Pfizer Ltd

Single Technology Appraisal

of

Sunitinib for the treatment of gastrointestinal stromal tumours

31st October 2008

Contents

Abbreviations and Acronyms

AE	Adverse Events
AIDS	Acquired Immunodeficiency Syndrome
ASCO	American Society of Clinical Oncology
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
DPSM	Duration of Performance Status Maintenance
DR	Duration of Response
DSMB	Data Safety Monitoring Board
EAP	Expanded Access Programme
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Evaluation Agency
ESMO	European Society of Medical Oncology
GIST	Gastrointestinal Stromal Tumour
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HTA	Health Technology Assessment
ITT	Intention To Treat
KM	Kaplan Meier
mITT	Modified Intention to Treat
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
OS	Overall Survival
ORR	Objective Response Rate
PD	Progressive Disease
PDGFRA	Platelet Derived Growth Factor Receptor Alpha
PFS	Progression Free Survival
PP	Per Protocol
PR	Partial Response
QALY	Quality Adjusted Life Year
QoL	Quality-of-Life
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank Preserved Structural Failure Time Models
RTK	Receptor Tyrosine Kinase
SmPC	Summary of Product Characteristics
TTP	Time to Tumour Progression
TTR	Time to Tumour Response
WHO	World Health Organisation

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name: Sutent®
Approved name: sunitinib malate
Therapeutic class: Oral Tyrosine Kinase Inhibitor
Product Licence Holder: Pfizer Limited

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Sunitinib gained marketing authorisation for the treatment of gastrointestinal stromal tumour (GIST) after the failure of imatinib mesylate (Glivec®) treatment due to resistance or intolerance in June 2006.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

Indication under consideration in this STA:
Unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Other indications:
Advanced and/or metastatic renal cell carcinoma (MRCC)

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

ONCOtrak data for 2008 suggests that 20-30 patients within the UK were receiving sunitinib for GIST.

No clinical trials that relate to the decision problem are expected to complete in the near future. The summaries below are ongoing Pfizer-sponsored clinical trials with sunitinib in GIST.

Study: Safety and effectiveness of daily dosing with sunitinib or imatinib in patients with gastrointestinal stromal tumours (A6181112).

Inclusion Criteria: Patients with gastrointestinal stromal tumours whose disease has progressed on imatinib 400mg daily

Design: A phase IIIb study of patients with gastrointestinal stromal tumours who have had progressive disease while on 400mg imatinib. Patients will be randomly assigned to either sunitinib 37.5mg daily or imatinib 800mg daily. This study will find out the benefits and potential side effects of taking sunitinib or imatinib for approximately one year.

Primary outcome measure is the duration of progression free survival while taking sunitinib or imatinib. PFS is defined as the time from date of first treatment dose to progression of the gastrointestinal stromal tumour or death for any reason, whichever comes first.

No of patient planned accrued: Planned = 200

Status: Recruiting

Study: A treatment protocol for patients with gastrointestinal stromal tumour (GIST) who may derive benefit from treatment with sunitinib (A6181036)

Inclusion criteria: Patients at least 18 years old, histologically proven GIST, failed prior treatment with imatinib mesylate, and adequate organ function

Design: A non-randomised, open label single group assignment, safety/efficacy study. The purpose of this study is to permit access to sunitinib for treatment use by patients with GIST given the following conditions: a) patients undergo screening, but are not eligible for participation in ongoing clinical studies such as A6181004; AND b) patients have GIST which standard treatments have not been able to control with acceptable toxicity AND c) patients have the potential to derive clinical benefit from treatment with sunitinib

No of patients planned accrued: planned = 1400

Status: Closed

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Sunitinib is available in all major European countries, Canada and the USA.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Sunitinib has been reviewed by the Scottish Medicines Consortium (SMC) in October 2006*.
Pfizer did not submit to the All Wales Medicines Strategy Group (AWMSG) and therefore received the recommendation below automatically.

SMC	Sunitinib is not recommended for use within NHS Scotland for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
AWMSG	In the absence of a submission from the holder of the marketing authorisation, Pfizer Limited, AWMSG is not in a position to endorse the use of sunitinib within NHS Wales for the treatment of patients with gastrointestinal stromal tumour (GIST).

*The offer of the first cycle of treatment for each patient being free was not in place at the time of the appraisal.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Sunitinib is available in the following formulation:

i) 12.5mg, 25mg and 50mg capsules containing sunitinib malate
Available in 28 and 30 capsule packs

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The sunitinib dose is 50mg daily for 4 weeks, followed by a 2-week treatment-free period to complete a 6-week cycle.

The duration of treatment depends on the success of treatment and the tolerability of the drug.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

Sunitinib malate is available in two pack sizes a 28 capsule pack and 30 capsule pack

12.5mg 28-capsule pack = £784.70
25mg 28-capsule pack = £1,569.40
50mg 28-capsule pack = £3,138.80

12.5mg 30-capsule pack = £840.75
25mg 30-capsule pack = £1,681.50
50mg 30-capsule pack = £3,363

1.10 What is the setting for the use of the technology?

Therapy should be initiated by a physician experienced in the treatment of GIST.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other therapies are likely to be prescribed with sunitinib either as a monotherapy or in combination.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with unresectable and/or metastatic GISTs after failure of imatinib due to resistance or intolerance	People with unresectable and/or metastatic GISTs after failure of imatinib due to resistance or intolerance
Intervention	Sunitinib	Sunitinib
Comparator(s)	Best supportive care	Best supportive care
Outcomes	Overall survival Progression free survival Response rates Adverse effects of treatment Health-related quality of life	Overall survival Time to tumour progression Progression free survival Response rates Adverse effects of treatment Health-related quality of life
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Outcomes to be included: • Incremental cost per quality-adjusted life year • Incremental cost per life year gained • Resource utilisation • Cost of treating adverse events The time horizon (6 years) for the economic evaluation reflects the life expectancy of patients with GIST. The costs were considered from a NHS and Personal Social Services perspective. As agreed with the Department of Health the first free cycle of sunitinib is free for all patients.

Special considerations, including issues related to equity or equality	Details of the components of best supportive care should be clearly described. Guidance will only be issued in accordance with the marketing authorisation	Best supportive care is taken to mean treatment to control, prevent and relieve complications and side effects and to improve comfort and quality of life. Within the model it is assumed to include palliative interventions but explicitly excludes the use of active therapy. The submission is in accordance with the marketing authorisation for sunitinib.

Section B

3 Executive summary

- Gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal neoplasms of the gastrointestinal tract.

- Imatinib mesylate is the only recommended first-line therapy for advanced GIST, with resistance and/or intolerance posing a significant clinical problem.

- Sunitinib (Sutent®) gained marketing authorisation for the treatment of gastrointestinal stromal tumour (GIST) after the failure of imatinib mesylate (Glivec®) treatment due to resistance or intolerance in June 2006. Sunitinib was given the first ever positive opinion on the granting of a conditional marketing authorisation (designed to facilitate early access to medicines) by the Committee for Medicinal Products for Human Use (CHMP) reflecting both the efficacy of sunitinib and that it was the first oral multi-receptor tyrosine kinase inhibitor to be brought into clinical use. Full authorisation was gained four months later.

- Sunitinib is administered orally at a recommended dose of 50mg/day (12.5mg and 25mg capsules are also available to enable administration of lower doses) for four weeks followed by a two week treatment free period, constituting a six week treatment cycle. The duration of treatment depends on the success of treatment and the tolerability of the drug.

- In the pivotal Phase III randomised placebo-controlled study, sunitinib demonstrated a statistically significant and clinically meaningful improvement in median PFS of 4.6 months (HR 0.3, $p<0.001$), and 5.2 months in median TTP (HR 0.3, $p<0.001$).

- An interim analysis (blinded phase) demonstrated that overall survival (OS) obtained with initial sunitinib treatment was better that that obtained with placebo (HR 0.49, 95% CI 0.29–0.83; $p=0.007$).

- An OS analysis using the Rank Preserved Structural Failure Time Model (RPSFT) method demonstrated an estimated median OS for the placebo group of 39.2 weeks and 72.7 weeks for sunitinib group (HR 0.505, 95% CI 0.388, 0.658; $p<0.0001$). The interim results from a on-going extended access programme involving over 1,000 patients, median survival of 75 weeks (95% CI 68 weeks, 84 weeks), underpins the validity of the final survival analysis from the pivotal phase III study..

- A Markov type model was developed to simulate disease progression in GIST, it used a 6 year time horizon to estimate the cost effectiveness of sunitinib compared to Best Supportive Care.

- The base case results from this analysis suggested that sunitinib has an incremental cost per life year gained of £17,695 and an incremental cost per QALY of £27,365 when compared to BSC The probabilistic sensitivity analysis of sunitinib being cost effective at a willingness to pay threshold of £30,000 per QALY is 50%.

- Based upon an estimate of 26 patients in 2009 and approx 88 patients being treated with sunitinib per annum thereafter, the anticipated cost to the England and Wales NHS is £247,033 in 2009 rising to £1,122,553 in 2013.

- Sunitinib has demonstrated clinical efficacy in second line use in GIST and, for patients who will benefit from treatment with sunitinib, it is a cost effective intervention.

- Sunitinib represents a valuable treatment option for GIST patients, a group with no effective treatment option after imatinib failure in England and Wales.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Disease/Condition

Gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal neoplasms of the gastrointestinal tract (Rubin et al. 2007; Joensuu et al. 2006). It is believed to originate from an intestinal pacemaker cell called the interstitial cell of Cajal (Kindblom et al. 1998). The incidence of gastrointestinal stromal tumour is estimated at 11 to 14.5 cases per million per year (Nilsson et al. 2005; Tryggvason et al. 2005). The most frequent primary sites are gastric (50%) and small bowel (25%). Colorectal, esophageal, and peritoneal GISTs are less frequent. GIST can be diagnosed at any age, with a median of 60 years (ESMO Guidelines Working Group, 2007).

Estimates vary widely on the incidence of new cases of GIST with figures between 200 and 2,000 quoted (NICE, 2004), with an apparent acceptance of an upper limit of 240 (NICE, 2004). Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation, the prognosis of which is poor with few, if any, people surviving beyond 5 years, in the absence of effective treatment (NICE 2004).

The clinical presentation of GIST is highly variable according to site and tumour size (Lau et al. 2004). GIST often remains clinically silent until tumours reach a large size, when mass effects, bleeding, or rupture may ensue (Ghazanfar et al. 2007).

The principal treatment of a patient with a primary GIST is complete surgical resection.

After resection of the primary tumour, most patients will subsequently develop recurrent GIST. In some cases, tumour rupture can account for the recurrence, particularly if it occurs in the peritoneum. However, in most patients, recurrence develops after what seemed to be a curative resection. The median time to recurrence is approximately 1.5 to 2 years (De Matteo et al. 2000; Ng et al.1992). Once patients develop recurrent disease, their chance of cure with conventional cytotoxic therapy is extremely low (<10%) (De Matteo 2002).

Metastatic disease is present at diagnosis in nearly half of patients with GIST, most commonly to the liver (65%) and peritoneum (21%), but also to the lymph nodes, bone and lungs (De Matteo et al. 2000; Lau et al. 2004). After radical resection, the 5-year overall survival is approximately 50%, whereas for unresectable or metastatic GISTs, before treatment with imatinib became available, the median survival was estimated at 10 to 20 months (Ng et al. 1992; De Matteo et al. 2000; Crosby et al. 2001; Pierie et al. 2001; Roberts et al. 2002).

Prior to sunitinib, imatinib mesylate was the only effective treatment for patients with unresectable and/or metastatic GISTs. Currently, imatinib is approved for the treatment of *KIT*-positive unresectable or metastatic GIST in the UK.

