European Medicines Agency

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Product name: **SUTENT**
Procedure No. **EMEA/H/C/687/II/01**

SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.eu.int http://www.emea.eu.int

Introduction

Sutent was authorised in the EU in July 2006 for the following indications:

"SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

SUTENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy.

Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC. (see section 5.1)."

The Marketing Authorisation (MA) was granted as a Conditional Marketing Authorisation pursuant to Article 14(7) of Regulation (EC) No 726/2004. The Applicant agreed to provide, as requested by the CHMP, results of an ongoing study (Study A6181034) in cytokine-naive patients with metastatic renal cell carcinoma as a specific obligation.

The Marketing Authorisation Holder (MAH) has now submitted a Type II variation, which includes the requested efficacy and safety data from an analysis of Study A6181034 (A phase III randomised study of sunitinib versus interferon-alfa as first line systemic therapy for patients with metastatic renal cell carcinoma).

An interim analysis of this study has already been presented to the CHMP during the assessment of the original marketing authorisation application early in 2006.

The provision of this specific obligation serves as an application to extend the indication from second to first line treatment of metastatic renal cell carcinoma, and to switch from a conditional to a 'normal' marketing authorisation in accordance with Article 7 of regulation (EC) No 507/2006.

Metastatic Renal Cell Carcinoma (MRCC)

Renal cell carcinoma (RCC), a malignancy originating from the tubular cells of the kidney, comprises 80% to 85% of all renal parenchymal malignancies reported from surgical series. Some 75% to 85% of RCCs are histologically classified as 'clear cell'; these tumors tend to be very vascular, and typically metastasize to lung, bone, lymph nodes, and adrenal glands.
Incidence rates for RCC vary by more than 10- to 20-fold around the world, with higher rates in Western countries such as Scandinavia, France, Canada and the US, and the lowest rates in Central and South America and Asia. RCC is nearly twice as common among men than among women: for example, in the US in 2004, it is estimated that there were over 22 000 new cases in males (6% of all cancer diagnoses in males) and nearly 8000 deaths (3% of cancer deaths in males), compared to nearly 14 000 new cases and nearly 5000 deaths among females. A number of etiological associations have been described, including smoking, obesity, long-term hemodialysis, hypertension, sickle-cell trait, and genetic factors.

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

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

The only systemic first-line treatments available for MRCC are cytokines, but their efficacy is limited. No satisfactory methods of treatment that have been authorised, exist in the Community for patients with MRCC who have failed prior cytokine-based treatment. Despite other agents that have shown activity in this setting, such as different regimens of cytokines and novel tyrosine kinase inhibitors such as sorafenib, there remains a large unmet medical need in the treatment of this condition.

For patients who fail to respond to cytokine-based therapy or relapse after an initial response or period of disease stabilization, treatment options are very limited and generally ineffective, with rates of response to chemotherapy alone of less than 5%. Drug resistance may be related to the expression of the multidrug resistance transporter in proximal-tubule cells — the cells from which clear-cell and papillary renal-cell carcinoma may originate. Chemotherapy may be more efficacious for advanced non–clear-cell renal-cell carcinoma, particularly the collecting-duct type.

About the product

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

Worldwide Marketing Experience

The US granted approval for 2 indications (GIST after disease progression on or intolerance to imatinib mesylate and advanced RCC) on 26 January 2006. Commercial drug was available for patients on 2 February 2006. Sunitinib has been approved for both indications in Argentina, Uruguay, Indonesia, Korea, and the Philippines. Sunitinib has been approved for GIST in Canada, Brazil, and Switzerland. Special service product permission has been granted for both indications in Venezuela.

Clinical aspects

Clinical Pharmacology

The applicant has in their clinical overview made reference to the information given in the original marketing authorisation application. No new Pharmacokinetic or Pharmacodynamic data have been provided, which is considered acceptable.

Clinical Efficacy

The table below summarises the sunitinib studies in MRCC, which supported the original application.

Studies of sunitinib in MRCC presented in the original application

Study Number	N	Study Status	Study Design	Treatment (daily dose)	Location	Continuation Studies	N
Phase 2							
RTKC-0511-014	63	Completed	Single-arm, open-label, multi-center	Sunitinib 50 mg on Schedule 4/2[a]	7 sites in the US	RTKC-0511-017 or A6181030	1 17
Pivotal							
A6181006	106	Ongoing	Single-arm, open-label, multi-center	Sunitinib 50 mg on Schedule 4/2[a]	11 sites in the US	NA, patients are continuing to receive treatment on this study.	NA

Two studies were conducted to evaluate the efficacy of sunitinib (starting dose of 50 mg, schedule 4/2) for the treatment of cytokine-refractory MRCC: **pivotal Study A6181006** and **supportive Study RTKC-0511-014.**

Study A6181034 was ongoing at the time of the submission of the original Marketing Authorisation Application (MAA) and was designed to study sunitinib for treatment of cytokine-naïve patients with MRCC. This was an open-label, multinational 1:1 randomized study comparing sunitinib to IFN-α, with progression-free survival (PFS) as the primary endpoint. The trial completed enrolment (N=750) in October 2005. The applicant presented an interim analysis of Study A6181034 during the assessment of the original MAA and made a commitment to provide the final analysis as a specific obligation post-authorisation. This was reflected in Annex IIC of the original Conditional Marketing Authorisation as a specific obligation. The final analysis has now been provided as part of the present application.

Study A6181034

Patient population

Study A6181034 enrolled patients with histologically confirmed metastatic RCC with a component of clear (conventional) cell histology who had not previously been treated with systemic therapy. Eligible patients were men or women of at least 18 years of age, with adequate vital organ function, an absence of known brain or leptomeningeal metastases, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The primary purpose of this planned analysis was to compare the primary endpoint, Progression-free survival (PFS), in the 2 treatment arms. Comparisons of safety in the 2 treatment arms were performed for AEs, drug exposure, demographics, and laboratory abnormalities.

750 patients are included in the efficacy analyses and are defined as the intent-to-treat (ITT) population. Fifteen patients randomized to the IFN-α arm withdrew consent after randomization prior to starting the study treatment; therefore, 735 patients are included in the safety analyses and are defined as the as-treated (AT) population. These 2 analysis populations are described in Table 1.

Population	Sunitinib	Interferon-α	Total
Intent-to-Treat[a]	375	375	750
As-Treated[b,c]	375	360	735

Note: Data up to 15 November 2005. a The intent-to-treat population included all patients who were randomized, with study drug assignment designated according to initial randomization, regardless of whether patients received study drug or received a different drug from that to which they were randomized. b The as-treated population included all patients who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. c Fifteen patients randomized to IFN-α withdrew consent prior to starting study treatment; these patients never received study treatment.

Baseline patient characteristics were well balanced between the 2 treatment arms for the ITT population. The majority of the patients were white (94.4% for sunitinib versus 90.7% for IFN-α, respectively) and men (71.2% versus 71.7%, respectively). The median ages were 62 versus 59 years, respectively. The majority of the patients had undergone nephrectomy (90.7% versus 89.3%, respectively). The most common site of metastases present at screening was the lung (77.9% versus 79.5%, respectively), followed by the lymph nodes (58.1% versus 52.8%, respectively), and the majority of the patients had multiple (2 or more) metastatic sites at baseline (80.3% versus 76.5%, respectively). The patient characteristics for Study A6181034 are representative of the general population of advanced RCC patients.

Study Design

Study A6181034 was a randomized, multicenter, international, Phase III study evaluating the efficacy and safety of single-agent sunitinib compared with IFN-α in patients with treatment-naïve metastatic RCC. Patients were randomized 1:1 to the treatment arms.

Based on a planned sample size of 690 patients, the trial was designed with 90% power to detect a 35% improvement in median PFS from 20 weeks to 27 weeks (2-sided unstratified log-rank test; significance level 0.05).

Patients received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily administration followed by 2 weeks off (Schedule 4/2), or IFN-α, administered as a subcutaneous injection of 3 million units (MU) the first week, 6 MU the second week, and 9 MU the third week and thereafter on 3 non-consecutive days each week. IFN-α is widely recognized as the current standard of care for patients with advanced RCC.

Radiographic (computed tomography or magnetic resonance imaging) assessments were performed 1) at screening, 2) at the end of the dosing period during the first 4 cycles, 3) at every other cycle after Cycle 4 until the end of the study, and 4) at the end of treatment/withdrawal visit. Additional scans were performed to confirm response, or whenever disease progression was suspected. All images were assessed by the investigators and also by the independent core imaging laboratory, which was blinded to the treatment assignment and to the investigator's assessment. The primary analysis was based on core imaging laboratory assessments according to Response Evaluation Criteria in Solid Tumors (RECIST).

Efficacy Endpoints

Primary endpoints

The primary efficacy endpoint, Progression-free survival (PFS), was analyzed based on independent core imaging laboratory assessments for the ITT population. PFS was defined as the time from randomization to first documentation of objective tumor progression according to RECIST or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. PFS data were censored on the day following the date of the last on-study tumor assessment (including the 28-day follow-up period) documenting absence of progressive disease for patients who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given antitumor treatment other than the study treatment prior to observing objective tumor progression. Data for patients lacking an evaluation of tumor response after randomization were censored on the date of randomization with a duration of 1 day.

An improvement in median PFS from 20 weeks to 27 weeks in patients randomized to receive sunitinib was considered to be clinically relevant for the purposes of this study.

Secondary endpoints

Secondary efficacy endpoints included objective response rate (ORR), time to progression (TTP), overall survival (OS), duration of response (DR), and patient reported outcomes (PROs).

