Impairment of Fertility***

Rat fertility was unaffected by doses of up to 10 mg/kg/day (males) or 5 mg/kg/day (females), which resulted in exposures (AUC) to sunitinib plus its primary metabolite that were respectively about 26 times and 5 times the human value with the recommended daily dose of 50 mg. Embryolethality was seen in treated females at 5 mg/kg/day, but not at 1.5 mg/kg/day.

Adverse effects on the female reproductive system were seen in toxicity studies in cynomolgus monkeys (including impaired ovarian follicular development, uterine endometrial atrophy and vaginal epithelial atrophy) and rats (corpora lutea degeneration and uterine atrophy). Adverse effects on the male reproductive system were also seen in toxicity studies in rats (including testicular tubular atrophy). In both species, these effects mainly occurred at doses that elicited major toxicity.

**Use in pregnancy** Pregnancy Category D

There are no studies in pregnant women using sunitinib.

As angiogenesis is a critical component of embryonic and foetal development, inhibition of angiogenesis following administration of SUTENT may result in adverse effects on pregnancy.

Sunitinib was shown to be embryotoxic and teratogenic when administered to pregnant rats and rabbits. Increased foetal resorptions, decreased foetal weights and skeletal malformations were observed in rats with a dose of 5 mg/kg/day, while increased foetal variations occurred at 3 mg/kg/day. These doses resulted in exposures of sunitinib plus its primary metabolite (AUC) that were about 6 and 2 times the human value with the recommended daily dose of 50 mg, respectively. Limited investigations in rabbits showed the occurrence of cleft lip at doses of 1 and 5 mg/kg/day, which resulted in exposures of sunitinib plus its primary metabolite that were about 0.3 times and 3 times the human value, respectively. Increased foetal resorptions were observed at 5 mg/kg/day.

SUTENT should not be used during pregnancy. Women of childbearing potential must be advised to avoid becoming pregnant while receiving treatment with SUTENT. 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. Adequate contraception should be used during therapy and for at least 4 weeks after completion of therapy.

**Use in lactation**

It is not known whether sunitinib or its primary metabolite are excreted in human milk. Sunitinib and/or its metabolites are readily excreted in rat milk (milk:plasma concentration ratio of approximately 5:1). Because of the potential for serious adverse reactions in nursing infants, women should not breastfeed while taking SUTENT.

**Use in children**

The safety and efficacy of SUTENT in paediatric patients have not been established.

**Use in the elderly**

Approximately 34% of the subjects in clinical studies of SUTENT were 65 or over. No significant differences in safety or effectiveness were observed between younger and older patients.

*** Use in hepatic insufficiency**

No adjustment to starting dose is required when administering SUTENT to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. SUTENT has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment (see Pharmacokinetics).

Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN (Upper Limit of Normal) or, if due to liver metastasis > 5.0 x ULN.

*** Use in renal insufficiency**

No adjustment to starting dose is required when administering SUTENT to patients with renal impairment (mild-severe) or with ESRD on haemodialysis (see Pharmacokinetics).

**Effects on ability to drive and use machines**

No studies on the effects on the ability to drive or operate machinery have been performed. Patients should be advised that they may experience fatigue or dizziness during treatment with SUTENT.

**Interactions with other medicines**

***In-vitro studies of CYP Inhibition and Induction:***

*In-vitro* studies indicate that sunitinib does not induce major CYP enzymes, including CYP3A4. The calculated in vitro Ki values for inhibition of CYP isoforms, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 AND CYP4A9/11, by sunitinib and its primary active metabolite indicated that neither compound is likely to have any clinically relevant drug-drug interactions with drugs that may be metabolised by these enzymes.

***Drugs that may increase sunitinib plasma concentrations:***

Concomitant administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib + primary active metabolite] Cmax and AUC0-∞ values, respectively, after a single dose of sunitinib malate in healthy volunteers.

Administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations. Concomitant administration with inhibitors should therefore be avoided or the selection of an alternative concomitant medication with no or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be reduced (see DOSAGE AND ADMINISTRATION).

***Drugs that may decrease sunitinib plasma concentrations:***

Concomitant use of SUTENT with the CYP3A4 inducer, rifampicin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary active metabolite] Cmax and AUC0-∞ values, respectively, after a single dose of SUTENT in healthy volunteers.