Despite the initial success of imatinib treatment, it has become apparent that the majority of patients eventually cease to respond to treatment, defined as either primary resistance within the first six months of treatment, or secondary resistance later (within 2 years). After failure of imatinib, progression is generally reported as

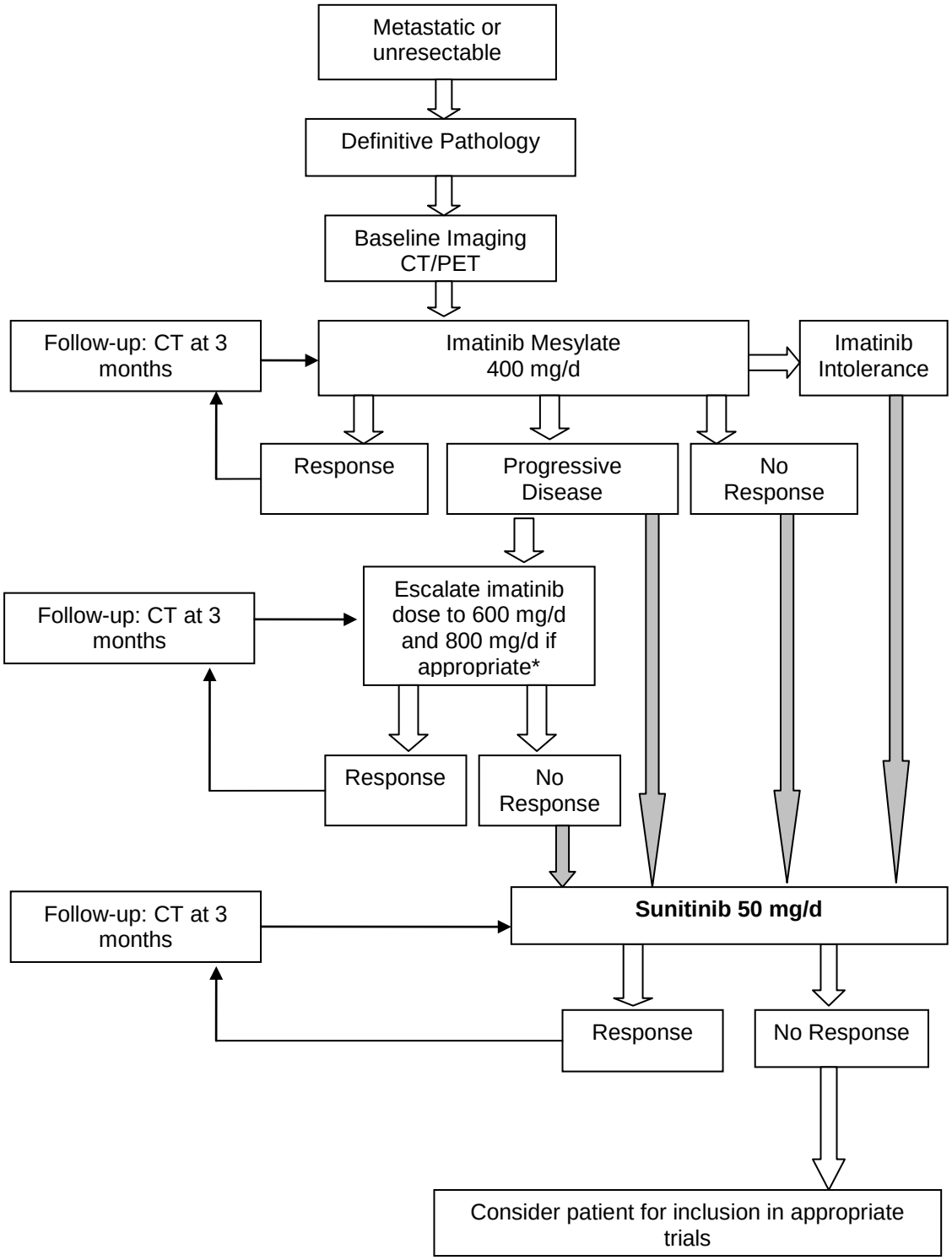
being less than 4 months (Demetri et al. 2006). It is estimated that approximately 15% of patients exhibit primary resistance and fail to respond to treatment. Although little published data are available on longer-term follow-up of GIST patients treated with imatinib, treatment failure is known to occur in approximately 70% of patients (EMEA 2006).

In addition, approximately 5% of patients are unable to tolerate imatinib therapy. The treatment algorithm for the management of patients with GISTs is presented in Figure1.

Most GISTs express a mutationally activated form of the tyrosine kinase growth factor receptor *KIT*, the activation of which, under normal conditions, causes cell growth, differentiation, and cell death. A similar mechanism also activates mutations in the platelet derived growth factor receptor alpha (*PDGFRA*). In GIST, *KIT* is permanently 'switched on' by activating mutations leading to unregulated cell growth (Mehren 2006). Mutations in *KIT* and *PDGFRA* are observed in 93% of patients with GIST (Mendel et al. 2003). These mutations are known to play a critical role in the genesis of GIST and have been implicated in other cancers (Sandberg & Bridge 2002).

Since no drug other than imatinib has demonstrated significant efficacy in the treatment of GIST, there remains an unmet medical need for patients who cannot tolerate imatinib, or who have tumours that are resistant to, or become resistant to, this drug.

Figure 1: Treatment algorithm for the management of patients with metastatic/unresectable GISTs.



* Imatinib dose escalation to 600 mg/d and 800 mg/d is not recommended in the UK. However, according to experts, imatinib dose escalation is sometimes considered appropriate in routine clinical practice.

4.2 What was the rationale for the development of the new technology?

GISTs contain oncogenic *KIT* or *PDGFRA* mutations and are remarkably sensitive to therapeutic *KIT* and/or *PDGFRA* inhibitors (Fletcher & Rubin 2007). Treatments targeted at *C-KIT* are particularly relevant since 90% of GISTs have *C-KIT* mutations (Heinrich et al. 2003). Prior to sunitinib, the only treatment available for metastatic GIST was imatinib mesylate (Glivec™, Novartis Pharmaceuticals). Imatinib is a signal-transduction inhibitor designed to selectively inhibit certain classes of tyrosine kinase including *KIT* and *PDGFRA* to prevent cell proliferation (NICE 2004). It is currently licensed for the treatment of adults with *KIT* positive unresectable and/or metastatic GIST at an initial dose of 400 mg/day and was approved by NICE in 2004 as first line treatment of this condition.

A minority of patients (15%-20%) will either not respond or be unable to tolerate imatinib mesylate.

A significant subset of patients treated with imatinib who initially respond to imatinib will eventually go on to develop progressive disease. As many as 75% of patients will have disease progression within two years (Demetri et al. 2002; Verweij et al. 2004).

In a pivotal study of imatinib in advanced gastrointestinal stromal tumour, 5% of patients showed primary resistance to imatinib and another 14% developed early resistance (within 6 months) (Verweij et al. 2004). These patients have a life expectancy of approximately one year (Demetri et al. 2002).

Secondary or acquired resistance develops after a median of about 2 years of treatment with the drug (Verweij et al. 2004). Such resistance can develop through various mechanisms, the most common being secondary *KIT* mutations in clonally expanded cancer cells (Demetri et al. 2006).

Once imatinib mesylate treatment has failed the only treatment option available to patients is best supportive care. Five year survival estimates for patients with malignant GIST range between 0% and 30% (Bucher et al. 2004).

As a result of emerging resistance, or lack of response to imatinib therapy, Pfizer developed a multiple receptor tyrosine kinase inhibitor sunitinib malate (Sutent™ SU11248) for imatinib intolerant, resistant, or progressive GIST.

Sunitinib was given the first ever positive opinion on the granting of a conditional marketing authorisation (designed to facilitate early access to medicines) by the CHMP effective July 2006 for second line use in mRCC and GIST.

In October 2006, sunitinib was granted a full marketing approval from the CHMP of the European Medicines Evaluation Agency (EMEA) in the EU for the treatment of unresectable and/or metastatic malignant GIST after failure of imatinib treatment due to resistance or, intolerance, based on the phase III clinical trial results (EMEA 2006).

4.3 What is the principal mechanism of action of the technology?

Receptor tyrosine kinases (RTKs) are a diverse group of transmembrane proteins that are involved in transmission of extracellular signals into the cell. After activation, RTKs trigger a series of intracellular pathways, leading to a variety of cellular responses such as differentiation, proliferation, migration and invasion, angiogenesis and cell survival. Sunitinib is an oral, small-molecule, multi-targeted tyrosine kinase inhibitor (TKI) that has demonstrated both direct antitumour activity and

antiangiogenic action. It produces this integrated effect by targeting the receptors for multiple signalling pathways fundamental for tumour growth and survival: vascular endothelial growth factor receptor (*VEGFR)-1*, *VEGFR-2*, *VEGFR-3*, platelet-derived growth factor receptor (*PDGFR*)-*α*, *PDGFR-β*, *c-KIT* and *fms*-like tyrosine kinase (*Flt-3*) (EMEA, EPAR 2006).

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

The current licensed indication of sunitinib reflects the phase III data and supports the use of sunitinib in patients following failure due to resistance or intolerance to imatinib.
Early resistance has been reported in 10–20% of cases (Hoeben et al. 2008). However, the vast majority of responding patients will eventually develop secondary tumour progression.

- Primary resistance is defined by experts in the field as failure within six months of imatinib therapy and these patients are unlikely to benefit from dose escalation. Therefore sunitinib should be considered as a second line option.
- Secondary resistance occurs later in therapy and sunitinib could be considered a treatment alternative to imatinib (400 mg/d) dose escalation based on an appropriate clinical decision. Current NICE guidelines do not recommend imatinib dose escalation for patients who develop progressive disease. However, even following failure of 800 mg/d imatinib, sunitinib has been shown to be an effective treatment option (See section 6.4).
- Sunitinib should be considered as a first-line therapy in patients who are intolerant to imatinib therapy.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

- Considerable variations exist in the clinical practice with regard to management of the imatinib resistant/intolerant patients. Many patients in clinical practice remain on imatinib 400 mg daily dose until performance status deteriorates or symptoms develop (Hopkins et al. 2008). Increasing the dose of imatinib in patients who have progressed on 400 mg daily is also deemed to be an appropriate option (Mehren & Watson 2005). Although dose escalation may overcome drug efflux mechanisms and increase therapeutic levels, that over time have decreased, imatinib has been escalated above 400 mg twice daily without clear data on its benefit (Mehren 2006). Current NICE guidelines do not recommend increase in dose of imatinib over 400 mg daily in patients who develop progressive disease. Patients could also remain on imatinib 400 mg/d, even if they become resistant to it. Some clinicians consider best supportive care as maintaining patients on imatinib 400 mg/d, regardless of resistance, with the aim of maintaining some symptomatic control.

  Pfizer supports the view that sunitinib does offer an additional second line choice after resistance or intolerance to imatinib 400 mg/d. Data from the pivotal phase III trial (Demetri et al. 2006) included a number of patients who had received less than or equal to 400 mg/d, in addition to patients who had received dose up to and beyond 800 mg/d. The results of this trial indicated that patients benefited from sunitinib treatment, irrespective of the prior dose of imatinib.
  An international, multi-centre prospective randomised phase III study comparing imatinib 800 mg per day with sunitinib 37.5 mg per day in patients who have relapsed on imatinib 400 mg daily is currently recruiting participants, and is

shortly to open in the UK. A companion sub-study will also assess the effect of *KIT* mutational status in these patients.

- The molecular screening of patients with GISTs is becoming an important part of the routine management of this disease. According to recent National Comprehensive Cancer Network (NCCN) clinical practice guidelines, GIST mutational analysis is strongly recommended for primary, intermediate or high-risk tumours (Hoeben et al. 2008). The guideline is aimed to help in predicting and identifying the risk of treatment failure in imatinib-treated patients and to switch them to a more appropriate treatment as early as possible. However, in patients progressing during treatment with standard dose escalation, and in patients failing the highest available doses of imatinib who are potential candidates for treatment with sunitinib, mutational analysis is currently in the early stages and is of academic purposes only. With regard to sunitinib, a hypothesis generating abstract was first presented at ASCO 2006 by Heinrich et al, and will be published in full in the Journal of Clinical Oncology on November 5th 2008. This study examined the relationship between tumour kinase genotypes and sunitinib clinical activity in 97 patients with metastatic imatinib resistant GIST, treated as part of a phase I/II trial. Tumours were imaged by CT or MRI for RECIST-defined response assessment. Tumour specimens were obtained prior to (n=76) and following (n=64) imatinib therapy and analyzed for primary or secondary *KIT* and *PDGFRA* mutations, respectively. The findings suggested that, similar to prior results observed using imatinib, clinical benefit of sunitinib following failure of imatinib treatment may be influenced by both primary and secondary mutations in the predominant pathogenic kinase. Overall clinical benefit with sunitinib was observed for all major molecular GIST subtypes however.

- It is important to acknowledge that these data are based on a retrospective analysis of a phase II study and should be interpreted with caution. In addition, the efficacy analysis was based on pre-imatinib mutational status. Therefore, these findings require further exploration prior to firm conclusions being drawn.

4.6 Provide details of any relevant guidelines or protocols.

Current guidelines for patients with unresectable, or malignant GIST, recommend 12 weeks of treatment with imatinib mesylate 400 mg/day (NICE 2004, www.nice.org.uk. Accessed 02 October 2008). If an initial response defined as tumour shrinkage (determined by diagnostic imaging) is not apparent within 12 weeks, treatment guidelines recommend cessation of imatinib mesylate.

Dose escalation above 400 mg/day is not recommended by NICE (NICE 2004, www.nice.org.uk. Accessed 02 October 2008).