Statistical methodology is summarized in Table 2.

Endpoint	Population	Statistical Method	Model/Covariates/Strata	Missing Data
PFS	ITT, AT	Unstratified log-rank test; stratified log-rank test; Cox model; median, 95% CI from K-M	Overall, LDH, ECOG, nephrectomy, age, sex, race and time from initial diagnosis	Censor the data from patients without PD and who do not die due to any cause while on treatment
ORR	ITT, AT	CMH/Pearson chi-square rate, relative risk ratio, difference of rate, 95% CI	Overall, LDH, ECOG, nephrectomy	Treat patients without on-study tumor assessment as nonresponders
DR	Subset of ITT (responders only)	Median, 95% CI from K-M	Overall	Censor the data from patients without PD or death due to any cause
TTP	ITT, AT	Unstratified log-rank test; stratified log-rank test; Cox model; median, 95% CI from K-M	Overall, LDH, ECOG, nephrectomy, age, sex, race and time from initial diagnosis	Censor the data from patients without PD
OS	ITT, AT	Unstratified log-rank test; stratified log-rank test; Cox model; median, 95% CI from K-M	Overall, LDH, ECOG, nephrectomy, age, sex, race and time from initial diagnosis	Censor the data from patients who are still alive

Note: Data up to 15 November 2005. AT = as-treated, CI = confidence interval, CMH = Cochran-Mantel-Haenszel, DR = duration of response, ECOG = Eastern Cooperative Oncology Group, ITT = intent-to-treat, K-M = Kaplan-Meier, LDH = lactic dehydrogenase, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, TTP = time to progression.

RESULTS

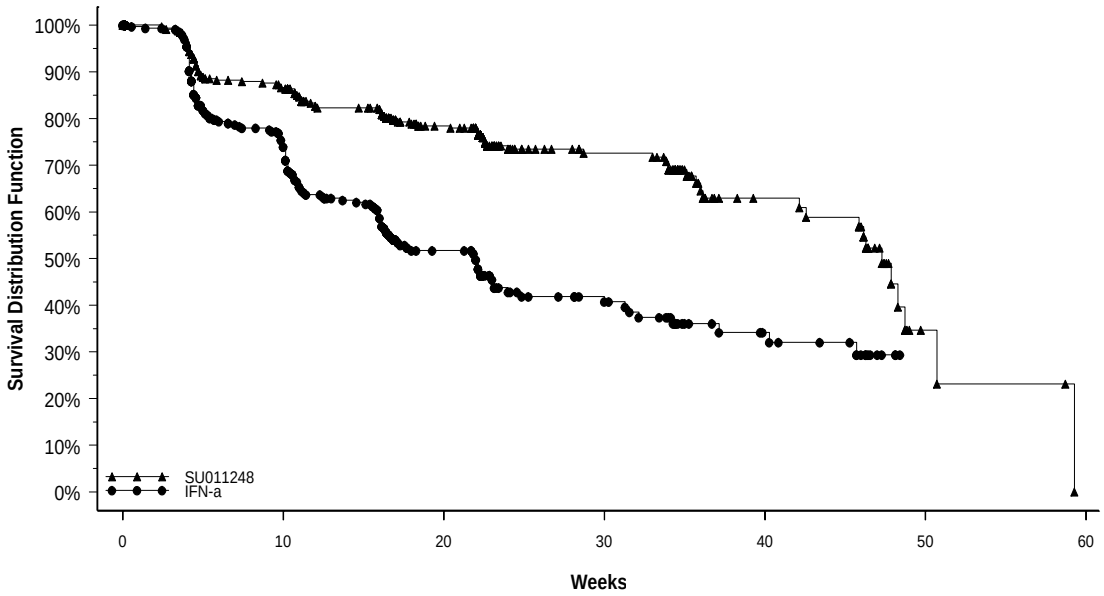
Time-to-event endpoints were stratified by baseline factors and further analyzed. Results of these additional analyses are presented in the original submission.

Progression-Free Survival

The median PFS for the sunitinib-treated group was 47.3 weeks compared with 22.0 weeks for the IFN-α-treated group; the hazard ratio was 0.415 (95% CI: 0.320-0.539, p <0.001). Ninety-six (25.6%) of the patients on sunitinib versus 154 (41.1%) of the patients on IFN-α had progressed or died based on the core imaging laboratory assessments, indicating a significant reduction in risk of progression or death in patients receiving sunitinib compared with IFN-α. These results demonstrate a treatment advantage in favor of sunitinib.

Results available for PFS are presented in Figure 1 and Table 3.

Figure 1: Kaplan-Meier Curve of Progression-Free Survival by Treatment (Core Imaging Laboratory Assessment, Intent-to-Treat Population)



Number of patients at risk

Sunitinib:	375	274	173	84	31	3	0
Interferon-α:	375	207	84	38	16	0	0

Note: Data up to 15 November 2005.

Table 3. Patients with Progression or Death in Study A6181034 (Intent-to-Treat Population)				
Parameter	**Sunitinib (N = 375)**	**Interferon-α (N = 375)**	**Hazard Ratio (95% CI)**	**Calculated p-value**
Core Imaging Laboratory Assessments (N = 750)				
Patients with progression or death due to any cause while on study, n (%)[a]	96 (25.6)	154 (41.1)	0.415 (0.320-0.539)	0.000000000007257846
Median PFS in weeks (95% CI)	47.3 (42.6, 50.7)	22.0 (16.4, 24.0)		
Investigator Assessments (N = 750)				
Patients with progression or death due to any cause while on study, n (%)[a]	118 (31.5)	193 (51.5)	0.416 (0.330-0.524)	0.000000000000015645
Median PFS in weeks (95% CI)	45.7 (35.7, 59.3)	17.3 (16.3, 22.4)		

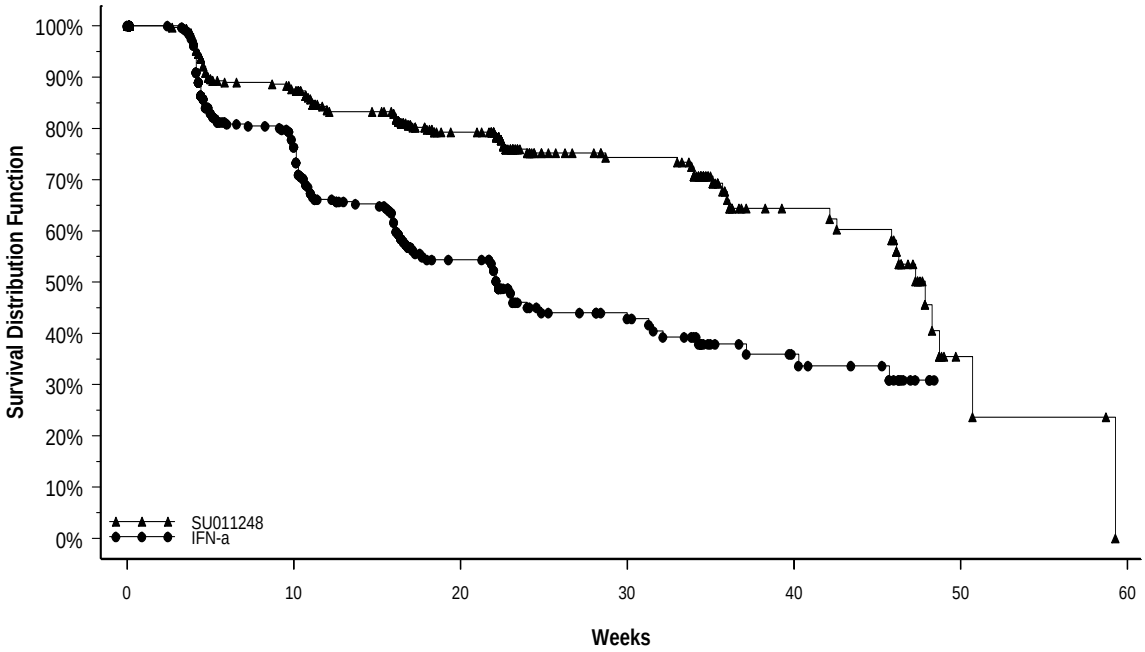
Note: Data up to 15 November 2005. N = number of patients in the population, n = number of patients, % = n/N×100, CI = confidence interval, PFS = progression-free survival. a On study includes a 28-day follow up period after the last dose of study drug.

Time to Progression

Results for TTP are similar to PFS, indicating a treatment advantage in favor of sunitinib. The median TTP for the sunitinib-treated group was 47.9 weeks compared to 22.3 weeks for the IFN-α-treated group; the hazard ratio was 0.416 (95% CI: 0.318-0.545, p <0.001). Ninety patients (24.0%) on sunitinib versus 142 patients (37.9%) on IFN-α had progressed based on the core imaging laboratory assessments, indicating a reduction in risk of progression in patients receiving sunitinib compared with IFN-α.

Results available for TTP are presented in Figure 2 and Table 4.

Figure 2: Kaplan-Meier Curve of Time to Progression by Treatment (Core Imaging Laboratory Assessment, Intent-to-Treat Population)



Number of patients at risk

Sunitinib:	375	273	171	84	31	3	0
Interferon-α:	375	201	84	37	16	0	0

Note: Data up to 15 November 2005.