Administration of SUTENT with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbitone or Hypericum perforatum known also as St. John's Wort) may decrease sunitinib concentrations. Concomitant administration with inducers should therefore be avoided, or selection of an alternative concomitant medication with no or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be increased (see DOSAGE AND ADMINISTRATION).

**Laboratory tests**

Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

## ADVERSE EFFECTS

*The data described below reflect exposure to SUTENT in patients who participated in the placebo-controlled trial for the treatment of GIST, the active-controlled trial for the treatment of mRCC or the placebo-controlled trial for the treatment of pancreatic NET. The GIST and mRCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles and the pancreatic NET patients received a starting oral dose of 37.5 mg daily without a scheduled rest period.

Adverse events occurring in the GIST, RCC and pancreatic NET studies are described below.

**Adverse Events in placebo-controlled GIST**

Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse events resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs. 51% of patients on SUTENT versus placebo, respectively. Diarrhoea, hypertension, bleeding, mucositis, skin abnormalities and altered taste were more common in patients receiving SUTENT. Table 5 compares the incidence of common (>10%) treatment-emergent adverse events for patients receiving SUTENT versus those on placebo.

**Table 5. Treatment-Emergent Adverse Events Reported in at Least 10% of GIST Patients who received SUTENT or Placebo in the placebo-controlled GIST Study***

| | GIST | | | |
|---|---|---|---|---|
| | SUTENT (n=202) | | Placebo (n=102) | |
| **Adverse Event, n (%)** | **All Grades** | **Grade 3/4[a]** | **All Grades** | **Grade 3/4[b]** |
| **Any** | | 114 (56) | | 52 (51) |
| **Constitutional** | | | | |
| Fatigue | 84 (42) | 17 (8) | 48 (47) | 8 (8) |
| Fever | 36 (18) | 3 (2) | 17 (17) | 1 (1) |
| **Gastrointestinal** | | | | |
| Diarrhoea | 81 (40) | 9 (4) | 27 (27) | 0 (0) |
| Nausea | 63 (31) | 3 (2) | 33 (32) | 5 (5) |
| Mucositis/stomatitis | 58 (29) | 2 (1) | 18 (18) | 2 (2) |
| Vomiting | 49 (24) | 4 (2) | 24 (24) | 3 (3) |
| Constipation | 41 (20) | 0 (0) | 14 (14) | 2 (2) |
| Abdominal pain[c] | 67 (33) | 22 (11) | 39 (38) | 12 (12) |
| **Cardiac** | | | | |
| Hypertension | 31 (15) | 9 (4) | 11 (11) | 0 (0) |
| **Dermatology** | | | | |
| Rash | 28 (14) | 2 (1) | 9 (9) | 0 (0) |
| Skin discolouration | 61 (30) | 0 (0) | 23 (23) | 0 (0) |
| Hand-foot syndrome | 28 (14) | 9 (4) | 10 (10) | 3 (3) |
| **Neurology** | | | | |
| Altered taste | 42 (21) | 0 (0) | 12 (12) | 0 (0) |
| Headache | 26 (13) | 3 (2) | 23 (23) | 0 (0) |
| **Musculoskeletal** | | | | |
| Arthralgia | 24 (12) | 2 (1) | 16 (16) | 0 (0) |
| Back pain | 23 (11) | 2 (1) | 16 (16) | 4 (4) |
| Myalgia/limb pain | 28 (14) | 1 (1) | 9 (9) | 1 (1) |
| **Respiratory** | | | | |
| Dyspnoea | 20 (10) | 0 (0) | 19 (19) | 3 (3) |
| Cough | 17 (8) | 0 (0) | 13 (13) | 0 (0) |
| **Metabolism/Nutrition** | | | | |
| Anorexia[d] | 67 (33) | 1 (1) | 30 (29) | 5 (5) |
| Asthenia | 45 (22) | 10 (5) | 11 (11) | 3 (3) |
| **Haemorrhage/bleeding** | | | | |
| Bleeding, all sites | 37 (18) | 14 (7) | 17 (17) | 9 (9) |

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patients on SUTENT included abdominal pain (2%) and bleeding (2%).

[b] Grade 4 AEs in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).

[c] Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank and cancer-related pain

[d] Includes decreased appetite

Oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair colour changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo.

Table 6 provides common (≥10%) treatment-emergent laboratory abnormalities.