NICE recommendations state:

- *"Imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs).*
- *Continuation with imatinib therapy is recommended only if a response to initial treatment (as defined below) is achieved within 12 weeks.*
- *Responders should be assessed at intervals of approximately 12 weeks thereafter. Continuation of treatment is recommended at 400 mg/day until the tumour ceases to respond, as defined below.*

- *An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding"*

It is our understanding that NICE is currently considering undertaking a re-review of imatinib in GIST that will incorporate evaluating whether dose escalation from 400mg to 800mg is an appropriate option in patients who develop resistance to the 400mg dose.

5 Equity and equality

The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, evidence on differential treatment effects in population groups, and epidemiological evidence on risks or incidence of the condition in population groups. Evidence submitters are asked to consider whether the chosen decision problem could be impacted by the Institute's responsibility in this respect; including in considering subgroups and access to recommendations that use a clinical or biological criterion.

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

There are no such issues that Pfizer is aware of and this is reflected in the formulation of the decision problem.

How has the analysis addressed these issues?

Not applicable - see above.

6 Clinical evidence

6.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Search Strategy for Published Data

The search strategy aimed to identify all literature relating to the clinical effectiveness of sunitinib in patients with unresectable or metastatic gastrointestinal stromal cancer after failure of imatinib mesylate due to resistance or intolerance. The main searches were conducted in collaboration with a medical librarian in September 2008. No language, study/publication, or date restrictions were applied to the searches. Searches were performed in Medline, Excerpta Medica Database (EMBASE) and Cochrane Database of Systematic Reviews (CDSR). The hand searching of the relevant conference proceedings was also utilised. A combination of free-text and thesaurus terms was used. GIST search terms (e.g. gastrointestinal stromal tumour, gastrointestinal neoplasm) were combined with 'sunitinib' terms (e.g. sunitinib malate, sunitinib, Sutent). The full details of the search strategy used are provided in Section 10.2, Appendix 2.

Search Strategy for Unpublished Manufacturer Data

The Pfizer clinical trials database, Documentum, was searched (23 September, 2008). The details of sunitinib clinical trial programme and published data are presented in section 6.2.

6.2 Study selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Published Randomised Controlled Trials

Phase II studies:

Sunitinib has been studied in patients with GIST in one phase II study, the results of which were presented at 2 international conferences:

> Demetri GD, Desai J, Fletcher JA, Morgan JA, Fletcher CDM, Kazanovicz A, et al. SU11248, A multi-targeted tyrosine kinase inhibitor, can overcome imatinib resistance caused by diverse genomic mechanisms in patients with

metastatic gastrointestinal stromal tumour (GIST). *40th Annual Meeting of American Society of Clinical Oncology* 2004, Abstract 3001.

Maki RG, Fletcher A, Heinrich MC et al. SU11248 in patients with imatinib-resistant GIST: results form a continuation trial. Oral presentation at: *41st Annual Meeting of American Society of Clinical Oncology* 2005, Abstract 9011.

Phase III studies

One pivotal, phase III study was undertaken in patients with GIST and has been the subject of a number of presentations at various meetings. For the purpose of clarity we have listed the key published paper describing the interim results of the trial and the most recent analysis of this data, inclusive of survival data, from ASCO 2008.

Demetri GD. Oosterom A, Garrett CR, Blackstein ME, Shah MH, Verweij J et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *The Lancet* 2006; 368 (9544):1329-1338

Demetri GD, Huang X, Garett CR, Schöffski P, Blackstein ME, Shah MH et al. Novel Statistical Analysis of Long-term Survival to Account for Cross-Over in a Phase III Trial of Sunitinib versus Placebo in Advanced GIST after Imatinib Failure. *The 44th Annual Meeting of the American Society of Clinical Oncology* 2008, Abstract 35113

Initial results from the ongoing worldwide, phase III, open label treatment use trial in patients with metastatic and/or unresectable GIST were presented at ASCO 2008:

Reichardt P, Kang YK, Ruka W et al. Detailed analysis of survival and safety with sunitinib in a worldwide treatment use trial of patients with advanced GIST. *The 44th Annual Meeting of the American Society of Clinical Oncology* 2008, Abstract 10548

The ongoing sunitinib phase II and phase III clinical trial programme in GIST is listed in Table 1.

Table 1: Summary of sunitinib phase II/III clinical trial programme for GIST

Efficacy and Safety Studies	Study start Study end	Design	Treatment duration Follow-up
Phase II Studies			
A6181047	28/09/2005 10/04/2008	Open-label, uncontrolled, multicentre study assessing the use of a continuous daily dose of sunitinib. Patients are randomised to a morning or evening continuous daily dose.	No. of days on treatment; Median, (range): 319 (17-654) Follow-up: 28 days after the last dose of the study drug
Phase III Studies			
A6181036 Worldwide treatment use trial	Dec 2007 - ongoing	An open label treatment use study designed to permit access to sunitinib prior to regulatory approval and also provide real world efficacy and safety data.	Latest update reported median follow up of 51 weeks (Reichardt et al. 2008)

A6181112	Recruiting	Phases 3b study of patients with GIST who have had progressive disease while on 400mg imatinib. Patients will be randomly assigned to either sunitinib 37.5mg daily or imatinib 800 mg daily.	Patients treated until progressive disease, withdrawal from study or survival until 2 years after final patient recruited

6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Phase III randomised controlled trials were included if they compared sunitinib with existing standard of care (best supportive care) for the treatment of unresectable or metastatic GIST failing on imatinib 400 mg/d. Primary outcomes of interest were time to tumour progression (TTP). Secondary outcomes were identified as progression free survival (PFS), overall survival (OS), objective response rates (ORR), adverse events and health-related quality-of-life (QoL). Studies were excluded if they did not report either of the primary outcomes. Use of data from phase II studies and from non-randomised studies was only considered where there was insufficient evidence from good quality phase III trials. Reports of any studies not available in English were excluded as the time scale of the review precluded time for translation. Data extraction was undertaken by one researcher and checked by another. Disagreement was resolved by consensus.

6.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 6.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

One phase III RCT (A6181004; Demetri et al. 2006, 2008) designed to assess efficacy and safety of sunitinib in patients with advanced GIST after failure of imatinib met the inclusion criteria. The details of this study are summarised overleaf with an overview of methods, design, treatments, patients and outcome measures in Table 2 below.

Table 2. Summary of A6181004 Trial Design, Inclusion criteria, Methods, Efficacy and Safety Outcomes

Study/Related Publications	Study Status	Objectives	Study Design	Treatment (No. of patients)	Efficacy and Safety Outcomes*
Trial A6181004 *Publications:* Demetri et al 2008 Demetri et al 2006	Started: December 2003 The blinded comparative phase of the trial was stopped early (27th January 2005) by the Data Safety Monitoring Committee as the efficacy results met pre-specified efficacy endpoints. All patients randomised to placebo were then offered open-label sunitinib. Data presented in this submission: as of March 2008. Data used for regulatory submission. Participated UK centres: 4	Efficacy and safety of sunitinib plus best supportive care versus placebo plus best supportive care for the treatment of patients with imatinib mesylate-resistant or intolerant malignant GIST.	RCT: Double-blind, parallel group (2:1), placebo controlled, multi-centre. Patients progressing* on placebo were crossed-over on to open-label sunitinib. At the data cut-off (January 2005), patients had been followed-up for a maximum of 54 weeks. Survival and safety data continued to be collected after unblinding but are not presented unless otherwise stated. *Jadad Score 5/5*	Sunitinib 50mg daily n=207 Placebo n=105 All patients received best supportive care Treatment administered in repeated 6-week cycles – 4 weeks daily sunitinib or placebo, followed by 2 weeks rest Patients with toxicity could reduce to 37.5 or 25mg.	<u>Primary:</u> Time To Tumour Progression (TTP) <u>Secondary</u>: Overall Survival (OS) Progression-Free Survival (PFS) Overall Confirmed Objective Response Rate (ORR) Time to Tumour Response (TTR) Adverse Events EQ-5D Health State Profile

*Definitions:
TTP: Time from randomisation to first documentation of objective tumour progression.
PFS: Time from randomisation to first documentation of objective tumour progression or to death due to any cause (on treatment or within 28 days of last dose).
OS: Time from date of randomisation to date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive.
ORR: Proportion of patients with confirmed complete (CR) or confirmed partial (PR) response according to RECIST, relative to the total population of randomised patients. Confirmed responses were those that persisted on repeat imaging study ≥ 4 weeks after initial documentation of response.
TTR: Time from date of randomisation to first documentation of objective tumour response that was subsequently confirmed. TTR was only calculated for the subgroup of patients with a confirmed objective tumour response.
Source: Demetri et al. 2006

6.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

An ongoing, open label treatment use study (A6181036), also known as an Expanded Access Programme designed to permit access to sunitinib prior to regulatory approval and also provide real world efficacy and safety data post approval was also identified. The initial results presented at ASCO 2008 are included in this submission (Reichardt et al. 2008).

6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

There are no ongoing studies under the current indication for which results will be available in the next 12 months. The interim analyses from ongoing treatment use are discussed in Sections 6.2.4 and 6.8.

6.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Trial Design

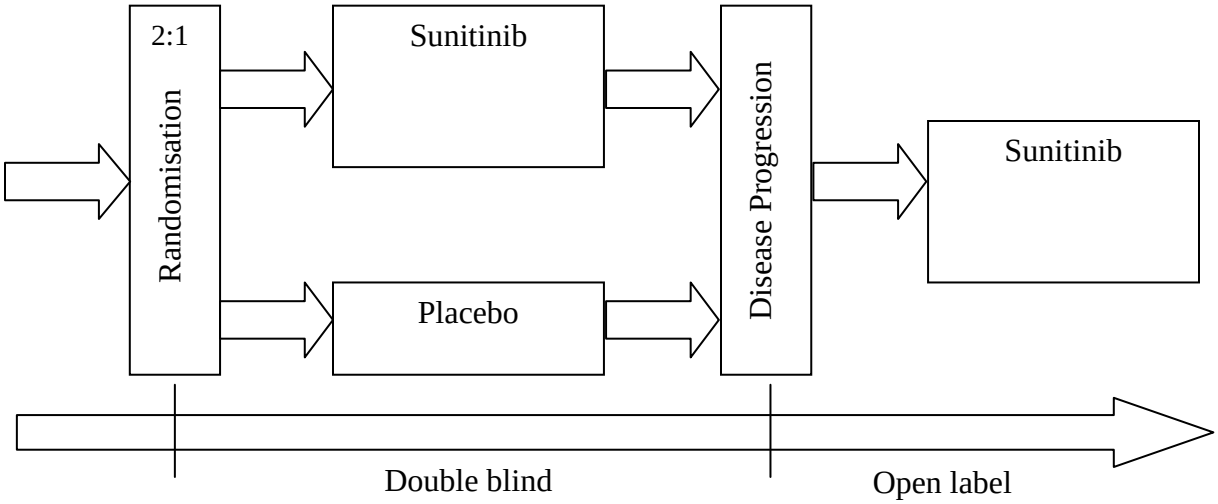
A6181004 was a randomised (2:1), double-blind, multi-centre, phase III study of sunitinib versus placebo in patients with GIST who had experienced disease progression on or intolerance to imatinib mesylate therapy. Patients on both treatment arms received best supportive care in addition to the study treatment. Patients received treatment in repeated 6-week cycles, consisting of 4 weeks of daily sunitinib (50 mg) or placebo administration followed by 2 weeks of rest (Schedule 4/2).

Patients whose disease met the Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse et al. 2000) definition for disease progression according to the independent third-party imaging core laboratory were unblinded. Patients who had been receiving placebo were crossed over to open-label treatment with sunitinib; patients who had been receiving sunitinib during the blinded phase study continued their treatment after unblinding if, in the opinion of the investigator, there was sufficient evidence of clinical benefit. The study design is summarised in Figure 2.

Randomisation was done centrally with an interactive voice response system. The centralised randomisation system assigned unique numbers to each patient and provided treatment group information. Patients were stratified by best outcome of

previous imatinib treatment (disease progression within 6 months vs. disease progression beyond 6 months of treatment initiation or intolerance to imatinib) and baseline McGill Pain Questionnaire score (0 vs. 1 or more) (Melzack 1975).

Figure 2: A6181004 Study Design



Source: Demetri et al. 2008

6.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Trial Participants

Inclusion and exclusion criteria in the pivotal study A6181004 were as follows:

Inclusion Criteria:

- Male or female, 18 years of age or older.
- Histologically proven malignant GIST that was not amenable to surgery, radiation, or a combination of different approaches with curative intent
- Confirmed objective failure of previous imatinib therapy.
- Evidence of disease that was unidimensionally measurable with CT or MRI.
- Failure of treatment with imatinib based either on progression of disease (according to RECIST or WHO criteria) or on unacceptably severe toxic effects during imatinib therapy that precluded further treatment.
- Imatinib last administered at least 2 weeks before randomisation.
- Resolution of all toxic effects of imatinib or other therapy to grade 1 or less.
- Adequate hepatic, renal, and cardiac function; absolute neutrophil count of at least 1500 per µL; platelet count of at least 100 000 per µL; haemoglobin concentration of 90 g/L or greater.

- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Exclusion Criteria:

- Treatment with any chemotherapy, chemoembolisation therapy, immunotherapy, or investigational anticancer agent after the last dose of imatinib mesylate.
- Treatment of patients with imatinib mesylate-resistant disease with surgery, radiotherapy, and/or cryotherapy that affected all areas of measurable disease where progression on imatinib mesylate therapy had been demonstrated.
- Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri.
- Any of the following within the 12 months prior to study drug administration: severe/unstable angina, symptomatic congestive heart failure, or cerebrovascular accident.
- Ongoing cardiac dysrhythmias of NCI CTCAE grade ≥ 2, atrial fibrillation of any grade, or prolongation of the QTc interval to > 450 msec for males or > 470 msec for females.
- Known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS)-related illness.
- Pregnancy or breastfeeding. Patients were required to be surgically sterile or be postmenopausal or to agree to use effective contraception during the period of therapy.
- All female patients with reproductive potential were required to have a negative pregnancy test (serum or urine) within the 21 days before enrolment. The definition of effective contraception was based on the judgment of the principal investigator or a designated associate.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that could have increased the risk associated with study participation or study drug administration or interfered with the interpretation of study results, and in the judgment of the investigator made the patient inappropriate for entry into this study.

Baseline Patient Characteristics

Summary of the baseline characteristics of the ITT population in the study A6181004 are shown in Table 3.

Table 3: Baseline characteristics and disease and treatment history (ITT population)

	Sunitinib (n=207)	**Placebo (n=105)**
Age (years)		
Median	58·0	55·0
Range	23–84	23–81
Sex		
Male	132 (63·8%)	64 (61·0%)
Female	75 (36·2%)	41 (39·0%)
ECOG status		
0	92 (44·4%)	48 (45·7%)
1	113 (54·6%)	55 (52·4%)
2*	2 (1·0%)	2 (1·9%)
GIST histology		
Spindle cell	125 (60·4%)	74 (70·5%)

Mixed spindle+epithelioid	33 (15·9%)	13 (12·4%)
Epithelioid	17 (8·2%)	7 (6·7%)
Other	31 (15·0%)	10 (9·5%)
Missing	1 (0·5%)	1 (1·0%)
Tumour burden at baseline (mm)		
Median	233	239
Range	26–722	29–749
Maximum dose of imatinib therapy (mg)		
Median	800	800
Range	300–1600	400–1600
Duration of imatinib therapy (weeks)		
Median	105·3	106·9
Range	0·3–205·1	11·4–187·7
Imatinib therapy outcome		
Progression within 6 months	36 (17·4%)	17 (16·2%)
Progression after >6 months	162 (78·3%)	84 (80·0%)
Intolerance	9 (4·3%)	4 (3·8%)
Best response to imatinib		
Complete response	6 (2·9%)	1 (1·0%)
Partial response	51 (24·6%)	36 (34·3%)
Stable disease	87 (42·0%)	36 (34·3%)
Progressive disease	58 (28·0%)	30 (28·6%)
Not applicable or missing	5 (2·4%)	2 (1·9%)

Source: Demetri et al. 2006

In the ITT population all characteristics were well balanced between the groups (e.g. age, sex, baseline ECOG performance status). The most common metastatic sites were the liver, peritoneum, and mesentery. The sunitinib and placebo groups were also similar in terms of median duration of previous imatinib mesylate treatment (105.3 vs. 106.9 weeks) median maximum dose (800 mg in both arms), median daily dose (503 mg vs. 485 mg), and median cumulative dose (367 400 mg vs. 376 400 mg) of previous imatinib therapy, as well as in other aspects of treatment history.
In general, the malignancy histories indicate that this was a population with advanced GIST subjected to fairly extensive prior therapy.

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Patient numbers are presented as a CONSORT flow chart (Figure 3), with additional detail provided in the Table 4.

Figure 3: A6181004 Patient Flowchart

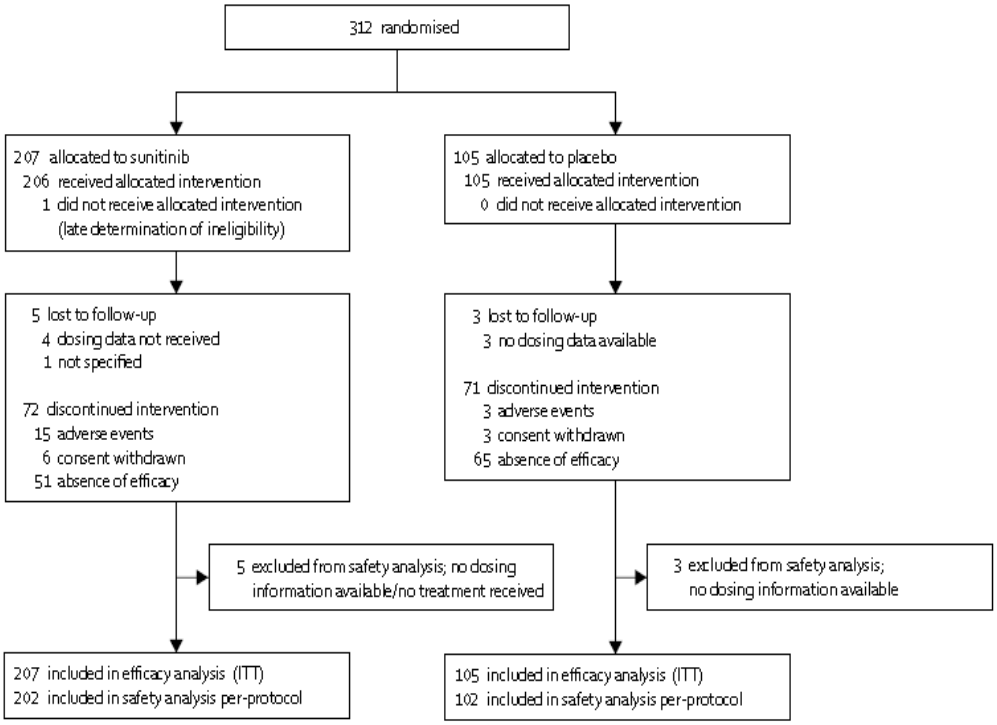


Table 4: Overall Summary of Patient Disposition (ITT population)

Reason for Discontinuation	Sunitinib	Placebo
Blinded Treatment Phase		
No. of randomised patients	**N = 207**	**N = 105**
Adverse events, n (%)	15 (7)	3 (3)
Consent withdrawn, n (%)	6 (3)	3 (3)
Lost to follow-up, n (%)	1 (1)	0 (0)
Lack of efficacy (disease progression)[a], n (%)	51 (25)	65 (62)
Crossed over to open-label treatment, n (%)	19 (9)	59 (56)[b]
Ongoing in blinded treatment, n (%)	134 (65)	34 (32)
Crossover Phase		
No. of initially randomised patients	**N = 19**	**N = 59**
Adverse events, n (%)	3 (16)	8 (14)
Lack of efficacy (disease progression)[a], n (%)	6 (32)	9 (15)
Patients completed study, n (%)	1 (1)	0 (0)
Ongoing, n (%) (as of cut-off date 1st January 2005)	9 (47)	42 (71)

[a] Includes patients who discontinued the study during the blinded phase because of lack of efficacy (disease progression), those who crossed over to open-label treatment after experiencing disease progression, and those who discontinued the study during the blinded phase because of an adverse event of "disease progression."
[b] One additional patient (Patient A6181004-039285-00253) was screened for cross-over but was not counted as having crossed over because no treatment record had been received at the time of this report.
Source: A6181004 trial report

6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Primary Efficacy Endpoint

In study A6181004, the primary efficacy endpoint was Time to Tumour Progression (TTP).

Secondary Efficacy Endpoints

Secondary endpoints included overall survival (OS), progression-free survival (PFS), overall confirmed objective response rate (ORR), time to tumour response (TTR), duration of response (DR), and duration of performance status maintenance (DPSM) (time from date of randomisation to the last time the performance status was no worse than at baseline or to death from cancer).
Safety and tolerability were assessed by analysis of adverse events. Patient reported outcomes were also assessed and included patient reported pain intensity and general quality of life (QoL) assessments.

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

Hypothesis

The TTP after imatinib failure was generally reported to be less than 4 months. A 50% improvement (Hazard Ratio 0.67) in median TTP from 4 months to 6 months in patients randomised to receive sunitinib is considered to be clinically meaningful. The study

A6181004 is designed to test the null hypothesis that the true median TTP is 4 months versus the alternative hypothesis that the true median TTP is at least 6 months.

Statistical Analysis
A total of 281 patients with disease progression were estimated to be needed to detect the above mentioned improvement using a two-sided, unstratified log-rank test with an overall two-sided significance level of 0.05 and power of 0.90. It was estimated that 357 patients (238 in sutent arm and 119 in placebo arm) would need to enrolled in order to observe 281 patients with progressive disease by the end of the minimum follow-up period.
Secondary analyses were tested at a significance level of 0.05.

Analysed study populations included intention-to-treat (ITT; all patients randomised to treatment), modified ITT (all ITT patients with disease progression on imatinib confirmed by central radiology laboratory), and per-protocol (all patients who received at least one dose of assigned study treatment). ITT data are presented for efficacy and per-protocol data for safety; modified ITT data are discussed where relevant. Protocol-defined interim analyses of efficacy and safety were planned after 141 and 211 patients had documented progressive disease. The nominal levels of significance for the interim analyses were determined using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary (Lan & DeMets, 1983).

Time to tumour progression in each group was assessed using Kaplan-Meier methods and compared with the log-rank test (primary efficacy analysis). A stratified log-rank test and Cox regression models were used to explore the potential effects of the stratification factors and patients' baseline characteristics on the primary endpoint (primary efficacy sub-analyses).

Other time-to-event data, including progression-free survival and overall survival, were assessed with Kaplan-Meier methods and log-rank tests. The proportion of patients who achieved an objective tumour response was calculated for each arm and compared by means of a χ^2 test.

To explore potential confounding influence of crossover, a *post-hoc* analysis of overall survival was recently published (Demetri et al, 2008). This analysis was performed using rank preserved structural failure time model (RPSFT) method (Robins & Tsiatis 1991). The RPSFT method estimates the true treatment effect, even in the presence of non-random non-compliance, i.e. the effect that would be realised if all individuals complied with the treatment protocol to which they were assigned, while preserving the unbiased test of the null hypothesis available from the ITT analysis.

The applicability of post-hoc analyses

In the study, OS was a pre-specified secondary endpoint; the primary endpoint being TTP. Pfizer acknowledges that the OS intention to treat (ITT) analysis of the full trial population is reflective of the study protocol and accepts that the primary statistical analysis plan failed to incorporate the need to develop strategies to handle confounding events of the cross-over that could reasonably be expected to occur, so as to enable application of the study results to the needs of patients, UK clinical practice and Health Technology Assessment (HTA) bodies.

The EMEA has recognised that there are significant issues with clinical trial design and measuring overall survival in the sphere of oncology, stating recently,

> *"While it is generally acknowledged that the aim of treatment is to improve quality of life and survival, restraints on the conduct of clinical trials may make these goals unattainable. It is thus recognised that investigators, patients and ethics committees may require, e.g. optional cross-over at time of tumour progression. Similarly, the use of active next-line therapies must be accepted. This may affect the possibility of detecting differences in OS as well as symptoms related to tumour progression."* (EMEA 2005)

Previous NICE Committees have also acknowledged the inadequacies of RCTs where cross-overs or multiple treatments have played a part; the Appraisal Committee reporting on the use of RCTs in TA30 (Breast cancer - taxanes [review]) stated,

> *"Conducting and interpreting randomised controlled trials of anti-cancer drugs is complicated by a number of issues; including protocol defined and undefined cross over to alternative treatment where there is evidence of disease progression on randomised treatment, unblinded studies and differential toxicity profiles"*

and have gone further to question how the findings should be interpreted,

> *"The evidence base for the management of advanced colorectal cancer includes a number of randomised controlled trials. However, results for overall survival from RCTs need cautious interpretation because the disease is often managed with sequences of either mono- or combination therapy, with the frequent use of unplanned second- or third-line salvage chemotherapy."*
> *(TA93 (Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer [(review of TA33])*

and Pfizer believes that similar caution needs to be applied in interpreting the phase III sunitinib RCT data relating to the current appraisal.