Parameter	Sunitinib (N = 375)	Interferon-α (N = 375)	Hazard Ratio (95% CI)	Calculated p-value
Core Imaging Laboratory Assessments (N = 750)				
Patients with progression while on study, n (%)[a]	90 (24.0)	142 (37.9)	0.416 (0.318-0.545)	0.000000000044039194
Median TTP in weeks (95% CI)	47.9 (45.9, 50.7)	22.3 (17.3, 31.3)		
Investigator Assessments (N = 750)				
Patients with progression while on study, n (%)[a]	114 (30.4)	185 (49.3)	0.415 (0.328-0.526)	0.000000000000043868
Median TTP in weeks (95% CI)	45.7 (36.0, 59.3)	18.0 (16.6, 23.1)		

Note: Data up to 15 November 2005. N = number of patients in the population, n = number of patients, % = n/N×100, CI = confidence interval, TTP = time to progression. a On study includes a 28-day follow up period after the last dose of study drug.

Overall Survival

Forty-nine (13.1%) of the patients treated with sunitinib and 65 (17.3%) of the patients treated with IFN-α had died up to 15 November 2005. The median OS had not yet been reached in either treatment arm due to the relatively small number of patients who died. Thus, meaningful comparisons between the 2 groups cannot be determined at this time.

Objective Response Rate

ORR data are summarized in Table 5 for the core imaging laboratory and investigator assessments that were evaluated by RECIST demonstrating a robust improvement in ORR with administration of sunitinib. The percentage of patients with measurable disease at baseline was similar between the 2 treatment groups.

The analysis for the ORR based on the core imaging laboratory assessments identified 103 patients with PRs on sunitinib (27.5%, 95% CI: 23.0-32.3) versus 20 patients with PRs on IFN-α (5.3%, 95% CI: 3.3-8.1), indicating a significantly higher response rate on sunitinib ($p < 0.001$). Of note, 88 patients were not yet assessed by the core imaging laboratory at the time of data analysis. The investigator-assessed ORR was 36.5% for sunitinib (95% CI: 31.7-41.7, including 1 CR and 136 PRs) compared with 8.8% for IFN-α (95% CI: 6.2-12.2, including 33 PRs, $p < 0.001$).

Parameter	Sunitinib (N = 375)	Interferon-α (N = 375)
Core Imaging Laboratory Assessments (N = 750)		
Patients with baseline assessment, n (%)	335 (89.3)	327 (87.2)
Patients with measurable disease at baseline, n (%)	335 (89.3)	327 (87.2)
Best Overall Response, n (%)		
Complete response	0 (0)	0 (0)
Partial response	103 (27.5)	20 (5.3)
Stable disease[a]	160 (42.7)	160 (42.7)
Progressive disease	52 (13.9)	99 (26.4)
Not evaluable[b]	20 (5.3)	46 (12.3)
Missing[c]	40 (10.7)	50 (13.3)
Overall Response Rate (CR+PR), n (%) (95% CI)	103 (27.5) (23.0, 32.3)	20 (5.3) (3.3, 8.1)
Investigator Assessments (N = 750)		
Patients with baseline assessment, n (%)	375 (100)	374 (99.7)
Patients with measurable disease at baseline, n (%)	374 (99.7)	373 (99.5)
Best Overall Response, n (%)		
Complete response	1 (0.3)	0 (0)
Partial response	136 (36.3)	33 (8.8)
Stable disease[a]	176 (46.9)	213 (56.8)
Progressive disease	28 (7.5)	67 (17.9)
Not evaluable[b]	26 (6.9)	29 (7.7)
Missing[d]	8 (2.1)	33 (8.8)
Overall Response Rate (CR+PR), n (%) (95% CI)	137 (36.5) (31.7, 41.7)	33 (8.8) (6.2, 12.2)

Note: Data up to 15 November 2005. N = number of patients in the population, n = number of patients, % = n/N×100, CI = confidence interval, CR = complete response, PR = partial response. a In order to be considered as stable disease, follow-up measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks. b Patients with less than 6 weeks on-study observation time were considered "Not Evaluable" for the core imaging and investigator assessments, unless they had disease progression. Patients were also considered "Not Evaluable" if any of their disease sites were not assessed. c Missing for the core laboratory assessment includes scans that were not sent by the investigator to the core imaging laboratory for evaluation, or scans that were sent to the core imaging laboratory but not evaluated in time for this analysis. d Missing for the investigator assessment includes patients lacking post-baseline assessments or incomplete data collection at the time of this analysis.

Response rates from Study A6181034 are consistent with efficacy results obtained in the pivotal Study A6181006 that evaluated sunitinib in patients with cytokine-refractory metastatic RCC. Using data from the pivotal Study A6181006 through 28 January 2005 (from the original marketing applications), the core-imaging laboratory reported an ORR of 25.5% (95% CI: 17.5-34.9), whereas the investigators reported an ORR of 35.8% (95% CI: 26.8–45.7, including 1 CR and 37 PRs). In Study A6181006, the response rates have increased with continued treatment and monitoring of patients. Based on updated efficacy assessments through December 2005, the core-imaging laboratory reported 38 PRs, yielding an ORR of 35.8% (95% CI: 26.8-45.7). Similarly, based on updated efficacy assessments through 1 August 2005, investigators reported 1 CR and 45 PRs, yielding an ORR of 43.4% (95% CI: 33.8–53.4).

Duration of Response

DR data were calculated for patients who had a response in either treatment arm. Median DR was 40.9 weeks (95% CI: 30.1–54.1) for the 16 responding patients in the sunitinib treatment arm who had subsequently progressed or died based on core imaging laboratory assessments. Median DR for patients receiving IFN-α could not be calculated because none of the 20 responding patients had subsequently progressed or died.

Patient Reported Outcomes (PROs)

PROs were measured using 3 validated instruments: 1) Functional Assessment of Cancer Therapy – General (FACT-G) Questionnaire, 2) Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI), and 3) EQ-5D Self-Report Questionnaire (EQ-5D).

The FACT-G evaluates cancer patients' general health-related quality of life; its endpoints include FACT-G Total score and 4 subscales (Physical Well-Being (PWB), Social/family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB). The FKSI measures common symptoms related to kidney cancer and its treatment; it also contains a Disease Related Symptoms subscale (FKSI-DRS), which measures the symptoms related to the disease only. The EQ-5D measures a patient's general health status; it includes 5 descriptors of current health state (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), from which the EQ-5D health state index (EQ-5D Index) is derived, and a visual analog scale (EQ-VAS) for current health status. The FKSI-DRS was pre-specified as the primary PRO endpoint. Between-treatment differences of the post-baseline measurements of all PRO endpoints were tested using the repeated measures mixed-effects model adjusting for the time, treatment-by-time interaction, and the baseline scores for the same PRO endpoints.

The between-treatment differences in the PRO endpoints over time from Cycle 1 Day 28 to Cycle 10 Day 1 and the p-value differences are summarized in Table 6; a score greater than zero indicates a difference favoring sunitinib.

Results demonstrate that patients in the sunitinib arm reported statistically significant ($p < 0.05$) better outcomes in their kidney disease-related symptoms, physical well-being, functional well-being, and overall quality of life than patients in the IFN-α arm at all assessment time points. For social/family well being and emotional well-being, the statistical significance dropped to below the 0.05 level after Cycle 8 and Cycle 5, respectively). Results consistently demonstrated that patients in the sunitinib arm generally reported better PROs over time.

Assessment Timepoint	FKSI-DRS	FACT-G Total	PWB	SWB	EWB	FWB	FKSI	EQ-5D Index	EQ-VAS
Between-Treatment Difference (Sunitinib – interferon-α)									
Cycle 1 Day 28	1.767	5.412	1.369	1.258	0.883	1.905	3.087	0.047	3.514
Cycle 2 Day 1	1.802	5.440	1.377	1.248	0.867	1.917	3.117	0.046	3.715
Cycle 2 Day 28	1.866	5.489	1.391	1.230	0.839	1.938	3.171	0.042	4.077
Cycle 3 Day 1	1.901	5.516	1.399	1.221	0.823	1.949	3.201	0.041	4.279
Cycle 3 Day 28	1.965	5.565	1.412	1.203	0.795	1.971	3.255	0.037	4.641
Cycle 4 Day 1	2.000	5.593	1.420	1.194	0.779	1.982	3.286	0.036	4.842
Cycle 4 Day 28	2.063	5.642	1.434	1.176	0.750	2.003	3.340	0.032	5.204
Cycle 5 Day 1	2.099	5.669	1.442	1.166	0.734	2.015	3.370	0.031	5.406
Cycle 5 Day 28	2.162	5.719	1.455	1.149	0.706	2.036	3.424	0.027	5.768
Cycle 6 Day 1	2.197	5.746	1.463	1.139	0.690	2.048	3.455	0.026	5.969
Cycle 6 Day 28	2.261	5.795	1.477	1.122	0.662	2.069	3.509	0.022	6.331
Cycle 7 Day 1	2.296	5.823	1.485	1.112	0.646	2.081	3.539	0.021	6.533
Cycle 7 Day 28	2.360	5.872	1.499	1.094	0.617	2.102	3.593	0.017	6.895
Cycle 8 Day 1	2.395	5.899	1.506	1.085	0.601	2.113	3.624	0.016	7.096
Cycle 8 Day 28	2.459	5.948	1.520	1.067	0.573	2.135	3.678	0.012	7.459
Cycle 9 Day 1	2.494	5.976	1.528	1.057	0.557	2.146	3.708	0.011	7.660
Cycle 9 Day 28	2.557	6.025	1.542	1.040	0.529	2.167	3.762	0.007	8.022
Cycle 10 Day 1	2.593	6.052	1.549	1.030	0.513	2.179	3.793	0.006	8.223
p-value									
Cycle 1 Day 28	<.0001	<.0001	<.0001	<.0001	0.0001	<.0001	<.0001	0.0007	0.0003
Cycle 2 Day 1	<.0001	<.0001	<.0001	<.0001	0.0001	<.0001	<.0001	0.0007	0.0001
Cycle 2 Day 28	<.0001	<.0001	<.0001	<.0001	0.0002	<.0001	<.0001	0.0010	<.0001
Cycle 3 Day 1	<.0001	<.0001	<.0001	<.0001	0.0003	<.0001	<.0001	0.0015	<.0001
Cycle 3 Day 28	<.0001	<.0001	<.0001	<.0001	0.0007	<.0001	<.0001	0.0039	<.0001
Cycle 4 Day 1	<.0001	<.0001	<.0001	<.0001	0.0012	<.0001	<.0001	0.0072	<.0001
Cycle 4 Day 28	<.0001	<.0001	<.0001	0.0001	0.0037	<.0001	<.0001	0.0218	<.0001
Cycle 5 Day 1	<.0001	<.0001	<.0001	0.0003	0.0066	<.0001	<.0001	0.0383	<.0001
Cycle 5 Day 28	<.0001	<.0001	0.0002	0.0012	0.0166	<.0001	<.0001	0.0904	<.0001
Cycle 6 Day 1	<.0001	<.0001	0.0004	0.0023	0.0259	<.0001	<.0001	0.1335	<.0001