**Table 6. Treatment-Emergent Laboratory Abnormalities (≥10%) in the placebo-controlled GIST Study ***

| Adverse Event, n (%) | SUTENT (n=202) | | Placebo (n=102) | |
|---|---|---|---|---|
| | All Grades | Grade 3/4[a] | All Grades | Grade 3/4[b] |
| **Any** | | 68 (34) | | 22 (22) |
| **Gastrointestinal** | | | | |
| AST / ALT | 78 (39) | 3 (2) | 23 (23) | 1 (1) |
| Alkaline phosphatase | 48 (24) | 7 (4) | 21 (21) | 4 (4) |
| Total Bilirubin | 32 (16) | 2 (1) | 8 (8) | 0 (0) |
| Indirect Bilirubin | 20 (10) | 0 (0) | 4 (4) | 0 (0) |
| Amylase | 35 (17) | 10 (5) | 12 (12) | 3 (3) |
| Lipase | 50 (25) | 20 (10) | 17 (17) | 7 (7) |
| **Cardiac** | | | | |
| Decreased LVEF | 22 (11) | 2 (1) | 3 (3) | 0 (0) |
| **Renal / Metabolic** | | | | |
| Creatinine | 25 (12) | 1 (1) | 7 (7) | 0 (0) |
| Hypokalaemia | 24 (12) | 1 (1) | 4 (4) | 0 (0) |
| Hypernatraemia | 20 (10) | 0 (0) | 4 (4) | 1 (1) |
| Uric acid | 31 (15) | 16 (8) | 16 (16) | 8 (8) |
| **Haematology** | | | | |
| Neutropenia | 107 (53) | 20 (10) | 4 (4) | 0 (0) |
| Lymphopenia | 76 (38) | 0 (0) | 16 (16) | 0 (0) |
| Anaemia | 52 (26) | 6 (3) | 22 (22) | 2 (2) |
| Thrombocytopenia | 76 (38) | 10 (5) | 4 (4) | 0 (0) |

***** Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalaemia (1%), neutropenia (2%), anaemia (2%), and thrombocytopenia (1%).

[b] Grade 4 AEs in patients on placebo included amylase (1%), lipase (1%), anaemia (2%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 68 (34%) versus 22 (22%) patients on SUTENT and placebo, respectively. Elevated liver function tests, pancreatic enzymes and creatinine were more common in patients treated with SUTENT than placebo. Decreased LVEF and myelosuppression were also more common with SUTENT treatment. Treatment-emergent electrolyte disturbances of all types were more common in patients on SUTENT than on placebo, including hyperkalaemia (6% vs. 4%), hypokalaemia (12% vs. 4%), hypernatraemia (10% vs. 4%), hyponatraemia (6% vs. 1%) and hypophosphataemia (9% vs. 0%). Three SUTENT patients (1.5%) had Grade 3 hypophosphataemia. Acquired hypothyroidism was noted in 8 patients (4%) on SUTENT versus 1 (1%) on placebo.

**Adverse Events in RCC Studies**

The as-treated patient population for the interim safety analysis of the Phase 3 RCC study included 250 patients, 129 randomised to SUTENT and 121 randomised to interferon-α. Dose reductions occurred in 42 patients (33%) on SUTENT and 15 patients (12%) on interferon-α. Dose interruptions occurred in 45 patients (35%) on SUTENT and 44 patients (36%) on interferon-α. The rates of treatment-emergent, non-fatal adverse events resulting in permanent discontinuation were 9% and 13% in the SUTENT and interferon-α groups, respectively. Most

treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 67% versus 49% of patients on SUTENT versus interferon-α, respectively. Diarrhoea, hypertension, bleeding, mucositis, skin abnormalities and altered taste were more common in patients receiving SUTENT. Table 7 compares the incidence of common (≥10%) treatment-emergent adverse events for patients receiving SUTENT versus those on interferon-α.

Data on treatment with SUTENT in the 169 patients enrolled in the pivotal and supportive studies in cytokine-refractory mRCC are also included in Table 7. The median duration of treatment was 5.5 months (range: 0.8-11.2) in the pivotal study and 7.7 months (range: 0.2-16.1) in the supportive study. Dose interruptions occurred in 48 patients (45%) in the pivotal study and 45 patients (71%) in the supportive study; one or more dose reductions occurred in 23 patients (22%) in the pivotal study and 22 patients (35%) in the supportive study.