The appropriateness of the analytical approach

In general unbiased statistical inference regarding the comparison of treatment regimens is obtained by an intention-to-treat analysis comparing the groups as randomised. Despite a significant number of cancer studies allowing crossover from control to experimental treatment, most of the studies have the objective of comparing the experimental arm with control arm, as if no patients in the control arm had ever crossed over to the experimental treatment.

Overall survival (OS) is recognised as the gold standard for clinical benefit in oncology clinical trials. However, the formal demonstration of the underlying survival benefit of a treatment can be diluted or confounded by effective later treatment. Although oncology trials have the objective of comparing the experimental arm with the control arm for OS, statistical analyses of OS by Intention-to-treatment (ITT) treatment groups based on

conventional approaches are biased towards the null because of the crossover. This has been, and remains, a real challenge in oncology drug development and regulatory approval.

Rationale for using Rank Preserved Structural Failure Time (RPSFT) model

Because of treatment crossovers in the placebo arm, the intention-to-treat analysis estimates the benefit of starting sunitinib immediately compared to deferring the start of sunitinib. However, the relevant parameter from a decision-making perspective is the benefit of starting sunitinib compared to not starting sunitinib. We therefore corrected for treatment crossovers in the placebo arm.

A common approach to this problem is to censor placebo arm patients at the point of crossover, but this is invalid because patients who cross over are unlikely to be comparable to those who do not. The only way to avoid selection bias is to use a method based entirely on the comparability of groups as randomised (White, 2005).

We used the method of Robins and Tsiatis (1991) which is the only method currently available in the literature that can correct for time-dependent treatment changes in survival data while respecting the randomisation. This method is based on the accelerated failure time model

$$U = T_{start} + \exp(\square)(T - T_{start})$$

where T is the observed event time, T_{start} is the time of starting treatment, U is the event time that would have been observed if no treatment had been given, and the parameter $\square$ represents the causal effect of having started treatment. $\square$ is estimated by computing U for a range of possible values of $\square$ and finding the value for which a log rank test of the equality of U across the two groups gives a zero test statistic. Finally, we estimated the hazard ratio for starting sunitinib compared to not starting sunitinib by running a Cox regression on the observed event times in the sunitinib arm and the estimated U values in the placebo arm.

Because this procedure is based on the randomisation, it does not change the level of evidence against the null hypothesis. It does however change the estimated hazard ratio, bringing it further from the null, as would be expected from the fact that crossovers make the overall treatment experience of the two arms more similar. As a result, the 95% confidence interval is wide.

The initial Hazard Ratios and 95% Confidence Intervals for all analyses utilizing the RPSFT method are derived from the Cox regression analysis as presented in the 2008 publication (Demetri et al, 2008). Advice received since the publication is that because this procedure is based on the randomisation, it does not change the level of evidence against the null hypothesis and therefore a different analytical approach needs to be used. Adopting this results in a wider 95% confidence interval and for transparency we have therefore also presented revised estimates from our updated analysis. It should also be noted that after review by an independent statistician Pfizer was made aware of a number of methodological issues with the original RPSFT analysis, we therefore took the opportunity of the availability of the final data to re-conduct the analysis. This updated analysis has been externally reviewed and approved.

6.3.6 Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study meeting the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- **How was allocation concealed?**
- **What randomisation technique was used?**
- **Was a justification of the sample size provided?**
- **Was follow-up adequate?**
- **Were the individuals undertaking the outcomes assessment aware of allocation?**
- **Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.**
- **Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?**
- **How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.**
- **For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?**
- **Were the study groups comparable?**
- **Were the statistical analyses used appropriate?**
- **Was an intention-to-treat analysis undertaken?**
- **Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?**

Critical appraisal of study A6181004 is summarised in Table 5 below.

Table 5: Critical appraisal of A6181004

How was allocation concealed?	The clinical site staff were provided patient identifiers, demographic information, and stratification variables only.
What randomisation technique was used?	Randomisation was done centrally with an interactive voice response system. The centralised randomisation system assigned unique numbers to each patient and provided treatment group information. Patients were stratified by best outcome of previous imatinib treatment (disease progression within 6 months vs. disease progression beyond 6 months of treatment initiation or intolerance to imatinib) and baseline McGill Pain Questionnaire score (0 vs. 1 or more). The 2:1 randomisation was used to minimise the number of patients treated with placebo.
Was a justification of the sample size provided?	Yes A total of 281 patients with disease progression were estimated to be needed to detect 50% improvement (Hazard Ratio 0.67) using a two-sided, unstratified log-rank test with an overall two-sided significance level of 0.05 and power of 0.90. It was estimated that 357 patients (238 in sunitinib arm and 119 in placebo arm) would need to be enrolled in order to observe

	281 patients with progressive disease by the end of the minimum follow-up period.
Was follow-up adequate?	Yes 10 December 2003 - 01 January 2005. At the data cut-off (January 2005), patients had been followed-up for maximum of 54 weeks.
Were the individuals undertaking the outcomes assessment aware of allocation?	A6181004 trial consisted of two phases, (1) double blinded and (2) open-label. Patients experiencing disease progression were unblinded, and patients who had been receiving placebo crossed over to open-label treatment with sunitinib; patients who had been receiving sunitinib during the blinded phase study continued to do so after unblinding if, in the opinion of the investigator, there was sufficient evidence of clinical benefit. Treatment was unblinded at the recommendation of the Independent Data and Safety Monitoring Board, and all patients were allowed to cross over to open-label sunitinib.
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	A6181004 trial consisted of two phases, (1) double blinded parallel group and (2) open-label crossover phases (See above).
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	A6181004 trial was a multicentre RCT that enrolled 56 centres from 11 countries, including four UK centres.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	There were four UK centers participated in A6181004 trial. There is no evidence to suggest that patients treated in the UK would differ from the overall patient population considered within the A6181004 trial, or importantly that UK patients would respond to sunitinib treatment in a different manner from that observed in the A6181004 trial.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics? Were the study groups comparable?	The dose of sunitinib was 50 mg orally once daily as a single agent for 4 consecutive weeks followed by a 2-week rest period to form a complete cycle of 6 weeks. Sunitinib was taken orally in the morning with a glass of water without regard to meals beginning on Day 1 of the study. This dosing regimen is detailed in the Summary of Product Characteristics (SmPC) (http://emc.medicines.org.uk) (See Appendix 1, Section 10.1). In A6181004 trial, study groups were comparable; all characteristics were well balanced between sunitinib and placebo groups (e.g. age, sex, baseline ECOG performance status).
Were the statistical analyses used appropriate?	Yes Kaplan-Meier methods and log-rank tests.

Was an intention-to-treat analysis undertaken?	Yes
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	A6181004 trial was a crossover study, 84% of patients randomised to receive placebo crossed over to sunitinib arm. In total, 247 (out of 312) patients ultimately received open-label sunitinib. The crossover design has a potential to give a biased estimates of treatment effect for OS data.

Source: Demetri et al. 2006; 2008; A6181004 trial report

6.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **The number of patients included in the analysis.**
- **The median follow-up time of analysis**
- **State whether intention-to-treat was used for the analysis and how data were imputed if necessary.**
- **Discuss and justify definitions of any clinically important differences.**
- **Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**

The clinical efficacy of sunitinib for the GIST indication is based on data from one pivotal phase III study A6181004.

All results for study A6181004 in this section are taken from the published interim analysis (Demetri et al, 2006), the interim clinical study report (Pfizer interim Clinical Study Report 2006) or the publication on Overall Survival published earlier this year (Demetri et al, 2008) and annotated as such.

Study A6181004

In study A6181004, the primary outcome measure was Time to Tumour Progression (TTP). The key secondary endpoints included overall survival (OS), progression free survival (PFS) and overall confirmed objective response rate (ORR).

Primary Endpoint Results

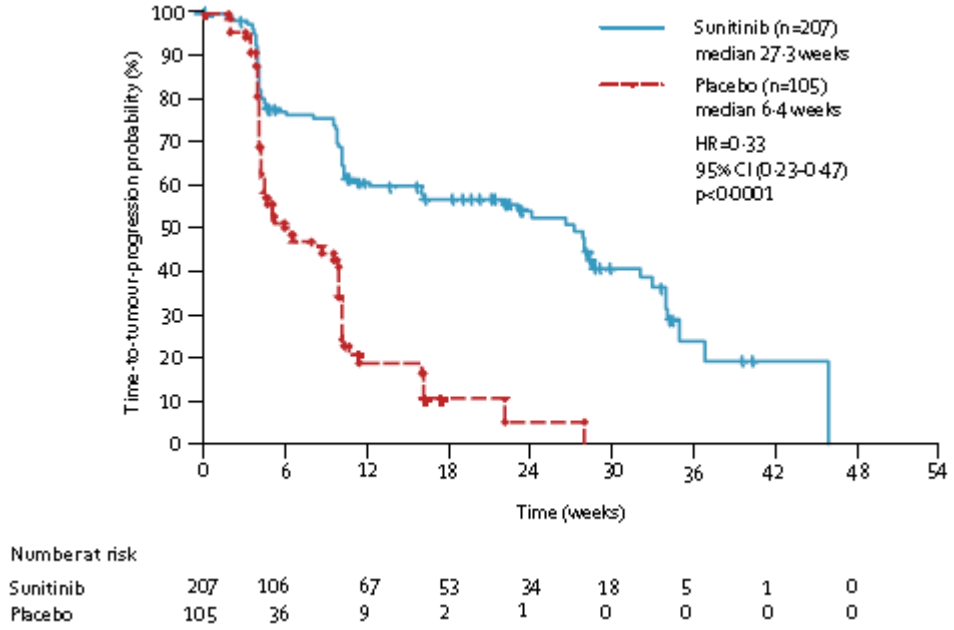
Time to Tumour Progression (TTP)

Time to Tumour Progression, defined as the time from the first dose of study drug to first documentation of progressive disease. Disease progression was assessed by using RECIST criteria and evaluated by the investigators as well as an independent, third-party radiology laboratory.

The blinded phase of the A6181004 trial was terminated early (January 2005) when a planned interim analysis revealed significantly longer TTP in patients treated with sunitinib compared with patients treated with placebo. Overall, 82 (40%) of sunitinib

treated patients and 67 (64%) of placebo treated patients, had disease progression at the time of analysis.

Figure 4: Kaplan-Meier estimates of time to tumour progression (ITT population).



Source: Demetri et al. 2006

Median time to tumour progression for the ITT population, the primary study endpoint, was more than four times as long with sunitinib (27.3 weeks, 95% CI 16.0–32.1) as with placebo treatment (6.4 weeks 4.4–10.0; HR 0.33, 95% CI 0.23–0.47; p<0.0001) on the basis of central radiology laboratory assessment (Figure 4, Table 6). A clear difference between the treatment groups was noted around week 4. The greater TTP obtained with sunitinib compared with placebo was confirmed by the stratified analysis when controlling for stratification factors (HR 0.33, 95% CI 0.22–0.46; p<0.0001).

Table 6: Summary of TTP (ITT Population)

Phase of Study	Median (weeks; 95% CI)		HR (95% CI)	P-value
	Sunitinib	Placebo		
Blinded phase	27.3 (16.0–32.1)	6.4 (4.4–10.0)	0.33 (0.23–0.47)	<0.0001
Entire study (blinded + open label)	28.6 (22.0-41.0)	N/A	N/A	N/A

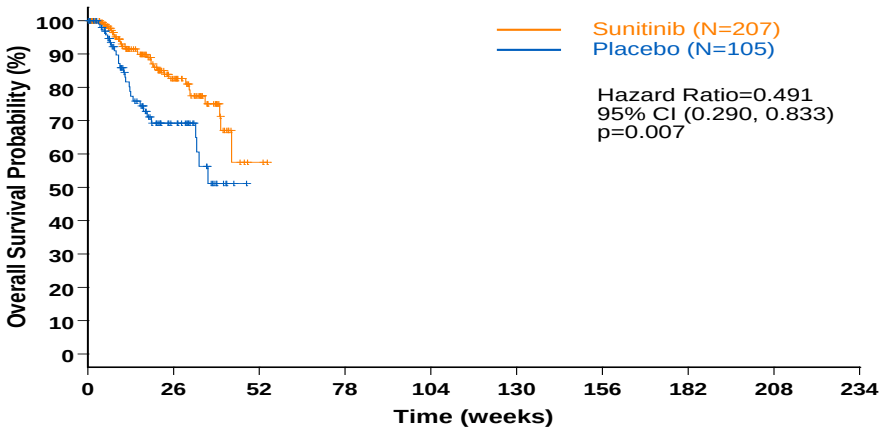
N/A-Not applicable
Source: Demetri et al. 2006; 2008

The median TTP for the 99 patients randomised to receive placebo who crossed over to sunitinib treatment was 28.6 weeks (95% CI 22.0-41.0) and similar to that observed during the blinded phase in the sunitinib group. The summary of TTP results are shown in Table 6 above.