Cycle 6 Day 28	<.0001	<.0001	0.0013	0.0064	0.0511	<.0001	<.0001	0.2341	0.0002
Cycle 7 Day 1	<.0001	<.0001	0.0021	0.0104	0.0700	<.0001	<.0001	0.2994	0.0002
Cycle 7 Day 28	<.0001	<.0001	0.0047	0.0212	0.1124	0.0002	<.0001	0.4255	0.0004
Cycle 8 Day 1	<.0001	0.0001	0.0069	0.0295	0.1399	0.0004	<.0001	0.4967	0.0005
Cycle 8 Day 28	<.0001	0.0004	0.0124	0.0488	0.1948	0.0010	0.0001	0.6208	0.0007
Cycle 9 Day 1	<.0001	0.0007	0.0163	0.0618	0.2274	0.0016	0.0003	0.6860	0.0009
Cycle 9 Day 28	<.0001	0.0015	0.0251	0.0886	0.2880	0.0032	0.0006	0.7944	0.0012
Cycle 10 Day 1	0.0001	0.0022	0.0308	0.1052	0.3219	0.0044	0.0009	0.8494	0.0014

Note: Data up to 15 November 2005.
FKSI-DRS = Functional Assessment of Cancer Therapy – Kidney Symptom Index Disease Related Symptoms subscale, FACT-G = Functional Assessment of Cancer Therapy – General, PWB = Physical Well-Being, SWB = Social/family Well-Being, EWB = Emotional Well-Being, FWB = Functional Well-Being, FKSI = Functional Assessment of Cancer Therapy – Kidney Symptom Index, EQ-5D Index = EQ-5D Self-Report Questionnaire Health State Index, VAS = visual analog scale.

Compared to the pre-established minimum clinically important differences for these endpoints (2-3 points for FKSI-DRS, 5 points for FACT-G Total, 2 points for PWB, SWB, EWB, and FWB, and 3-5 points for FKSI), the between-treatment differences for kidney cancer-related symptoms (FKSI-DRS and FKSI), overall quality of life (FACT-G) and FWB were considered clinically meaningful. The EQ-VAS results indicated that patients receiving sunitinib also had better overall health status.

Discussion on Clinical Efficacy

Results from Study A6181034 demonstrate that sunitinib significantly prolongs PFS compared with IFN-α for patients with treatment-naïve metastatic RCC. The superior efficacy, also demonstrated by a robust improvement in ORR of sunitinib over IFN-α, was evident at the time of this analysis. These positive ORR results were consistent with those observed in Study A6181006 in patients with cytokine-refractory metastatic RCC. Additionally, patient reported outcomes were better for patients receiving sunitinib. Taken together, these results demonstrate a treatment advantage for sunitinib compared with IFN-α.

Further to the assessment of Study A6181034, two additional complementary analyses are requested as follow-up measures:

- Considering the relatively high rate of dose reductions in the Sunitinib arm of Study A6181034, the MAH should provide a complementary analysis of the efficacy and safety data in the subgroup of patients for whom the dose was reduced.

- The MAH will provide further information regarding possible pharmacodynamic markers, such as the target RTKs or the VHL mutation, as well as a justification for why such studies were not considered necessary to perform as part of study A6181034.

Clinical Safety

Data presented in this section are based primarily on safety analyses presented in the A6181034 Clinical Study Report (CSR), with data available through 15 November 2005. Additionally, comparisons are made to an additional overall Safety Update (SU) with data available from 2451 subjects through 15 November 2005, which presents patient demographic and other characteristics, treatment-emergent serious adverse events (SAEs) (including deaths), discontinuations due to treatment-related AEs, laboratory abnormalities, and disposition for all ongoing sunitinib studies. Cross references are also made to the general safety profile of sunitinib and specifically to the metastatic RCC safety profile.

Exposure to Study Drug

Extent of exposure to sunitinib and IFN-α in Study A6181034 is summarized for the ITT population in Table 7.

Exposure Duration	Sunitinib (N = 375)	Interferon-α (N = 375)
Number of cycles started[a]		
Mean (SD)	4.5 (2.3)	3.3 (2.2)
Median (range)	4.0 (1-11)	3.0 (1-10)
Number of days on treatment[b]		
Mean (SD)	182.8 (98.1)	132.8 (93.8)
Median (range)	169.0 (13-469)	123.5 (4-410)
Number of days on drug[c] or number of doses[d]		
Mean (SD)	115.7 (62.2)	52.2 (38.1)
Median (range)	112.0 (8-295)	48.0 (1-170)
Patients with dosing interruptions or missed doses, n (%)	142 (37.9)	115 (31.9)
Interruption due to adverse event	116 (30.9)	99 (27.5)
Patients with dose reductions, n (%)[e]	121 (32.3)	77 (21.4)
Relative dose intensity[f]		
Mean (SD)	97.1 (6.4)	95.9 (9.4)
Median (range)	100.0 (54–100)	100.0 (33–100)

Note: Data up to 15 November 2005.

N = number of patients in the population, n = number of patients, % = n/N×100, SD = standard deviation. a A patient was considered to have started a cycle if the patient took at least one dose of drug (sunitinib or IFN-α). b Days on treatment is defined as the time period starting from the date of first dose and ending at the earlier of the termination date, the data cutoff date, or 2 weeks after the last dose. c Number of days on drug is calculated for sunitinib and is defined as the total number of days on which drug was actually administered, excluding the 2-week off period and temporary dosing delays. d Number of doses is calculated for IFN-α. e Dose reduction is defined as a daily dose prescribed below 50 mg for sunitinib and as a dose less than the protocol-defined dose for IFN-α due to any reason at any time during the study. f Relative dose intensity = [(total dose administered)/(total dose assigned)]*100. The total dose assigned is calculated based on the dose at the beginning of each cycle and does not include dose reductions occurring within a cycle.

The median number of days on study was approximately 37% longer for patients receiving sunitinib than for patients receiving IFN-α through 15 November 2005. The difference in the median number of days on study (169.0 days for sunitinib versus 123.5 days for IFN-α) is expected due to the higher rate of disease progression for patients in the IFN-α treatment arm. Dose interruptions were similar in both arms (37.9% versus 31.9%, respectively); however, dose reductions were more frequent with sunitinib than with IFN-α (32.3% versus 21.4%, respectively).

Demographic and Other Characteristics of the Study Population

The demographic characteristics of the safety population appear similar to the population described in published epidemiologic data.

Common Adverse Events

The majority of patients in both treatment arms experienced at least 1 treatment-emergent AE (98.7% on sunitinib and 98.3% on IFN-α). The most commonly occurring AEs (those occurring in 10% or more of patients in either treatment arm) are summarized in Table 8.

Table 8. Treatment-Emergent, All-Causality Adverse Events Reported for at Least 10% of

MedDRA Version 8.1 Preferred Term	Sunitinib (N = 375)	Interferon-α (N = 360)
Patients with any AE, n (%)	370 (98.7)	354 (98.3)
Diarrhea	218 (58.1)	71 (19.7)
Fatigue	215 (57.3)	199 (55.3)
Nausea	182 (48.5)	134 (37.2)
Dysgeusia	160 (42.7)	50 (13.9)
Anorexia	109 (29.1)	102 (28.3)
Vomiting	104 (27.7)	49 (13.6)
Dyspepsia	104 (27.7)	14 (3.9)
Hypertension	101 (26.9)	13 (3.6)
Stomatitis	97 (25.9)	8 (2.2)
Rash	85 (22.7)	31 (8.6)
Asthenia	78 (20.8)	85 (23.6)
Palmar-plantar erythrodysesthesia syndrome	77 (20.5)	3 (0.8)
Mucosal inflammation	77 (20.5)	5 (1.4)
Headache	68 (18.1)	61 (16.9)
Back pain	68 (18.1)	43 (11.9)
Arthralgia	66 (17.6)	60 (16.7)
Dry skin	64 (17.1)	23 (6.4)
Pain in extremity	63 (16.8)	27 (7.5)
Cough	62 (16.5)	43 (11.9)
Pyrexia	61 (16.3)	129 (35.8)
Skin discoloration	60 (16.0)	0 (0)
Thrombocytopenia	59 (15.7)	7 (1.9)
Constipation	59 (15.7)	44 (12.2)
Dyspnea	57 (15.2)	64 (17.8)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, AE = adverse event.