**Table 7. Treatment-Emergent Adverse Events Reported in at Least 10% of Patients with mRCC who received SUTENT or Interferon-α***

| | Treatment-naïve | | | | Cytokine-refractory | |
|---|---|---|---|---|---|---|
| | SUTENT (n=129) | | Interferon-α (n=121) | | SUTENT (N=169) | |
| **Adverse Event, n (%)** | **All Grades** | **Grade 3/4[a]** | **All Grades** | **Grade 3/4[b]** | **All Grades** | **Grade 3/4[c]** |
| **Any** | 129 (100) | 87 (67) | 119 (98) | 59 (49) | 169 (100) | 123 (73) |
| **Constitutional** | | | | | | |
| Fatigue | 81 (63) | 12 (9) | 77 (64) | 21 (17) | 125 (74) | 19 (11) |
| Asthenia | 20 (16) | 6 (5) | 26 (22) | 7 (6) | 16 (9) | 4 (2) |
| Fever | 20 (16) | 2 (2) | 43 (36) | 0 (0) | 26 (15) | 2 (1) |
| Weight decreased | 13 (10) | 0 (0) | 15 (12) | 1 (1) | 19 (11) | 1 (1) |
| Chills | 12 (9) | 0 (0) | 45 (37) | 0 (0) | 18 (11) | 0 (0) |
| **Gastrointestinal** | | | | | | |
| Diarrhoea | 78 (60) | 9 (7) | 24 (20) | 0 (0) | 93 (55) | 8 (5) |
| Mucositis/stomatitis | 63 (49) | 6 (5) | 4 (3) | 2 (2) | 90 (53) | 7 (4) |
| Nausea | 59 (46) | 6 (5) | 50 (41) | 1 (1) | 92 (54) | 4 (2) |
| Vomiting | 37 (29) | 7 (5) | 17 (14) | 1 (1) | 63 (37) | 7 (4) |
| Dyspepsia | 35 (27) | 1 (1) | 7 (6) | 0 (0) | 77 (46) | 1 (1) |
| Abdominal pain[d] | 31 (24) | 5 (4) | 16 (13) | 2 (2) | 34 (20) | 5 (3) |
| Constipation | 21 (16) | 0 (0) | 16 (13) | 0 (0) | 57 (34) | 1 (1) |
| Flatulence | 19 (15) | 0 (0) | 5 (4) | 0 (0) | 24 (14) | 0 (0) |
| Dry mouth | 14 (11) | 0 (0) | 9 (7) | 1 (1) | 10 (6) | 0 (0) |
| Glossodynia | 14 (11) | 0 (0) | 1 (1) | 0 (0) | 25 (15) | 0 (0) |
| **Cardiac** | | | | | | |
| Hypertension | 32 (25) | 9 (7) | 2 (2) | 1 (1) | 48 (28) | 10 (6) |
| Oedema, peripheral | 15 (12) | 1 (1) | 7 (6) | 0 (0) | 28 (17) | 1 (1) |
| **Dermatology** | | | | | | |
| Dry skin | 30 (23) | 0 (0) | 10 (8) | 0 (0) | 29 (17) | 0 (0) |
| Rash | 29 (23) | 1 (1) | 15 (12) | 1 (1) | 64 (38) | 1 (1) |
| Hair colour changes | 25 (19) | 0 (0) | 0 (0) | 0 (0) | 29 (17) | 0 (0) |
| Hand-foot syndrome | 26 (20) | 5 (4) | 0 (0) | 0 (0) | 21 (12) | 5 (3) |
| Skin discolouration | 23 (18) | 0 (0) | 0 (0) | 0 (0) | 55 (33) | 0 (0) |
| Alopecia | 8 (6) | 0 (0) | 15 (12) | 0 (0) | 20 (12) | 0 (0) |