Secondary Endpoint Results

Overall Survival (OS)
Interim analysis (blinded phase) demonstrated that overall survival obtained with initial sunitinib treatment was better that that obtained with placebo (HR 0.49, 95% CI 0.29–0.83; p=0.007, Figure 5). Since more than half the patients in the sunitinib group were still alive at the time of the interim analysis, a median overall survival value could not be calculated (Table 7).

Figure 5: Kaplan-Meier Curves of Overall Survival from the Interim Analysis



Source: Demetri et al. 2006

In general unbiased statistical inference regarding the comparison of treatment regimens is obtained by an intention-to-treat analysis comparing the groups as randomised. Despite a significant number of cancer studies allowing crossover from control to experimental treatment, most of the studies have the objective of comparing the experimental arm with control arm, as if no patients in the control arm had ever crossed over to the experimental treatment.

Overall survival (OS) is recognised as the gold standard for clinical benefit in oncology clinical trials. However, the formal demonstration of the underlying survival benefit of a treatment can be diluted or confounded by effective later treatment. Although oncology trials have the objective of comparing the experimental arm with the control arm for OS, statistical analyses of OS by Intention-to-treatment (ITT) treatment groups based on conventional approaches are biased towards the null because of the crossover. This has been, and remains, a real challenge in oncology drug development and regulatory approval.

Robins and Tsiatis developed rank preserving structural failure time models (RPSFT) for survival outcomes which relate a patient's observed event time to an event time that would have been observed if no treatment had been administered, assuming treatment has a multiplicative effect on a patient's lifetime. Their approach produces a randomisation-based effect estimator that is; the treatment estimate is based on the treatment groups as randomised, thus avoiding many of the potential pitfalls and biases introduced with subgroup analyses. People have applied RPSFT method to some HIV trials.

Study A6181004 was a two-arm, double-blind, placebo-controlled, multicentre, Phase 3 clinical trial with 2:1 randomisation evaluating the efficacy and safety of single-agent sunitinib in patients with imatinib mesylate-resistant or intolerant malignant GIST. Patients in both arms were offered the opportunity to receive open-label sunitinib treatment upon development of RECIST-defined disease progression as documented by an independent third party core radiology laboratory, provided that patient crossover eligibility criteria were met. The randomised double-blind clinical trial design was selected to optimize the validity of TTP, the primary efficacy endpoint. The incorporation of a placebo control arm was considered to be acceptable in the absence of a proven effective treatment for this patient population, and it permitted a more reliable assessment of efficacy and safety of sunitinib.

The first interim analysis of efficacy and safety was performed and reviewed by the DSMB on January 24, 2005. The DSMB found that there was a markedly longer TTP on the treatment arm relative to the placebo arm. The hazard ratio estimate of 0.346 was clinically meaningful and highly statistically significant. DSMB also noted a lower incidence of death from all causes in the treatment arm relative to the placebo arm. The median Overall Survival (OS) had not been reached in either treatment group; the hazard ratio was 0.491 with 95% CI of (0.290, 0.831) and p-value of 0.0067 in favor of the SU011248 group. Six-month survival rates were 81% for sunitinib treated group and 65% for placebo treated group, respectively. The DSMB was therefore unanimous in its recommendation to Pfizer management and the FDA that having met the criteria predefined in the protocol stopping rule, that all placebo patients be switched to sunitinib. Given the clinically significant improvement in TTP and OS in the sunitinib treated group, the DSMB concluded that it was not appropriate to continue the blinded randomization. Over 80 percent patients in placebo arm crossed over and received open-label sunitinib treatment.

Although the sunitinib arm performed significantly better in the primary endpoint of TTP than the placebo arm, it is important for both patients and clinicians to understand the true treatment effect of sunitinib vs. placebo in OS. Although the crossover situation was relatively simple (placebo control; only crossover in one direction; no other treatments available, etc.) in this study in comparison to other trials with more complicated crossover scenarios, the conventional statistical methods still could not provide an unbiased estimation of the treatment effect. In this situation, the RPSFT approach becomes the most appropriate choice to estimate the treatment effect of OS when it is diluted or confounded by the crossover in a trial like this.

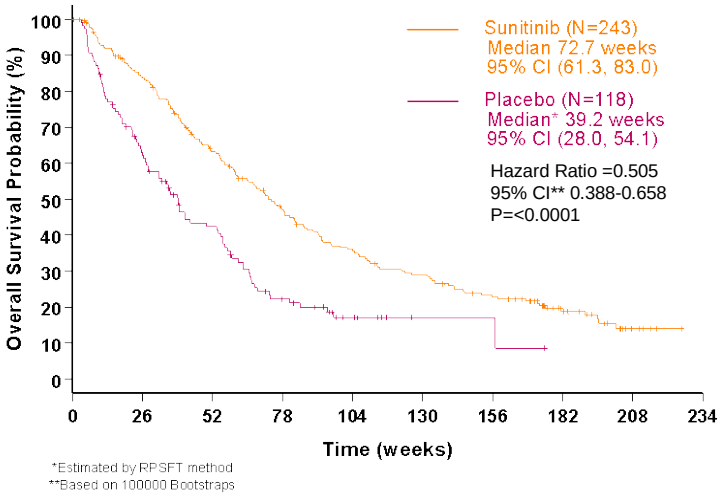
Table 7: OS estimated using different statistical methods (ITT Population)

	Median (weeks; 95% CI)			
Phase of Study	**Sunitinib**	**Placebo**	**HR (95% CI)**	**P-value**
Blinded phase* Kaplan Meier Method	Not reached	Not reached	0.491 (0.290-0831)	0.007
Entire study (blinded + open label) RPSFT Method	72.7 (61.3-83.0)	39.2 (28.0-54.1)	0.505 (0.388-0.658)	<0.001
Entire study (blinded + open label) Kaplan Meier Method	72.7 (61.3-83.0)	64.9 (45.7-96.0)	0.876 (0.679-1.129)	0.306

*Interim analysis, empirical 95%CI was obtained using bootstrap samples
Source: Demetri et al. 2008 (revised estimates)

The analysis using RPSFT approach demonstrated an estimated median OS for the placebo group of 39.2 weeks (95% CI 28.0.-54.1) based on the ITT population. This revealed as statistically significant sunitinib treatment effect (HR 0.505, 95% CI 0.388-0.658, p<0.0001) comparable to that of the interim OS results (Table 7 and Figure 6). The re-calculated confidence intervals for the HR from the RPSFT approach, following external recommendation, are 0.262-1.134.

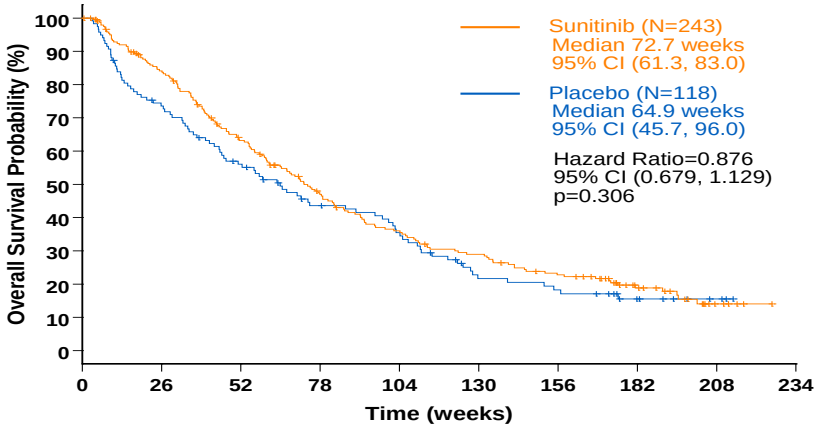
Figure 6: Final OS estimated with correcting for crossover (RPSFT Method)



Source: Demetri et al. 2008 (revised estimates, for details see Section 6.3.5)

Figure 7 demonstrates the final OS estimated without correcting for crossover using the Kaplan Meier method.

Figure 7: Final OS estimated without correcting for crossover (Kaplan Meier Method)



Source: Demetri et al. 2008

The analysis of OS using the Kaplan Meier method includes data collected after unblinding of individual patients randomised to placebo who experienced disease progression and crossed over into open-label treatment, the analysis is not fully blinded and includes potential influence of open-label sunitinib treatment on patients randomised to placebo.
The median sunitinib overall survival of 74 weeks was consistent with that of currently ongoing expanded-access trial A6181036 (see section 6.2.1). The latest update (median follow up of 51 weeks) of this trial demonstrated OS survival of 75 weeks (95% CI: 68–84) in patients treated with sunitinib (Reichardt et al. 2008).

Progression-Free Survival (PFS)
Eighty-nine (43%) patients treated with sunitinib and 70 (67%) patients treated with placebo had disease progression, or were dead at the time of this interim analysis. There was a statistically significant difference in median PFS with sunitinib (24.6 weeks 95% CI: 12.1 to 28.3 weeks) compared with 6.4 weeks (95% CI: 4.4 to 10.0 weeks) on placebo (HR 0.333, 95% CI: 0.238 to 0.467; p< 0.001). The risk of disease progression, or death in the sunitinib group was approximately 33% of that in the placebo group. These results are consistent with the analysis of TTP in this study.

Overall Confirmed Objective Response Rate (ORR)
Fourteen (6.8%) patients on sunitinib and no (0%) patients on placebo responded (PR) indicating a significantly higher response rate on sunitinib (treatment difference: 6.8%; 95% CI: 3.34 - 10.18; p=0.006).

Time to Tumour Response (TTR)
TTR was only determined for patients with a confirmed objective response (CR or PR); no patients on placebo had a response. Fourteen patients (6.8%) patients on sunitinib had experienced a response at the time of this interim analysis. The median TTR on sunitinib was ten weeks (95% CI: 9.7 to 16.1 weeks).

Duration of Response (DR)
DR was only determined for patients with an objective response (complete response or partial response) who subsequently experienced disease progression or death. Of the 14 sunitinib patients with a confirmed objective response, only three of these patients (21%) had subsequently experienced progression at the time of this analysis. The observed DRs were 29.9, 23.3, and 15.9 weeks.

Duration of Performance Status Maintenance (DPSM)
Seventy-nine (38%) sunitinib treated patients and 38 (36%) placebo treated patients, had experienced performance status worsening at the time of analysis. The median DPSM was 18.9 (95% CI: 12.1 - 33.9 weeks) vs. 16.1 weeks (95% CI: 6.1 weeks to (upper limit could not be calculated because the data were not mature).

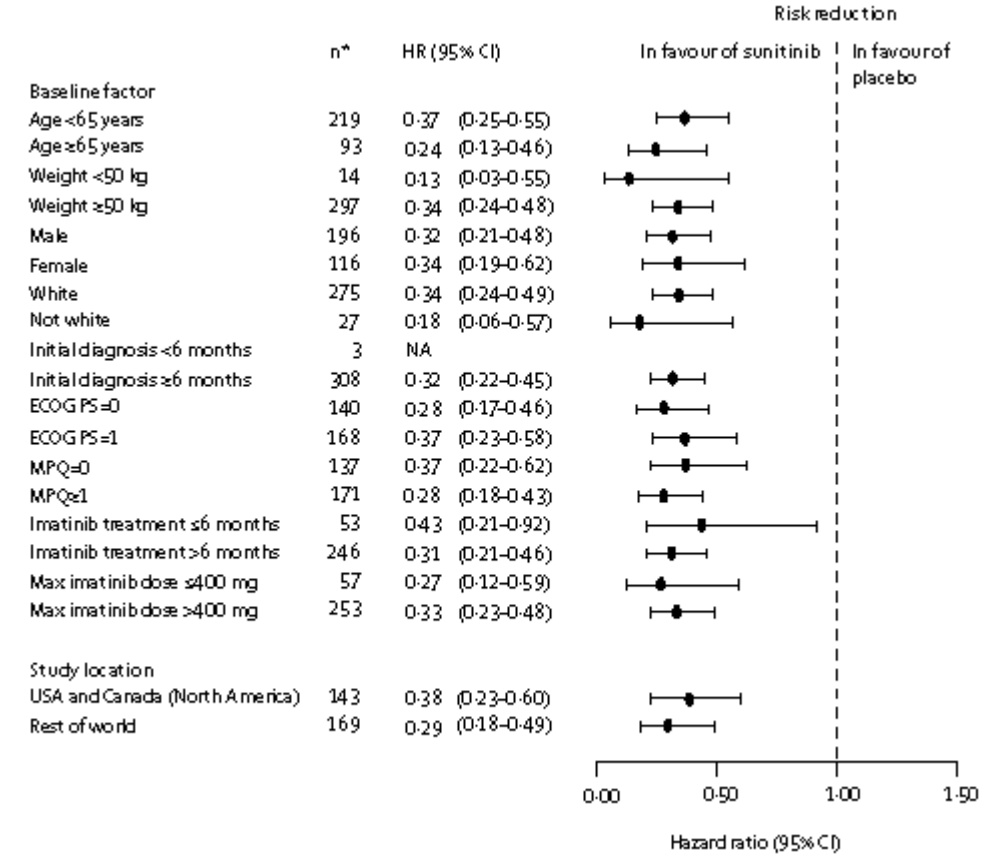
EQ-5D Health State Profile
EQ-5D health state profile was analysed to compare the difference in treatments between patients who answered "no problem" and who answered "at least some problem". Compliance was generally high, with > 75% expected patients completing questionnaire at each time point.