Table 8. Treatment-Emergent, All-Causality Adverse Events Reported for at Least 10% of Patients in Either Treatment Arm in Study A6181034 (As-Treated Population) (Continued)

MedDRA Version 8.1 Preferred Term	Sunitinib (N = 375)	Interferon-α (N = 360)
Hair color changes	54 (14.4)	1 (0.3)
Neutropenia	52 (13.9)	27 (7.5)
Epistaxis	52 (13.9)	7 (1.9)
Abdominal pain	48 (12.8)	26 (7.2)
Dry mouth	44 (11.7)	26 (7.2)
Ejection fraction decreased	44 (11.7)	17 (4.7)
Anemia	43 (11.5)	56 (15.6)
Weight decreased	43 (11.5)	52 (14.4)
Edema peripheral	42 (11.2)	15 (4.2)
Insomnia	42 (11.2)	31 (8.6)
Chills	41 (10.9)	108 (30.0)
Oral pain	38 (10.1)	2 (0.6)
Decreased appetite	38 (10.1)	45 (12.5)
Myalgia	31 (8.3)	63 (17.5)
Depression	28 (7.5)	42 (11.7)
Dizziness	28 (7.5)	39 (10.8)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, AE = adverse event.
[a] Data are reported for AEs that occurred in more than 10% of patients in either treatment arm.

For patients receiving sunitinib, gastrointestinal events such as diarrhea, nausea, and vomiting were commonly reported, as well as fatigue, dysgeusia, anorexia, dyspepsia, hypertension, and stomatitis. Hematologic events (thrombocytopenia, neutropenia, and anemia) were somewhat less common but nonetheless occurred in more than 10% of patients receiving sunitinib. The most common AEs in the IFN-α group were fatigue, nausea, pyrexia, chills, and anorexia. One hematologic event that occurred in more than 10% of patients receiving IFN-α was anemia.

In general, the safety profile of sunitinib was consistent with that reported in the SU and in particular, was consistent with data presented in the metastatic RCC portion of the initial MAA.

Table 9 summarizes those treatment-emergent AEs that the investigator judged to be related to the study drug. This safety profile is similar to that of the all-causality AEs.

Common sunitinib-related events (reported for at least 20% of patients) included constitutional (fatigue, dysgeusia, anorexia, mucosal inflammation, and asthenia), GI (diarrhea, nausea, dyspepsia, stomatitis, and vomiting), cutaneous (palmar-plantar erythrodysesthesia syndrome and rash) events, and hypertension. These events have previously been reported (as part of the initial MAA) and are also currently reported in the SU. The most common IFN-α-related events were fatigue, pyrexia, nausea, chills, anorexia, and asthenia.

Table 9. Treatment-Related Adverse Events Reported for at Least 10% of Patients in Either		
MedDRA Version 8.1 Preferred Term	**Sunitinib (N = 375)**	**Interferon-α (N = 360)**
Patients with any treatment-related AE, n (%)	357 (95.2)	329 (91.4)
Diarrhea	199 (53.1)	45 (12.5)
Fatigue	191 (50.9)	184 (51.1)
Nausea	166 (44.3)	120 (33.3)
Dysgeusia	158 (42.1)	49 (13.6)
Dyspepsia	96 (25.6)	11 (3.1)
Anorexia	96 (25.6)	94 (26.1)
Stomatitis	94 (25.1)	6 (7.1)
Vomiting	90 (24.0)	36 (10.0)
Hypertension	89 (23.7)	4 (1.1)
Palmar-plantar erythrodysesthesia syndrome	76 (20.3)	2 (0.6)
Mucosal inflammation	75 (20.0)	4 (1.1)
Rash	72 (19.2)	22 (6.1)
Asthenia	63 (16.8)	71 (19.7)
Dry skin	60 (16.0)	17 (4.7)
Skin discoloration	58 (15.5)	0 (0)
Thrombocytopenia	57 (15.2)	5 (1.4)
Hair color changes	54 (14.4)	1 (0.3)
Neutropenia	51 (13.6)	25 (6.9)
Epistaxis	44 (11.7)	4 (1.1)
Pain in extremity	42 (11.2)	11 (3.1)
Headache	41 (10.9)	50 (13.9)
Dry mouth	40 (10.7)	23 (6.4)
Ejection fraction decreased	38 (10.1)	10 (2.8)
Pyrexia	27 (7.2)	121 (33.6)
Chills	24 (6.4)	103 (28.6)
Myalgia	20 (5.3)	56 (15.6)
Arthralgia	33 (8.8)	45 (12.5)
Weight decreased	34 (9.1)	43 (11.9)
Decreased appetite	29 (7.7)	37 (10.3)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, AE = adverse event.

Serious Adverse Events: Deaths

As summarized in Table 10, 13.1% of the patients receiving sunitinib and 17.5% of the patients receiving IFN-α died. Study disease was the most common cause of death for patients on either treatment, consistent with the most common cause of death for all studies reported in the SU.

Deaths	Sunitinib (N = 375)	Interferon-α (N = 360)
All deaths, n (%)	49 (13.1)	63 (17.5)
Patients who died on-study, n (%)[a]	13 (3.5)	17 (4.7)
Patients who died during follow-up, n (%)[b]	36 (9.6)	46 (12.8)

Note: Data up to 15 November 2005. N = number of patients in the population who received at least 1 dose of study drug, n = number of patients % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities. [a] Includes deaths reported during treatment and within 28 days after the last dose of study drug. [b] Follow-up period is more than 28 days after the last dose of study drug.

One death was associated with a treatment-related SAE in sunitinib-treated patients (Patient 110114-00436 experienced an SAE of sudden death). Two deaths in patients receiving IFN-α were associated with a treatment-related SAE (Patient 056590-00146 experienced an SAE of cardiac disorder and Patient 068012-00681 experienced an SAE of myocardial infarction). Narratives for these patients are located in the A6181034 CSR. The remaining deaths during treatment or within 28 days after last dose of study drug for patients receiving sunitinib or IFN-α were due to disease progression or to adverse events considered to be related to the underlying disease as described in Table 11.

Table 11. Patients Who Died During Treatment or Within 28 Days After Last Dose in Study

Patient No.	Age (Years)	Sex	Race	Preferred Term Reported at the Time of Death (MedDRA Version 8.1) With an Outcome of Death	Relationship[a]	Days Since First Dose[b]
Sunitinib						
039238-00208	67	F	W	Respiratory failure	Disease	14
043999-00620	65	F	W	Disease progression	Disease	51
056129-00009	65	M	A	Disease progression	Disease	22
056590-00131	67	M	W	Disease progression	Disease	44
110114-00436	69	M	W	Sudden death	Sunitinib	12
113571-00017	62	F	W	Disease progression	Disease	29
113972-00245	49	M	W	Disease progression	Disease	83
117102-00488	49	M	W	Disease progression	Disease	50
117102-00643	27	M	W	Disease progression	Disease	40
152071-00355	55	F	W	Disease progression	Disease	142
165503-00512	68	M	W	Disease progression	Disease	138
165709-00232	76	M	W	Disease progression	Disease	240
170349-00550	64	F	W	Gastric hemorrhage	Other	150

Note: Data up to 15 November 2005. N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, No. = number, MedDRA = Medical Dictionary for Regulatory Activities, F = female, M = male, W = white, A = Asian, NA = not available. [a] If the relationship to study drug was unknown, the event was considered to be related to treatment. [b] Days since first dose = (death date – first dose date).

Table 11. Patients Who Died During Treatment or Within 28 Days After Last Dose in Study A6181034 (As-Treated Population) (Continued)

Patient No.	Age (Years)	Sex	Race	Preferred Term Reported at the Time of Death (MedDRA Version 8.1) With an Outcome of Death	Relationship[a]	Days Since First Dose[b]
Interferon-α						
019318-00492	69	F	W	Disease progression	Disease	101
043999-00635	62	F	W	NA[c]	NA[c]	45
056590-00146	79	M	W	Cardiac disorder	Interferon-α	9
068012-00681	72	M	W	Myocardial infarction	Interferon-α	79
068473-00082	55	M	W	Disease progression	Disease	33
077790-00447	55	F	W	Respiratory failure	Disease	17
103636-00426	70	F	W	Disease progression	Disease	33
103636-00509	78	M	W	Disease progression	Disease	26
127044-00222	59	M	W	Disease progression	Disease	30
138236-00277	45	M	W	Disease progression	Disease	95
152071-00239	67	M	W	Disease progression	Disease	48
152071-00267	40	F	W	Disease progression	Disease	146
168284-00316	64	M	W	Disease progression	Disease	36
168839-00348	56	M	W	Disease progression	Disease	44
168839-00451	60	F	W	Disease progression[c]	Disease	3
169417-00357	56	F	W	Cerebral hemorrhage	Disease	79
180991-00272	55	M	W	Disease progression	Disease	44

Note: Data up to 15 November 2005. N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, No. = number, MedDRA = Medical Dictionary for Regulatory Activities, F = female, M = male, W = white, A = Asian, NA = not available. [a] If the relationship to study drug was unknown, the event was considered to be related to treatment. [b] Days since first dose = (death date – first dose date). [c] Detailed information for Patient 043999-00635 was not available at the time of this analysis due to incomplete data reconciliation. [d] One patient (168839-00451) receiving interferon-α who died due to disease progression also had an adverse event of dyspnea at the time of death. Dyspnea was incorrectly classified as a contributing cause of death at the time of this analysis, but has since been corrected to reflect that the cause of death was solely disease progression (and not dyspnea). Therefore, dyspnea is not listed as a cause of death in this table.