| | Treatment-naïve | | | | Cytokine-refractory | |
|---|---|---|---|---|---|---|
| | SUTENT (n=129) | | Interferon-α (n=121) | | SUTENT (N=169) | |
| **Adverse Event, n (%)** | **All Grades** | **Grade 3/4[a]** | **All Grades** | **Grade 3/4[b]** | **All Grades** | **Grade 3/4[c]** |
| **Neurology** | | | | | | |
| Altered taste[e] | 60 (47) | 0 (0) | 22 (18) | 0 (0) | 73 (43) | 0 (0) |
| Headache | 27 (21) | 1 (1) | 22 (18) | 0 (0) | 43 (25) | 2 (1) |
| Dizziness | 9 (7) | 0 (0) | 22 (18) | 1 (1) | 27 (16) | 3 (2) |
| **Musculoskeletal** | | | | | | |
| Back pain | 31 (24) | 5 (4) | 14 (12) | 2 (2) | 29 (17) | 1 (1) |
| Myalgia/limb pain | 30 (23) | 2 (2) | 31 (26) | 1 (1) | 60 (36) | 2 (2) |
| Arthralgia | 25 (19) | 0 (0) | 22 (18) | 0 (0) | 48 (28) | 2 (1) |
| **Respiratory** | | | | | | |
| Cough | 34 (26) | 1 (1) | 22 (18) | 0 (0) | 29 (17) | 1 (1) |
| Dyspnoea | 20 (16) | 5 (4) | 23 (19) | 5 (4) | 47 (28) | 8 (5) |
| **Metabolism/Nutrition** | | | | | | |
| Anorexia[f] | 58 (45) | 0 (0) | 60 (50) | 2 (2) | 53 (31) | 1 (1) |
| Dehydration | 13 (10) | 5 (4) | 6 (5) | 2 (2) | 19 (11) | 5 (3) |
| **Haemorrhage/bleeding** | | | | | | |
| Bleeding, all sites | 43 (33) | 2 (2) | 7 (6) | 0 (0) | 44 (26) | 1 (1) |
| **Psychiatric** | | | | | | |
| Insomnia | 14 (11) | 0 (0) | 10 (8) | 0 (0) | 22 (13) | 1 (1) |
| Depression | 6 (5) | 0 (0) | 16 (13) | 3 (3) | 14 (8) | 1 (1) |

***** Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patients on SUTENT included back pain (2%) and rash (1%).

[b] Grade 4 AEs in patients on interferon-α included dyspnoea (2%), depression (1%) and fatigue (1%).

[c] There were no Grade 4 adverse events among the events reported with a ≥10% incidence in the cytokine-refractory mRCC population.

[d] Includes flank pain. [e] Includes ageusia, hypogeusia and dysgeusia. [f] Includes decreased appetite.

Other significant adverse events occurring in cytokine-refractory mRCC patients receiving SUTENT included peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), periorbital oedema (7%) and increased lacrimation (6%).

In the Phase 3 study, 20 (16%) versus 14 patients (12%) experienced treatment-emergent Grade 4 chemistry laboratory abnormalities on SUTENT versus interferon-α, respectively. The most common Grade 4 chemistry abnormalities were hyperuricaemia (10% on each arm) and increased lipase (4% on SUTENT, 2% on interferon-α). The most common Grade 3 chemistry abnormalities observed on both arms were increased lipase (15% on SUTENT, 5% on interferon-α) and hyperglycaemia (4% on each arm). Other common Grade 3 laboratory abnormalities on SUTENT were increased amylase (5%) and hyponatraemia (5%), and on interferon-α were hypophosphataemia (5%) and AST (3%). Common treatment-emergent Grade 3 and 4 chemistry laboratory abnormalities in patients on SUTENT in the cytokine-refractory mRCC studies included increased lipase (16%), increased amylase (5%), hypophosphataemia (10%) and hyperuricaemia (10%).

Haematology laboratory abnormalities are presented in Table 8.

**Table 8. Treatment-Emergent Grade 3 and 4 Haematology Laboratory Abnormalities*in Patients with mRCC who received SUTENT or Interferon-α**

| | Treatment-naïve | | | | Cytokine-refractory | |
|---|---|---|---|---|---|---|
| | SUTENT (n=129) | | Interferon-α (n=121) | | (N=169) | |
| Laboratory Test | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| **Haematology, n (%)** | | | | | | |
| Neutropenia | 15 (12) | 2 (2) | 7 (6) | 1 (1) | 21 (12) | 1 (1) |
| Anaemia | 4 (3) | 0 (0) | 3 (3) | 0 (0) | 9 (5) | 3 (2) |
| Lymphopenia | 19 (14) | 0 (0) | 26 (21) | 0 (0) | 33 (20) | 2 (1) |
| Thrombocytopenia | 9 (7) | 0 (0) | 0 (0) | 0 (0) | 5 (3) | 0 (0) |
| Leukopenia | 8 (6) | 0 (0) | 2 (2) | 0 (0) | 12 (7) | 0 (0) |