The numbers and percents of patients who reported “no problem,” “some problem,” or “extreme problem,” and the number and percentage of patients reporting at least some problem (some or extreme problem), were measured by time point, dimension of the EQ-5D descriptive system, and treatment arm. The statistical significance tests of between-treatment differences did not show significant differences. Utility values were calculated for the cost effectiveness analysis (Section 7).

Subgroup analysis

The influence of baseline factors on the treatment effect in different populations was analysed by using a Cox proportional hazards model including TTP on previous imatinib mesylate therapy (≤ vs. > 6 months), baseline MPQ-PPI score (0 vs. ≥ 1), age (< vs. ≥ 65 years), sex (male vs. female), race (white vs. non-white), ECOG performance status (0 vs. 1), and time since initial diagnosis with GIST (< vs. ≥ 6 months), controlling for each factor 1 at a time (Figure 8).

Figure 8: Result of Cox Proportional Hazards Analysis of TTP in various subgroups



Source: Demetri et al. 2006; A6181004 trial report

In the primary analysis, the treatment effect was statistically significant ($p < 0.001$) overall and when controlling for each individual baseline factor. The only baseline factors considered of interest to pursue in the multivariate model (i.e., with $p < 0.10$) were TTP on previous imatinib mesylate therapy (≤ vs. > 6 months; hazard ratio: 1.657; 95% CI: 1.109 to 2.475; $p = 0.014$), indicating longer TTP for patients who had previously experienced longer (> 6 months) disease control on imatinib mesylate, gender (male vs. female; HR: 1.457; 95% CI: 1.029 to 2.064; $p = 0.034$), indicating longer TTP for female patients, and weight (HR: 0.991; 95% CI: 0.983 to 1.000; $p = 0.041$) indicating a trend for longer TTP in patients with lower body weight. The results for the treatment effect were similar in the MITT and PP populations. The Cox proportional hazards models were repeated, with treatment-by-baseline factor interactions included, and the hazard ratios and 95% CIs are presented in Figure 5 above. For all subgroups, the hazard ratio was significantly less than 1.000 (i.e., the 95% CI did not overlap 1.000), indicating that all subgroups, defined on the basis of baseline factors, benefited from sunitinib.

6.5 Meta-analysis

Not applicable to this submission.

6.6 Indirect/mixed treatment comparisons

Not applicable to this submission.

6.7 Safety

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

The safety of sunitinib for the GIST indication is based on data from one pivotal phase III study A6181004.

Study A6181004

Overview of Safety Results

In the A6181004 trial, the safety was analysed in the per protocol (PP) population, which consists of all patients who received at least 1 capsule of study medication with treatment assignments designated according to actual study treatment received. On sunitinib, the PP population included 202 of 207 randomised patients (98%; 4 randomised patients had been treated but did not have drug dosing data available and are excluded from the PP population; 1 patient randomised to sunitinib but did not receive treatment), and, on placebo, the PP population included 102 of 105 randomised patients (97%). The overall adverse experience during the blinded phase is summarised by treatment arm in Table 8.

Table 8: Overall Adverse Event Experience during the Blinded Phase (PP population)

Category	Sunitinib (N=202)	Placebo (N=102)
Patients with ≥ 1 adverse event, n (%)	190 (94)	99 (97)
Patients with ≥ 1 serious adverse event, n (%)	70 (35)	25 (25)
Patients with ≥ 1 treatment-related adverse event, n (%)	168 (83)	60 (59)
Patients with ≥ 1 treatment-related serious adverse event, n (%)	40 (20)	5 (5)
Patients who discontinued due to adverse events, n (%)	19 (9)	8 (8)
Patients who died within 28 days of treatment, n (%)	13 (6)	8 (8)

Source: A6181004 trial report

Treatment-related adverse events, serious adverse events, and treatment-related serious adverse events appeared to be more common on the sunitinib arm. Nineteen (9%) patients in the sunitinib group and eight (8%) in the placebo groups discontinued treatment because of adverse events.

Table 9 presents a summary of adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in the per-protocol population.

Table 9: Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population

	Sunitinib (n=202)			Placebo (n=102)		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Non-haematological*						
Fatigue	58 (29%)	10 (5%)	0 (0%)	20 (20%)	2 (2%)	0 (0%)
Diarrhoea	52 (26%)	7 (3%)	0 (0%)	8 (8%)	0 (0%)	0 (0%)
Skin discolouration	50 (25%)	0 (0%)	0 (0%)	6 (6%)	0 (0%)	0 (0%)
Nausea	47 (23%)	1 (1%)	0 (0%)	10 (10%)	1 (1%)	0 (0%)
Anorexia	38 (19%)	0 (0%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Dysgeusia	36 (18%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Stomatitis	30 (15%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Vomiting	30 (15%)	1 (1%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Hand-foot syndrome	19 (9%)	9 (4%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Rash	24 (12%)	2 (1%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Asthenia	18 (9%)	6 (3%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Mucosal inflammation	24 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspepsia	22 (11%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Hypertension	15 (8%)	6 (3%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)
Epistaxis	14 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hair-colour changes	14 (7%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Dry mouth	13 (6%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Glossodynia	11 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haematological						
Anaemia†	117 (58%)	7 (4%)	0 (0%)	59 (58%)	2 (2%)	0 (0%)
Leucopenia	104 (52%)	7 (4%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Neutropenia	86 (43%)	17 (8%)	3 (2%)	4 (4%)	0 (0%)	0 (0%)
Lymphopenia	80 (40%)	18 (9%)	1 (1%)	31 (30%)	2 (2%)	1 (1%)
Thrombocytopenia	72 (36%)	8 (4%)	1 (1%)	4 (4%)	0 (0%)	0 (0%)

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Source: Demetri et al. 2006

Adverse events were generally mild to moderate in intensity and easily managed by dose reduction, dose interruption, or standard supportive medical treatments. Overall numbers of events of any grade for the most common treatment-related adverse event, fatigue, were 68 (34%) for sunitinib and 22 (22%) for placebo (Table 9). The incidence of grade 3 fatigue was similar between the treatment groups; there were no cases of grade 4 fatigue. Other serious treatment-related non-haematological adverse events that seemed to be experienced more frequently on sunitinib treatment included hand-foot syndrome, diarrhoea, and hypertension; serious haematological adverse events also seemed to be more frequent with sunitinib than with placebo.

Patients Completing the Study

Three hundred and twelve patients were enrolled into the study. 207 (66%) patients were randomised to sunitinib and 105 (34%) to placebo. At the cut-off for analysis 134 (65%)

of the sunitinib treated patients compared with 34 (32%) of the placebo-treated patients were ongoing in double-blind treatment. Nineteen (9%) sunitinib treated patients and 59 (56%) placebo treated patients went on to receive open-label sunitinib.

Adverse Events Resulting in Dose Reduction
Blinded phase: Sixty two (31%) patients treated with sunitinib reported 149 adverse events that resulted in either a delay or change in dose. Twelve (12%) patients treated with placebo reported 16 adverse events that resulted in either a delay, or change in dose. Adverse events that most commonly led to dose reductions, or delays for sunitinib treated patients included gastrointestinal disorders (11%) and blood and lymphatic disorders (6%). No commonly occurring adverse event led to dose reduction or treatment delay in patients treated with placebo.

Adverse Events Resulting in Discontinuation of Study Treatment
Blinded phase: Nineteen (9%) patients treated with sunitinib and eight (8%) patients treated with placebo discontinued treatment due to adverse events. Eleven (5%) and two (2%) were considered as treatment related.

Cross-over phase: Seventeen patients (22%) discontinued because of adverse events during the crossover phase, including disease progression (9 patients, 12%) and fatigue (2 patients, 3%). Five patients (6%) discontinued because of adverse events of which at least one was considered to be related to the study treatment; 12 patients (15%) discontinued because of adverse events that were solely related to the study disease. This low rate of discontinuations due to adverse events during the crossover phase (especially those unrelated to disease progression) helps support the conclusion that the toxicities experienced were generally manageable.

Treatment-Related Adverse Events
Blinded phase: Fatigue, diarrhoea, skin discolouration, nausea, anorexia, stomatitis, asthenia, constipation, dysgeusia, vomiting, palmar-plantar erythrodysesthesia syndrome, rash, anaemia, mucosal inflammation, dyspepsia, and hypertension occurred 5% more frequently with sunitinib compared with placebo. No adverse events occurred more frequently with placebo.

Cross-over phase: The most common adverse events during the cross-over phase included constitutional symptoms (fatigue, asthenia, anorexia, and pyrexia), gastrointestinal symptoms (abdominal pain, nausea, dyspepsia, vomiting, diarrhoea, and stomatitis), and skin and subcutaneous disorders (skin discoloration). Apparently more common during the crossover phase than the blinded phase were oedema peripheral, disease progression, and dyspnoea; the increase in these events may reflect the more advanced disease state of patients in the crossover population. (Patients were required to experience disease progression during the blinded treatment phase before crossing over to open-label treatment.)

Severe Treatment-Related Adverse Events (Grade 3 and 4)
Blinded phase: The most frequently reported sunitinib treatment-related severe adverse events included fatigue, diarrhoea, palmar-plantar erythrodysesthesia syndrome and anaemia. Only two kinds of severe treatment-related adverse events occurred more frequently with placebo, abdominal pain and disease progression. Seventeen (8%) patients treated with sunitinib versus one patient (1%) treated with placebo experienced treatment-related adverse events, of a maximum severity (grade 4).

Cross-over phase: One patient (1%) experienced a grade 5 (fatal) adverse event. Three patients (4%) experienced adverse events with a maximum severity of grade 4; the grade 4 events were fatigue, leucopoenia, thrombocytopenia, perirectal abscess, mucosal inflammation, and transient ischemic attack (each 1 patient, 1%). Treatment-related grade 3 events experienced by 2 or more patients during the crossover phase were fatigue (7 patients, 9%); neutropoenia (5 patients, 6%); nausea (4 patients, 5%); anorexia and palmar-plantar erythrodysesthesia syndrome (each 3 patients, 4%); and leucopoenia, stomatitis, and abdominal pain (each 2 patients, 3%).

Serious Treatment-Related Adverse Events

Blinded phase: Forty (20%) patients treated with sunitinib and five (5%) patients treated with placebo reported serious treatment related adverse events. Treatment-related serious adverse events that were experienced by patients treated with sunitinib include anaemia (2%), abdominal pain and tumour haemorrhage (2%), thrombocytopenia (1%), diarrhoea (1%), pulmonary embolism (1%), neutropoenia (1%), melaena (1%), nausea (1%), vomiting (1%) and pyrexia (1%). Treatment-related serious adverse events that were experienced by patients on placebo were vomiting (2%) and fatigue (2%).

Cross-over phase: Thirty one patients (40%) experienced serious adverse events during the crossover phase, including 16 patients (21%) who experienced treatment-related serious adverse events. The only treatment-related serious adverse events that were experienced by more than 1 patient during the crossover phase were nausea and vomiting (each 2 patients, 1%).

Deaths

Blinded phase: Twenty-three (11%) patients treated with sunitinib and 11 patients (11%) treated with placebo died during the blinded phase, or after discontinuing the randomised double blind treatment phase without crossing over to receive open-label sunitinib.

Cross-over phase: Eighteen patients (23%) died on study during the crossover phase. Seventeen on-study deaths (22% overall) were secondary to progressive disease, and 1 (1%) was related only to the study drug. Four patients (5%) died during the follow-up period (i.e., more than 28 days after their last treatment); all deaths during the follow-up period were secondary to progressive disease.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.
Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

6.8.1 Details of how the relevant non-RCTs have been identified and selected

Search Strategy for Published Data

Search for non-RCTs was part of the overall search strategy that aimed to identify all literature relating to the clinical effectiveness of sunitinib in patients with unresectable or metastatic GIST after failure of imatinib mesylate due to resistance or intolerance. The full details of the search strategy used are provided in Section 6.2 and Section 10.2 , Appendix 2

One phase III, ongoing, open label treatment use study (A6181036) was identified and included in the current submission. The treatment use study was designed to permit access to sunitinib to GIST patients who might benefit from this therapy, but who are ineligible for sunitinib clinical trials because of pre-specified entry criteria, or for whom there are no GIST trials available in a particular country in which regulatory approval has not yet been granted The initial results presented at ASCO 2008 are included in this submission (Reichardt et al. 2008).