Other Serious Adverse Events

In Study A6181034, 116 (30.9%) of the patients treated with sunitinib versus 79 (21.9%) of the patients treated with IFN-α experienced at least 1 treatment-emergent SAE.
Those SAEs that occurred in more than 1 patient in either treatment arm are summarized in Table 12. The overall incidence of SAEs was comparable between Study A6181034 and the general population of patients receiving sunitinib, although there was some variation in the rates of individual SAEs.

Table 12. Treatment-Emergent, All-Causality Serious Adverse Events Occurring in More Than 1 Patient in Either Treatment Arm in Study A6181034 (As-Treated Population)

MedDRA Version 8.1 Preferred Term	Sunitinib (N = 375)	Interferon-α (N = 360)
Any SAE in more than 1 patient, n (%)	94 (25.1)	69 (19.2)
Disease progression	11 (2.9)	12 (3.3)
Vomiting	11 (2.9)	2 (0.6)
Asthenia	10 (2.7)	5 (1.4)
Dehydration	9 (2.4)	4 (1.1)
Nausea	8 (2.1)	2 (0.6)
Hypertension	7 (1.9)	0 (0)
Abdominal pain	6 (1.6)	3 (0.8)
Anemia	6 (1.6)	11 (3.1)
Dyspnea	6 (1.6)	9 (2.5)
Pleural effusion	6 (1.6)	2 (0.6)
Hyponatremia	5 (1.3)	0 (0)
Back pain	4 (1.1)	1 (0.3)
Epistaxis	4 (1.1)	0 (0)
Pulmonary embolism	4 (1.1)	4 (1.1)
Spinal cord compression	4 (1.1)	0 (0)
Thrombocytopenia	4 (1.1)	0 (0)
Condition aggravated	3 (0.8)	2 (0.6)
Confusional state	3 (0.8)	0 (0)
Ejection fraction decreased	3 (0.8)	0 (0)
Fatigue	3 (0.8)	5 (1.4)
Pyrexia	3 (0.8)	0 (0)
Hematuria	3 (0.8)	1 (0.3)
Renal failure	3 (0.8)	1 (0.3)
Anorexia	2 (0.5)	0 (0)
Blood bilirubin increased	2 (0.5)	0 (0)
Cellulitis	2 (0.5)	0 (0)
Chest pain	2 (0.5)	5 (1.4)
Deep vein thrombosis	2 (0.5)	1 (0.3)
Diarrhea	2 (0.5)	0 (0)
Dysphagia	2 (0.5)	0 (0)
Gastric hemorrhage	2 (0.5)	0 (0)
Hypoglycemia	2 (0.5)	0 (0)
Idiopathic thrombocytopenic purpura	2 (0.5)	0 (0)
Intestinal perforation	2 (0.5)	1 (0.3)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

Table 12. Treatment-Emergent, All-Causality Serious Adverse Events Occurring in More Than 1 Patient in Either Treatment Arm in Study A6181034 (As-Treated Population) (Continued)

MedDRA Version 8.1 Preferred Term	Sunitinib (N = 375)	Interferon-α (N = 360)
Mental status changes	2 (0.5)	1 (0.3)
Myocardial infarction	2 (0.5)	1 (0.3)
Pancreatitis	2 (0.5)	0 (0)
Platelet count decreased	2 (0.5)	0 (0)
Pneumonia	2 (0.5)	1 (0.3)
Bone pain	1 (0.3)	1 (0.3)
Convulsion	1 (0.3)	1 (0.3)
Fistula	1 (0.3)	1 (0.3)
Hemiparesis	1 (0.3)	1 (0.3)
Humerus fracture	1 (0.3)	1 (0.3)
Hypercalcemia	1 (0.3)	3 (0.8)
Hyperkalemia	1 (0.3)	1 (0.3)
Hypoxia	1 (0.3)	1 (0.3)
Pain	1 (0.3)	1 (0.3)
Pain in extremity	1 (0.3)	1 (0.3)
Pathological fracture	1 (0.3)	4 (1.1)
Pericardial effusion	1 (0.3)	1 (0.3)
Renal failure acute	1 (0.3)	1 (0.3)
Rectal hemorrhage	1 (0.3)	1 (0.3)
Respiratory failure	1 (0.3)	1 (0.3)
Sepsis	1 (0.3)	2 (0.6)
Transient ischemic attack	1 (0.3)	1 (0.3)
Urinary tract infection	1 (0.3)	2 (0.6)
Abdominal pain upper	0 (0)	2 (0.6)
Infection	0 (0)	2 (0.6)
Performance status decreased	0 (0)	2 (0.6)
Pulmonary edema	0 (0)	2 (0.6)
Urinary retention	0 (0)	2 (0.6)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

In Study A6181034, 66 (17.6%) of the patients treated with sunitinib versus 18 (5.0%) of the patients treated with IFN-α experienced at least 1 treatment-related SAE.

Table 13 summarizes those SAEs that were judged by the investigator to be treatment-related and which occurred in more than 1 patient in either treatment arm. The overall incidence of treatment-related SAEs was comparable between Study A6181034 and the general population of patients receiving sunitinib, although there was some variation in the rates of individual treatment-related SAEs.

Table 13. Treatment-Related Serious Adverse Events Occurring in More Than 1 Patient in		
MedDRA Version 8.1 Preferred Term	**Sunitinib (N = 375)**	**Interferon-α (N = 360)**
Any treatment-related SAE in more than 1 patient, n (%)	46 (12.3)	14 (3.9)
Vomiting	8 (2.1)	1 (0.3)
Dehydration	7 (1.9)	3 (0.8)
Hypertension	6 (1.6)	0 (0)
Nausea	6 (1.6)	1 (0.3)
Abdominal pain	4 (1.1)	0 (0)
Anemia	4 (1.1)	3 (0.8)
Asthenia	4 (1.1)	2 (0.6)
Hyponatremia	4 (1.1)	0 (0)
Epistaxis	3 (0.8)	0 (0)
Pleural effusion	3 (0.8)	0 (0)
Thrombocytopenia	3 (0.8)	0 (0)
Anorexia	2 (0.5)	0 (0)
Condition aggravated	2 (0.5)	0 (0)
Deep vein thrombosis	2 (0.5)	0 (0)
Dysphagia	2 (0.5)	0 (0)
Ejection fraction decreased	2 (0.5)	0 (0)
Intestinal perforation	2 (0.5)	0 (0)
Platelet count decreased	2 (0.5)	0 (0)
Pyrexia	2 (0.5)	0 (0)
Chest pain	1 (0.3)	1 (0.3)
Dyspnea	1 (0.3)	2 (0.6)
Fatigue	1 (0.3)	3 (0.8)
Myocardial infarction	1 (0.3)	1 (0.3)
Pulmonary embolism	1 (0.3)	1 (0.3)
Performance status decreased	0 (0)	2 (0.6)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

Treatment Discontinuations

Table 14 summarizes patient disposition for Study A6181034. As of 15 November 2005, 374 patients were continuing treatment on study (248 patients [66.1%] on sunitinib and 126 patients [33.6%] on IFN-α).

Lack of efficacy (disease progression) was the most common reason for discontinuation in both the sunitinib and IFN-α groups. A substantially greater number of patients discontinued due to lack of efficacy on IFN-α (45.3%) compared with sunitinib (24.5%). Thirty (8.0%) of the patients on sunitinib discontinued because of an adverse event compared with 47 (12.5%) of the patients on IFN-α.

Primary Reason for Discontinuation, n (%)	**Sunitinib (N = 375)**	**Interferon-α (N = 375)**
Adverse event	30 (8.0)	47 (12.5)
Protocol violation	1 (0.3)	1 (0.3)
Consent withdrawn[a]	4 (1.1)	16 (4.3)
Lack of efficacy (disease progression)	92 (24.5)	170 (45.3)
Randomized but did not receive any study drug	0 (0)	15 (4.0)
Ongoing	248 (66.1)	126 (33.6)

Note: Data up to 15 November 2005.
N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities. [a] "Consent withdrawn" does not include the 15 patients randomized to the IFN-α arm who withdrew consent after randomization prior to starting the study treatment. These 15 patients are listed separately with the primary reason for discontinuation as "randomized but did not receive any study drug".

Table 15 summarizes the treatment-related AEs that were reported as ongoing in more than 1 patient in either treatment arm at the time of treatment discontinuations. Fewer events (fatigue, nausea, and vomiting) leading to discontinuation occurred in patients on sunitinib as compared with events (fatigue, depression, dyspnea, nausea, asthenia, and weight decreased) leading to discontinuation while on IFN-α.