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

## * Adverse Events in the Phase 3 Pancreatic NET Study

The median number of days on treatment was 139 days (range 13-532 days) for patients on SUTENT and 113 days (range 1-614 days) for patients on placebo. Nineteen patients (23%) on SUTENT and 3 patients (4%) on placebo were on study for >1 year. Dose interruptions occurred in 25 patients (30%) on SUTENT and 10 patients (12%) on placebo. Dose reductions occurred in 26 patients (31%) on SUTENT and 9 patients (11%) on placebo. Discontinuation rates due to adverse events were 22% for SUTENT and 17% for placebo.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 54% versus 50% of patients on SUTENT versus placebo, respectively. Table 9 compares the incidence of common (≥10%) treatment-emergent adverse events for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.

**Table 9. Adverse Events Reported in the Phase 3 Pancreatic NET Study in at Least 10% of Patients who Received SUTENT and More Commonly Than in Patients Given Placebo***

| Adverse event n (%) | Pancreatic NET | | | |
|---|---|---|---|---|
| | SUTENT (n=83) | | Placebo (n=82) | |
| | All Grades | Grade 3/4[a] | All Grades | Grade 3/4 |
| **Any** | 82 (99) | 45 (54) | 78 (95) | 41 (50) |
| **Constitutional** | | | | |
| Asthenia | 28 (34) | 4 (5) | 22 (27) | 3 (4) |
| Fatigue | 27 (33) | 4 (5) | 22 (27) | 7 (9) |
| Weight decreased | 13 (16) | 1(1) | 9 (11) | 0 (0) |
| **Gastrointestinal** | | | | |
| Diarrhoea | 49 (59) | 4 (5) | 32 (39) | 2 (2) |
| Stomatitis/oral Syndromes[b] | 40 (48) | 5 (6) | 15 (18) | 0 (0) |
| Nausea | 37 (45) | 1 (1) | 24 (29) | 1 (1) |
| Vomiting | 28 (34) | 0 (0) | 25 (31) | 2 (2) |
| Dyspepsia | 12 (15) | 0 (0) | 5 (6) | 0 (0) |
| Abdominal pain - upper | 11 (13) | 1 (1) | 6 (7) | 0 (0) |
| **Cardiac** | | | | |
| Hypertension | 22 (27) | 8 (10) | 4 (5) | 1 (1) |

| Adverse event n (%) | Pancreatic NET | | | |
|---|---|---|---|---|
| | SUTENT (n=83) | | Placebo (n=82) | |
| | All Grades | Grade 3/4[a] | All Grades | Grade 3/4 |
| **Dermatology** | | | | |
| Hair colour changes | 24 (29) | 1 (1) | 1 (1) | 0 (0) |
| Hand-foot syndrome | 19 (23) | 5 (6) | 2 (2) | 0 (0) |
| Rash | 15 (18) | 0 (0) | 4 (5) | 0 (0) |
| Dry skin | 12 (15) | 0 (0) | 9 (11) | 0 (0) |
| **Neurology** | | | | |
| Dysgeusia | 17 (21) | 0 (0) | 4 (5) | 0 (0) |
| Headache | 15 (18) | 0 (0) | 11 (13) | 1 (1) |
| **Musculoskeletal** | | | | |
| Arthralgia | 12 (15) | 0 (0) | 5 (6) | 0 (0) |
| **Psychiatric** | | | | |
| Insomnia | 15 (18) | 0 (0) | 10 (12) | 0 (0) |
| **Haemorrhage/Bleeding** | | | | |
| Bleeding events[c] | 18 (22) | 0 (0) | 8 (10) | 3 (4) |
| Epistaxis | 17 (21) | 1 (1) | 4 (5) | 0 (0) |

* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patients on SUTENT included fatigue (1%).

[b] Includes aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral pain, tongue ulceration, mucosal dryness, mucosal inflammation, and dry mouth.

[c] Includes hematemesis, hematochezia, hematoma, hemoptysis, hemorrhage, melena, and metrorrhagia.

Table 10 provides common (≥10%) treatment-emergent laboratory abnormalities.