Table 15. Treatment-Related Adverse Events Reported in More Than 1 Patient in Either Treatment Arm at the Time of Treatment Discontinuation in Study A6181034 (As-Treated Population)

MedDRA Version 8.1 Preferred Term	**Sunitinib (N = 375)**	**Interferon-α (N = 360)**
Patients with treatment-related AE reported at discontinuation, n (%)	23 (6.1)	34 (9.4)
Fatigue	3 (0.8)	17 (4.7)
Nausea	2 (0.5)	3 (0.8)
Vomiting	2 (0.5)	1 (0.3)
Anorexia	1 (0.3)	1 (0.3)
Asthenia	1 (0.3)	3 (0.8)
Back pain	1 (0.3)	0 (0)
Cardiac failure congestive	1 (0.3)	0 (0)
Cerebral hematoma	1 (0.3)	0 (0)
Dyspnea	1 (0.3)	4 (1.1)
Ejection fraction decreased	1 (0.3)	0 (0)
Electrocardiogram QT corrected interval prolonged	1 (0.3)	0 (0)
Hemiparesis	1 (0.3)	0 (0)
Hypertension	1 (0.3)	0 (0)
Idiopathic thrombocytopenic purpura	1 (0.3)	0 (0)
Lethargy	1 (0.3)	0 (0)
Leukopenia	1 (0.3)	0 (0)
Malignant hypertension	1 (0.3)	0 (0)
Myocardial infarction	1 (0.3)	1 (0.3)
Neutropenia	1 (0.3)	1 (0.3)
Depression	0 (0)	4 (1.1)
Weight decreased	0 (0)	2 (0.6)

N = number of patients in the population who received at least 1 dose of study drug, n = number of patients, % = n/N×100, MedDRA = Medical Dictionary for Regulatory Activities, AE = adverse event.

Overall Safety Profile – Other Safety Assessments

Laboratory Tests

Sixty-two (16.5%) of the patients on sunitinib versus 37 (10.3%) of the patients on IFN-α experienced Grade 4 serum chemistry abnormalities in Study A6181034. The most common Grade 4 chemistry abnormalities for patients receiving sunitinib were hyperuricemia (43 patients, 11.5%) and increased lipase (11 patients, 2.9%). These 2 abnormal findings were also the most common for the IFN-α arm, with hyperuricemia in 29 patients (8.1%) and increased lipase in 4 patients (1.1%).

One hundred fifty-one (40.3%) of the patients on sunitinib versus 115 (31.9%) of the patients on IFN-α experienced Grade 3 serum chemistry abnormalities. The most common Grade 3 serum chemistry abnormalities in the sunitinib-treated group were hyperlipasemia (49 patients, 13.1%), hyponatremia (17 patients, 4.5%), hyperamylasemia (16 patients, 4.3%), hypophosphatemia (16 patients, 4.3%), and hyperglycemia (10 patients, 2.7%); whereas the most common abnormalities in the IFN-α-treated group were hypophosphatemia (22 patients, 6.1%), hyperglycemia (20 patients, 5.6%), hyperlipasemia (19 patients, 5.3%), and hyperkalemia (12 patients, 3.3%). For patients treated with IFN-α, Grade 3 hyponatremia was reported for 9 patients (2.5%) while Grade 3 hyperamylasemia was reported for 7 patients (1.9%).

These laboratory changes were generally not associated with clinical signs and symptoms. One SAE of hyperuricemia (for 1 patient on IFN-α) was reported; no SAEs of gout were reported. There were 2 SAEs of pancreatitis (for 2 patients on sunitinib).

Results for sunitinib-treated patients from Study A6181034 are consistent with the most common Grade 3 and 4 chemistry abnormalities reported previously in the SU for other ongoing studies.

There were few Grade 4 hematologic abnormalities (3 patients [0.8%] had decreases in absolute neutrophil count and 1 patient [0.3%] had a decrease in hemoglobin count on sunitinib while 1 patient [0.3%] had a decrease in hemoglobin count on IFN-α).

Grade 3 hematologic abnormalities for patients receiving sunitinib in Study A6181034 were decreases in lymphocyte count (44 patients, 11.7%), absolute neutrophil count (41 patients, 10.9%), platelet count (30 patients, 8.0%), total white blood cell count (19 patients, 5.1%), and hemoglobin (10 patients, 2.7%). The most common Grade 3 hematologic abnormalities for patients receiving IFN-α in Study A6181034 were decreases in lymphocyte count (79 patients, 21.9%), absolute neutrophil count (24 patients, 6.7%), hemoglobin (15 patients, 4.2%), and total white blood cell count (8 patients, 2.2%). Clinical manifestations of these hematologic abnormalities were rare: for instance, febrile neutropenia was reported as an SAE in only 1 patient (in the sunitinib group).

These laboratory abnormalities for sunitinib-treated patients from Study A6181034 were consistent with those reported in the SU.

QT Analysis

A dedicated QT Study A6181005 ("A Phase l Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors") was completed as of 15 November 2005. Study A6181005 was conducted in subjects with various solid malignant tumors to assess the potential effects of sunitinib treatment on the QT/QTc interval at exposures approximately 2-fold higher than the mean exposures observed at the recommended 50-mg QD dose of sunitinib. This study was a single-blind, nonrandomized, 3-treatment, single-center trial, which included both the placebo and positive (moxifloxacin) controls. Time-matched serial triplicate ECGs were recorded at baseline and after administration of sunitinib, moxifloxacin, and placebo. The QT intervals were corrected for heart rate using Fridericia's correction.

As described in the Study A6181005 CSR, QTcF prolongation was determined 24 hours after sunitinib administration on Day 3 (at therapeutic plasma concentrations of sunitinib and its active metabolite, SU012662) and at multiple time-points on Day 9 (at 2-times therapeutic plasma concentrations of sunitinib and SU012662). On Day 3, the maximum mean prolongation of QTcF was 14.5 msec with a 90% CI upper limit of 19.5 msec after the placebo-adjusted within-day correction was used and 9.6 msec with a 90% CI upper limit of 15.1 msec after the placebo-adjusted time-matched correction was used. On Day 9, the maximum mean prolongation of QTcF was 20.3 msec with a 90% CI upper limit of 27.1 msec after the placebo-adjusted within-day correction was used and 15.4 msec with a 90% CI upper limit of 22.4 msec after the placebo-adjusted time-matched correction was used. The observed changes in QTcF correlated with the sunitinib, SU012662, and total (sunitinib+SU012662) exposures; however, maximum QTcF prolongation was observed later than the times at which maximum plasma concentrations of these analytes were observed, suggesting a delay in QTcF effect.

The outlier QTcF values greater than 450 msec were generally higher among women than men; however, no subject had a QTcF value greater than 500 msec.

The incidence of cardiac-related abnormalities was low as no subject's ECG was assessed as abnormal and no case of torsade de pointes was reported. One subject each experienced nontreatment-related tachycardia, treatment-related bradycardia, and treatment-related syncope (the event of syncope was not related to cardiac causes in the investigator's opinion).

In conclusion, although an effect on QTcF was observed at the therapeutic plasma concentrations of sunitinib and SU012662 expected after the recommended starting sunitinib QD dose of 50 mg (24 hours after sunitinib administration on Day 3), the clinical significance of this finding is unclear, since none of the subjects developed QTcF prolongation of at least Grade 3 severity at the therapeutic or 2-times therapeutic exposures.

Special Safety Topics

There have been no additional special safety concerns from those AEs of special interest reported in the initial marketing applications.

Safety in Special Groups and Situations

Use in Adolescents and Children

Sunitinib is currently indicated in adults only.
Limited use in pediatric patients is permitted on a case-by-case basis for patients with GIST in the expanded-access Study A6181036. Preliminary data for 7 pediatric patients up to 15 November 2005 reports 3 patients (42.9%) experienced SAEs of acute renal failure, abdominal pain, and GI tube removal. None of these SAEs was considered related to sunitinib treatment by the investigator. No robust conclusions specific to pediatric patients can be determined from this limited set of data up to 15 November 2005.

Use in Elderly

Analysis of AE data shows that the safety profile of sunitinib was similar between the 2 age groups (ages 18 to 65 and ages 65 or older), with no particular safety concerns particular to either group.

Use in Renal or Hepatic Impairment

Results from Study A6181079 determined that dose adjustments were not necessary for patients with mild or moderate hepatic impairment. A clinical study is ongoing to evaluate the PK of sunitinib in subjects with renal impairment. The study results for patients with renal impairment are not yet available.

Pregnancy and Lactation

No clinical studies with sunitinib have been conducted in pregnant women, and no pregnancies occurred during clinical studies of sunitinib. Sunitinib and its metabolite, SU012662, are excreted in rat milk, but it is not known whether they are excreted in human milk. Women should be advised against breastfeeding while taking sunitinib.

Overdose

No overdose of sunitinib was reported in completed clinical studies. In Phase 1 dose-escalation studies with multiple doses of sunitinib, fatigue was the most commonly reported AE (experienced by approximately 70% of the patients overall); other AEs included GI events such as nausea and vomiting. Similar occurrences might be expected with sunitinib overdosage.

No specific antidote is known for treating the effects of sunitinib overdose. Treatment should consist of general supportive measures. If indicated, elimination of unabsorbed drug can be achieved by inducing emesis or by gastric lavage.

Discussion on Clinical Safety

Among all ongoing studies reported in the Safety Update, the majority of the on-study deaths were causally attributed to study disease (disease progression). The frequencies of treatment-emergent, SAEs reported in the SU were comparable with the respective SAE data reported previously. Lack of efficacy (disease progression) was the most common reason for treatment discontinuations among the majority of patients, consistent with the respective data for treatment discontinuations reported previously.

Safety information presented for the first time in the SU include safety data collected from patients receiving continuous doses of sunitinib in the morning or in the evening and safety assessments performed in a small number of the Japanese and paediatric (<18 years of age) patients with GIST. At this time, no definitive conclusions with regard to sunitinib safety for patients receiving continuous sunitinib dosing (n=44) or the Japanese (n=11) and pediatric (n=7) patients can be made because of the small number of patients and the relatively short period of exposure to sunitinib up to 15 November 2005.

With reference to Study A6181034, safety data (with the exception of drug exposure, demographics, and disposition data) are presented for the AT population of 735 patients who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received (15 patients in the IFN-α arm withdrew consent after randomization prior to starting the study treatment).

Data presented for Study A6181034 through 15 November 2005 are consistent with the general safety profile from previous studies; there have been no new safety trends or concerns identified since the initial marketing applications.

In Study A6181034, the majority of the on-study deaths were causally attributed to study disease (disease progression). The frequencies of SAEs for patients receiving sunitinib were comparable with the respective SAE data reported previously. The higher overall frequency of SAEs in the sunitinib treatment group, as compared with that in the IFN-α treatment group, may be attributed to the fact that patients in the sunitinib treatment group were exposed to drug for a longer period of time on average than those in the IFN-α treatment group in Study A6181034. As a result, the maximum possible follow-up period for patients on sunitinib treatment was longer than for patients on IFN-α treatment.

Lack of efficacy (disease progression) was the most common reason for treatment discontinuations among the majority of patients in Study A6181034, consistent with the respective data on treatment

discontinuations reported in the original MAA. The rate of treatment discontinuations resulting from disease progression in the IFN-α treatment group was approximately double that in the sunitinib treatment group, accounting for the approximately 2-fold higher overall rate of treatment discontinuations among patients on IFN-α treatment versus patients on sunitinib treatment. In addition, the rate of treatment discontinuations resulting from AEs was also higher in the IFN-α treatment group than the rate in the sunitinib treatment group.

Fatigue, GI disorders (such as nausea, diarrhea, stomatitis, dyspepsia, constipation, and vomiting), and anorexia were the most commonly reported all-causality AEs in patients receiving sunitinib. Anemia, thrombocytopenia, and neutropenia were also noted, as was hypertension, the latter supported by vital sign data. Although elevations in amylase and lipase were among the more common laboratory abnormalities, clinical manifestations of pancreatitis were rare. Most AEs were manageable by dose interruptions or modifications and through specific therapies.

There was 1 death (1/375, 0.27%) considered by the investigator to be at least possibly related to study drug in sunitinib-treated patients in Study A6181034. Two deaths in the IFN-α group were considered by the investigator to be at least possibly related to IFN-α (2/360, 0.56%). One hundred sixteen (30.9%) of the patients versus 79 (21.9%) of the patients experienced SAEs on sunitinib versus IFN-α treatment, respectively. Sixty-six (17.6%) of the patients on sunitinib treatment and 18 (5.0%) of the patients on IFN-α treatment experienced a treatment-related SAE. However, only 23 (6.1%) of the patients on sunitinib and 34 (9.4%) of the patients on IFN-α experienced a treatment-related AE that was temporally associated with discontinuation. Of these 57 patients with treatment-related AEs temporally associated with discontinuation, 14 patients (3.7%) on sunitinib and 6 patients (1.7%) on IFN-α had AEs that were serious.

In summary, prescribing physicians should be aware of sunitinib's safety profile, including the potential for GI, hematologic, and blood pressure effects. However, SAEs with sunitinib treatment were manageable and generally did not lead to treatment discontinuation.

Benefit/ Risk assessment

Patients with MRCC face a short expected survival with significant morbidity.
The only systemic first-line treatments available for MRCC are cytokines, but their efficacy is limited and they are often poorly tolerated. Therefore, there is an unmet medical need for further treatment options and new therapies need to be assessed in the context of the affected target population.

At the time of the initial MAA, no satisfactory methods of treatment that had been authorised, existed in the Community for patients with MRCC who have failed prior cytokine-based treatment. Despite other agents that have shown activity in this setting, such as different regimens of cytokines and novel tyrosine kinase inhibitors such as sorafenib, there remained a large unmet medical need in the treatment of this patient population.

In the initial MAA, the demonstration of efficacy in patients with MRCC who were refractory to prior cytokine therapy with interleukin-2 or interferon-α was based on the proportion of patients achieving an objective response (i.e. a major shrinkage of the overall tumor burden) observed in two single-arm, open-label phase II studies. In one study the objective response rate (ORR) was 36.5% (95% C.I. 24.7% - 49.6%). In the second study, ORR was 35.8% (95% C.I. 26.8% - 45.7%). These results were observed in a homogenous group of progressive patients with a predictable outcome of the disease. The effect in terms of ORR was unprecedented, even with the most active available agents in a non-refractory population for which response rates in the order of 5 to 15% have been reported. Also, the response rate observed for sunitinib was much higher than the reported proportion of patients with an objective response for the novel targeted kinase agent sorafenib (2.1%).
Overall, compared to other agents that have shown activity in MRCC, sunitinib had demonstrated a distinct pharmacodynamic profile, and the proportion of patients achieving an objective response observed for sunitinib in this MRCC patient population was very high compared to what had been reported for other agents including sorafenib.

At the time of the initial CHMP opinion, the Committee considered that the data presented supported a clinical benefit for Sutent (sunitinib) in the treatment of patients with MRCC who have failed prior cytokine-based treatment. Taking into account the favourable safety profile observed, the benefit/risk of sunitinib in the MRCC indication was considered positive. However, comprehensive clinical data in the MRCC indication were not yet available, and the CHMP therefore recommended the granting of a conditional marketing authorisation.

The CHMP considered that the efficacy results from a trial in a first line setting would provide additional comprehensive clinical data to confirm that treatment with Sutent is associated with an effect on important time-related clinical endpoints, such as progression-free survival and overall survival. The demonstration of a favourable effect in first-line would be considered relevant also for patients with MRCC who have failed prior cytokine-based treatment confirming the existence of an effect in terms of relevant clinical endpoints even if the precise magnitude of this effect would not be known in this indication. The requested trial, Study A6181034, was ongoing at the time of the granting of the original MA, although recruitment had been completed.

Consequently the Marketing Authorisation was granted as a Conditional Marketing Authorisation pursuant to Article 14(7) of Regulation (EC) No 726/2004. The applicant agreed to provide, as requested by the CHMP, the results of Study A6181034 in cytokine-naive patients with metastatic renal cell carcinoma as a Specific Obligation post-marketing.

The MAH has now submitted a Type II variation, which included the requested efficacy and safety data from an analysis of Study A6181034 (A phase III randomised study of sunitinib versus interferon-alfa as first line systemic therapy for patients with metastatic renal cell carcinoma) in order to fulfill the Specific Obligation.
The MAH, on the basis of the results of Study A6181034, requested to extend the indication to include first-line treatment of patients with advanced and/or metastatic renal cell carcinoma (MRCC).
As part of this application, the MAH also requested a switch from a conditional to a 'normal' marketing authorisation in accordance with Article 7 of Regulation (EC) No 507/2006.

Following the assessment of the data provided, the CHMP considers that a positive benefit-risk balance has been established for the proposed extended indication. Sunitinib has shown significantly superior efficacy as demonstrated by a prolonged PFS and an improved ORR compared to IFN-α. Further, sunitinib was found to have a tolerable safety profile in patients with MRCC. The low rates of discontinuation for the sunitinib-treated patients indicate that the AEs associated with sunitinib (fatigue, GI disorders, and myelosuppression) were generally not severe enough to result in discontinuation of therapy. Most AEs can be managed effectively through recourse to specific therapies, supportive care, or, when required, a reduction or temporary delay in dosing. The AEs reported with sunitinib are not considered unusual or unfamiliar, and physicians should therefore be able to recognize and manage them.

The proposed starting dose of sunitinib is 50 mg once daily, with 4 weeks of treatment followed by 2 weeks off (Schedule 4/2). The dosage may be decreased, in increments of 12.5 mg, if required for tolerability. The oral, once-daily administration of sunitinib lends itself to outpatient treatment, with attendant quality-of-life benefits and a tolerable safety profile that is comparable to or better than most other cancer treatments.

With reference to the wording of the new indication, the Committee considered it inappropriate to include outcome variables in section 4.1 of the SPC since according to the SPC Guideline such information should be presented in section 5.1. The Committee therefore recommended that the indication be revised as follows:

"Gastrointestinal Stromal Tumour (GIST)
Sutent is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Metastatic Renal Cell Carcinoma (MRCC)
Sutent is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC)".

Further, the CHMP considered that the new efficacy and safety data available for patients with treatment-naïve RCC are consistent with the data presented in the initial MAA for patients with cytokine-refractory MRCC. The data confirm the positive results presented in the initial MAA with a significant improvement in PFS and a robust improvement in ORR compared with IFN-α in the treatment-naïve MRCC patient population. Patients in the sunitinib arm also reported better patient reported outcomes compared with patients in the IFN-α arm.

Therefore, the Committee considered that the submitted data from Study A6181034 are sufficient to conclude that comprehensive clinical data on sunitinib have been provided.

The CHMP concluded that the specific obligation for Sutent is resolved and since there is no remaining specific obligation, the Committee recommended a switch from a conditional to a 'normal' Marketing Authorisation under Article 14(1) of Regulation (EC) No. 726/2004.

IV. CONCLUSION

On 19 October 2006 the CHMP agreed to extend the indication and on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

Furthermore, the CHMP reviewed the evidence of compliance with the Specific Obligation submitted by the Marketing Authorisation Holder.

Since all Specific Obligations stated in Annex II.C of the CHMP Opinion for the original MAA have been fulfilled, the Committee considers that there are no remaining grounds for a Conditional Marketing Authorisation and recommends a switch to a 'normal' Marketing Authorisation in accordance with Article 7 of regulation (EC) No 507/2006. Annex II has been revised accordingly.