**Table 10. Laboratory Abnormalities Reported in the Phase 3 Pancreatic NET Study in at Least 10% of Patients Who Received SUTENT**

| Laboratory Parameter, n (%) | Pancreatic NET | | | | | |
|---|---|---|---|---|---|---|
| | SUTENT | | | Placebo | | |
| | N | All Grades* | Grade 3/4*[a] | N | All Grades* | Grade 3/4*[b] |
| **Gastrointestinal** | | | | | | |
| AST | 82 | 59 (72) | 4 (5) | 80 | 56 (70) | 2 (3) |
| ALT | 82 | 50 (61) | 3 (4) | 80 | 44 (55) | 2 (3) |
| Alkaline phosphatase | 82 | 52 (63) | 8 (10) | 80 | 56 (70) | 9 (11) |
| Total bilirubin | 82 | 30 (37) | 1 (1) | 80 | 22 (28) | 3 (4) |
| Amylase | 74 | 15 (20) | 3 (4) | 74 | 7 (10) | 1 (1) |
| Lipase | 75 | 13 (17) | 4 (5) | 72 | 8 (11) | 3 (4) |
| **Renal/Metabolic** | | | | | | |
| Glucose increased | 82 | 58 (71) | 10 (12) | 80 | 62 (78) | 14 (18) |
| Albumin | 81 | 33 (41) | 1 (1) | 79 | 29 (37) | 1 (1) |
| Phosphorus | 81 | 29 (36) | 6 (7) | 77 | 17 (22) | 4 (5) |
| Calcium decreased | 82 | 28 (34) | 0 (0) | 80 | 15 (19) | 0 (0) |
| Sodium decreased | 82 | 24 (29) | 2 (2) | 80 | 27 (34) | 2 (3) |
| Creatinine | 82 | 22 (27) | 4 (5) | 80 | 22 (28) | 4 (5) |
| Glucose decreased | 82 | 18 (22) | 2 (2) | 80 | 12 (15) | 3 (4) |
| Potassium decreased | 82 | 17 (21) | 3 (4) | 80 | 11 (14) | 0 (0) |
| Magnesium decreased | 52 | 10 (19) | 0 (0) | 39 | 4 (10) | 0 (0) |
| Potassium increased | 82 | 15 (18) | 1 (1) | 80 | 9 (11) | 1 (1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Haematology** | | | | | | |
| Neutrophils | 82 | 58 (71) | 13 (16) | 80 | 13 (16) | 0 (0) |
| Hemoglobin | 82 | 53 (65) | 0 (0) | 80 | 44 (55) | 1 (1) |
| Platelets | 82 | 49 (60) | 4 (5) | 80 | 12 (15) | 0 (0) |
| Lymphocytes | 82 | 46 (56) | 6 (7) | 80 | 28 (35) | 3 (4) |

***** Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 laboratory abnormalities in patients on SUTENT included creatinine (4%), lipase (4%), glucose decreased (2%), glucose increased (2%), neutrophils (2%), ALT (1%), AST (1%), platelets (1%), potassium increased (1%) and total bilirubin (1%).

[b] Grade 4 laboratory abnormalities in patients on placebo included creatinine (3%), alkaline phosphatase (1%), glucose increased (1%) and lipase (1%).

**Post-marketing Experience**

The following adverse events have been identified during post-approval use of sunitinib. Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

***Blood and lymphatic system disorders***

Rare cases of thrombotic microangiopathy have been reported. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

***Cardiac disorders***

Cardiovascular events, including heart failure, cardiomyopathy and myocardial disorders, some of which were fatal, have been reported.

***Endocrine disorders***

Rare cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see PRECAUTIONS, Thyroid Dysfunction).

***Haemorrhagic events***

Haemorrhagic events reported, some of which were fatal, have included GI, respiratory, tumour, urinary tract and brain haemorrhages. Some cases of fatal haemorrhage associated with thrombocytopenia have been reported.

***Immune system disorders***

Hypersensitivity reactions, including angioedema, have been reported.

***Infections and infestations***

Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported.

***Musculoskeletal and connective tissue disorders***

Rare cases of myopathy and/or rhabdomyolysis, with or without acute renal failure, in some cases with fatal outcome, have been reported. Most of these patients had pre-existing risk factors and/or were receiving concomitant medications known to be associated with these adverse reactions. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Cases of fistula formation, sometimes associated with tumour necrosis and/or regression, in some cases with fatal outcome, have been reported.

*Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with SUTENT, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to i.v. bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see PRECAUTIONS).

***Nervous system disorders***

Taste disturbances, including ageusia, have been reported.

***Renal and urinary disorders***

Cases of renal impairment, in some cases with fatal outcome, have been reported.

Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended and patients should be monitored for the development or worsening of proteinuria. The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue sunitinib in patients with nephrotic syndrome.

***Respiratory disorders***

Pulmonary embolism, in some cases with fatal outcome, has been reported.

* ***Vascular disorders***

Cases of arterial thromboembolic events (ATE), sometimes fatal, have been reported in patients treated with sunitinib. The most frequent events included cerebrovascular accident, transient ischaemic attack and cerebral infarction. Risk factors associated with ATE, in addition to the underlying malignant disease and age ≥ 65 years, included hypertension, diabetes mellitus and prior thromboembolic disease.

## DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the administration of anti-cancer agents.

For GIST and mRCC, the recommended dose of SUTENT is 50 mg taken orally once daily for 4 consecutive weeks followed by a 2 week rest period (Schedule 4/2) to comprise a complete cycle of 6 weeks.

*For pancreatic NET, the recommended dose of SUTENT is 37.5 mg taken orally once daily without a scheduled rest period.

SUTENT may be taken with or without food.

If a dose is missed, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

***Dose adjustments**

For GIST and mRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. The daily dose should not exceed 75 mg nor be decreased below 25 mg.

For pancreatic NET, dose modification in 12.5 mg steps may be applied based on individual safety and tolerability. The maximum dose administered in the Phase 3 pancreatic NET study was 50 mg daily.

Dose interruptions may be required based on individual safety and tolerability.

No adjustment to starting dose is required when administering SUTENT to patients with mild or moderate hepatic impairment or with renal impairment (see Pharmacokinetics and PRECAUTIONS). Subsequent dose adjustments should be based on individual safety and tolerability.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for age, body weight, race, gender or ECOG score.

**CYP3A4 inhibitors/inducers*

Strong CYP3A4 inhibitors such as ketoconazole may increase SUTENT plasma concentrations. Co-administration of SUTENT with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see Interactions with other medicines). If this is not possible, the dose of SUTENT may need to be reduced to a minimum of 37.5 mg daily for GIST and mRCC or 25 mg daily for pancreatic NET, based on careful monitoring of tolerability.*

CYP3A4 inducers such as rifampicin may decrease SUTENT plasma concentrations. Co-administration of SUTENT with potent CYP3A4 inducers, such as rifampicin, should be avoided (see Interactions with other medicines). If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg steps (up to 87.5 mg per day for GIST and RCC or 62.5 mg per day for pancreatic NET) based on careful monitoring of tolerability.

Selection of an alternative concomitant medication with no or minimal potential to induce or inhibit CYP3A4 should be considered.

## OVERDOSAGE

There is no specific antidote for overdosage with SUTENT and treatment of overdose should consist of general supportive measures.

Sunitinib is not removed from blood by dialysis.

Contact the Poisons Information Centre for advice on the management of an overdose.

## PRESENTATION AND STORAGE CONDITIONS

12.5 mg strength: Hard gelatin capsule with orange cap and orange body, printed with white ink "Pfizer" on the cap, "STN 12.5mg" on the body. Bottles or blister packs containing 28 capsules.

25 mg strength: Hard gelatin capsule with caramel cap and orange body, printed with white ink "Pfizer" on the cap, "STN 25mg" on the body. Bottles or blister packs containing 28 capsules.

37.5 mg strength: Hard gelatin capsule with yellow cap and yellow body, printed with black ink "Pfizer" on the cap, "STN 37.5mg" on the body. Bottles or blister packs containing 28 capsules. (Not currently available)

50 mg strength: Hard gelatin capsule with caramel cap and caramel body, printed with white ink "Pfizer" on the cap, "STN 50mg" on the body. Bottles or blister packs containing 28 capsules.

Store below 25°C.

## NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114

## POISON SCHEDULE

S4 (Prescription Medicine)

## DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 24 February 2011.

* Please note changes in Product Information.

® Registered trademark.

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
**www.tga.gov.au**

Reference/Publication #