The details of this study are summarised overleaf with an overview of methods, design, treatments, patients and outcome measures in Table 10 below.

Table 10: Summary of A6181036 Trial Design, Inclusion criteria, Methods, Efficacy and Safety Outcomes

Study/Related Publications	Study Status	Objectives	Study Design Treatment Dosing Regimen	No. of patients	Efficacy and Safety Outcomes
Trial A6181036 Worldwide treatment use *Publications:* Reichardt et al. 2008 (Median follow up of 51 weeks).	Dec 2007 - ongoing	Provision of access to sunitinib to GIST patients who might benefit from this therapy.	Phase III, ongoing, multicenter, open-label treatment-use trial. Sunitinib is administered to patients in repeated 6-week cycles at a starting dose of 50 mg once daily on a 4/2 schedule (4 weeks on treatment, followed by 2 weeks off treatment). Treatment is continued for as long as there is evidence of disease control in the judgment of the investigator. Survival is monitored for up to 2 years after the last dose of sunitinib.	As of December 2007, 1,126 patients were enrolled in the study and 1,117 patients comprised the ITT population.	Safety and tolerability ORR TTP OS

Source: Reichardt et al. 2008

6.8.2 Summary of methodology of relevant non-RCTs

Study A6181036

A6181036 is ongoing worldwide, phase III, multicentre, open-label treatment-use trial that aimed to provide an access to sunitinib to GIST patients who might benefit from this therapy, but who are ineligible for sunitinib clinical trials because of pre-specified entry criteria, or for whom there are no GIST trials available in a particular country in which regulatory approval has not yet been granted.

Methods

Study Population

The study population comprises patients aged 18 years or older (country-specific protocol amendments allow patients as young as 12 years to enroll), meeting the following key patient inclusion criteria:

- histologically confirmed malignant GIST that is not amenable to standard therapy with curative intent
- undergone screening and found to be ineligible for participation in ongoing sunitinib clinical studies
- the potential to derive clinical benefit from treatment with sunitinib, as judged by the investigator

- failed prior treatment with imatinib mesylate, defined either as progression of disease or as significant toxicity that precluded further treatment with imatinib
- resolution of all acute toxic effects of prior therapy or surgical procedure to grade ≤ 1
- adequate organ function

Patients meeting any of the following criteria are excluded:

- current treatment in another clinical trial
- symptomatic central nervous system metastases
- symptomatic congestive heart failure, myocardial infarction, or coronary artery bypass graft in the previous 6 months
- ongoing severe or unstable angina or unstable arrhythmia requiring medication
- pregnancy or breastfeeding
- any severe acute or chronic medical or psychiatric condition or laboratory abnormality making the patient inappropriate for entry into the study

Patient Disposition and Baseline Characteristics

Patients had started a median of five cycles of sunitinib treatment (range, 1–33) and were treated (period from first dose to termination or 2 weeks after last dose) for a median of 30 weeks (range, 0.1–152).

Overall, 661 patients (59%) had dose interruptions, of which 79% were due to an AE. Four hundred and sixty-five patients (42%) had dose reductions, of which 70% were to 37.5 mg, 29% were to 25 mg, and 1% was to 12.5 mg (these patients had their daily dose prescribed below 50 mg for any reason at any time during the study). Nine hundred and six patients (81%) discontinued treatment for any reason. Overall patient disposition is presented in the Table 11.

Table 11: Overall Summary of Patient Disposition

	Sunitinib (N=1,117) **n (%)**
Missing/ongoing	199 (18)
Completed treatment	12 (1)
Discontinuations	906 (81)
Reason for discontinuation:	
AE	214 (19)
Consent withdrawn	166 (15)
Lack of efficacy	510 (46)
Other	16 (1)

Source: Reichardt et al. 2008

Patient baseline characteristics and prior treatment history are summarised in Table 12.

Table 12: Baseline patient characteristics and prior treatment history

	Sunitinib (N=1,117) **n (%)**
Age in years, median (range)	59 (10–92)*
Male/female, n (%)	665 (60)/451 (40)*
0 ECOG PS, n (%)	420 (38)
1	515 (46)
2	134 (12)
>2	38 (3)
Missing	10 (1)
GIST histology, n (%)	

Epithelioid	120 (11)
Spindle cell	589 (53)
Epithelioid and spindle cell	148 (13)
Other	252 (23)
Missing	8 (1)
Previous systemic chemotherapy, n (%)	
Yes	225 (20)
No	839 (75)
Missing	53 (5)
Previous radiotherapy, n (%)	
Yes	78 (7)
No	983 (88)
Missing	56 (5)
Reason for stopping imatinib, n (%)	
PD within 6 months of start	150 (13)
PD beyond 6 months of start	862 (77)
Intolerance	104 (9)
Missing	1 (0.1)
Time between last imatinib dose and first sunitinib dose in days, median (range)	15 (1–1,423)†

ECOG PS = Eastern Cooperative Oncology Group performance status;
PD = progressive disease. *One patient missing; †25 patients missing
Source: Reichardt et al. 2008

Study Design and Dosing Regimen
Sunitinib is administered to patients in repeated 6-week cycles at a starting dose of 50 mg once daily on a 4/2 schedule (4 weeks on treatment, followed by 2 weeks off treatment). Provision is made for dose reduction in the event of toxicity. Treatment is continued for as long as there is evidence of disease control in the judgment of the investigator. Survival is monitored for up to 2 years after the last dose of sunitinib.

Assessments
Tumour measurements/assessments are performed as per local standard of care. Safety and tolerability are assessed by monitoring adverse events and laboratory abnormalities, and by physical examination. Toxicities are graded according to the NCI CTCAE version 3.0.

Statistical Analysis
The number of patients to be enrolled was not predetermined and no inferential analyses were planned due to the nature of this study. Descriptive statistics (mean, standard deviation, median, minimum and maximum values) are utilized to summarize all continuous data. All categorical data are summarized using frequencies and percentages.
The study population for updated efficacy and safety analyses includes all patients enrolled in the study receiving at least one dose of sunitinib (ITT population). TTP and OS are estimated using the product-limit method of Kaplan and Meier.

6.8.3 Critical appraisal of relevant non-RCTs
Critical appraisal of study A6181036 is summarised in Table 13 below.

Table 13: Critical appraisal of A6181036

Did the study address a clearly focused issue?	Yes
Did the authors use an appropriate method to answer their question?	Yes Expanded Access Programme to facilitate early access

	to sunitinib.
Was the cohort recruited in an acceptable way?	Yes. The cohort in the study A6181036 was representative of a defined population. The study included patients who might benefit from this therapy, but who are ineligible for sunitinib clinical trials because of pre-specified entry criteria, or for whom there are no GIST trials available in a particular country in which regulatory approval has not yet been granted.
Was the exposure accurately measured to minimize bias?	Yes Study A6181036 used objective measurements and clear inclusion/exclusion criteria. These measure are reflect the clinical practice.
Was the outcome accurately measured to minimize bias?	Yes Study A6181036 prospectively assessed objective measurements: AEs, ORR, TTP and OS. All tumour measurements/assessments were in the ITT population to minimise bias.
Have the authors identified all important confounding factors?	Yes Study A6181036 identified all potential confounding factors that might affect the clinical outcome such as age, ECOG PS, and prior imatinib dosage.
Was the follow up of subjects complete enough?	Yes. Study A6181036 is currently ongoing. As of December 2007, 1,126 patients were enrolled in the study and 1,117 patients comprised the ITT population.
Was the follow up of subjects long enough?	Treatment is continued for as long as there is evidence of disease control in the judgment of the investigator. Survival is monitored for up to 2 years after the last dose of sunitinib.
What are the results of this study?	Based on results from this treatment-use trial, sunitinib appears to be generally well tolerated in patients with imatinib-resistant or-intolerant advanced GIST who were ineligible for other sunitinib clinical trials. The safety profile observed in this study was similar to that seen with sunitinib in a prior phase III GIST study, with most AEs mild to moderate in severity. Sunitinib was effective in the treatment of patients with advanced GIST after imatinib failure, corroborating previous studies. The median estimated TTP and OS from this ongoing study are 41 and 75 weeks, respectively.
How precise are the results? How precise is the estimate of the risk?	The ITT population was followed up for a median of 51 weeks (range, 0.1–159). The median estimated TTP was 41 weeks (95% CI: 36–47).

	564 patients (50%) in the ITT population were alive at time of data cut-off. The median estimated OS was 75 weeks (95% CI: 68–84).
Were the results valid?	Yes. Median sunitinib OS of 75 weeks was consistent to that seen with a pivotal phase III RCT (74 weeks, see Section 6). The safety profile observed in this study was similar to that seen with sunitinib in a pivotal phase III GIST study (see Section 6.7), with most AEs mild to moderate in severity.
Can the results be applied to the local population?	There is no evidence to suggest that patients treated in the UK would differ from the overall patient population considered within the A6181036 trial, or importantly that UK patients would respond to sunitinib treatment in a different manner from that observed in the A6181036 trial.
Do the results of this study fit with other available evidence?	Yes (See Section 6 for details of the pivotal phase III RCT)

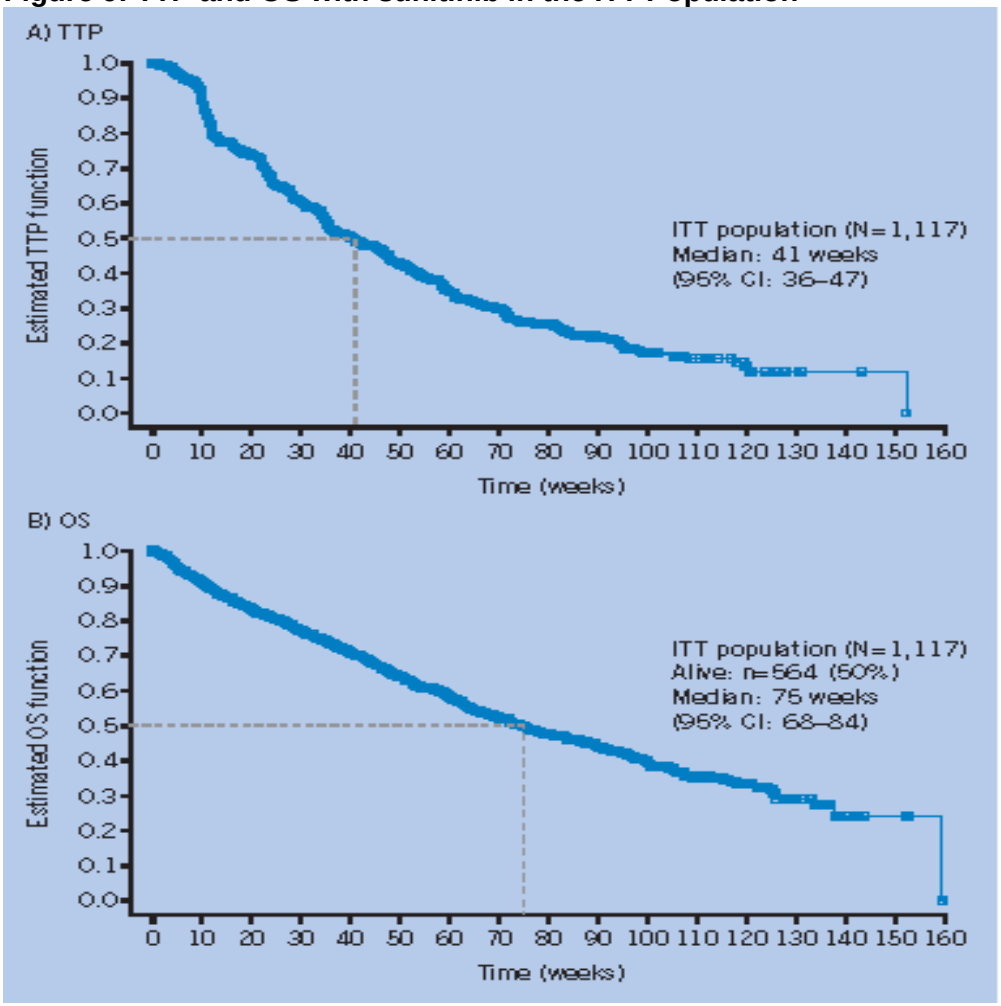
Source: Critical Appraisal Skills Programme (CASP) for Cohort studies
(CASP http://www.chsrf.ca/kte_docs/casp_cohort_tool.pdf)

6.8.4 Results of the relevant non- RCTs

Efficacy Results

The ITT population was followed up for a median of 51 weeks (range, 0.1–159).
Figure 9 below show TTP and OS in the ITT population

Figure 9: TTP and OS with sunitinib in the ITT Population

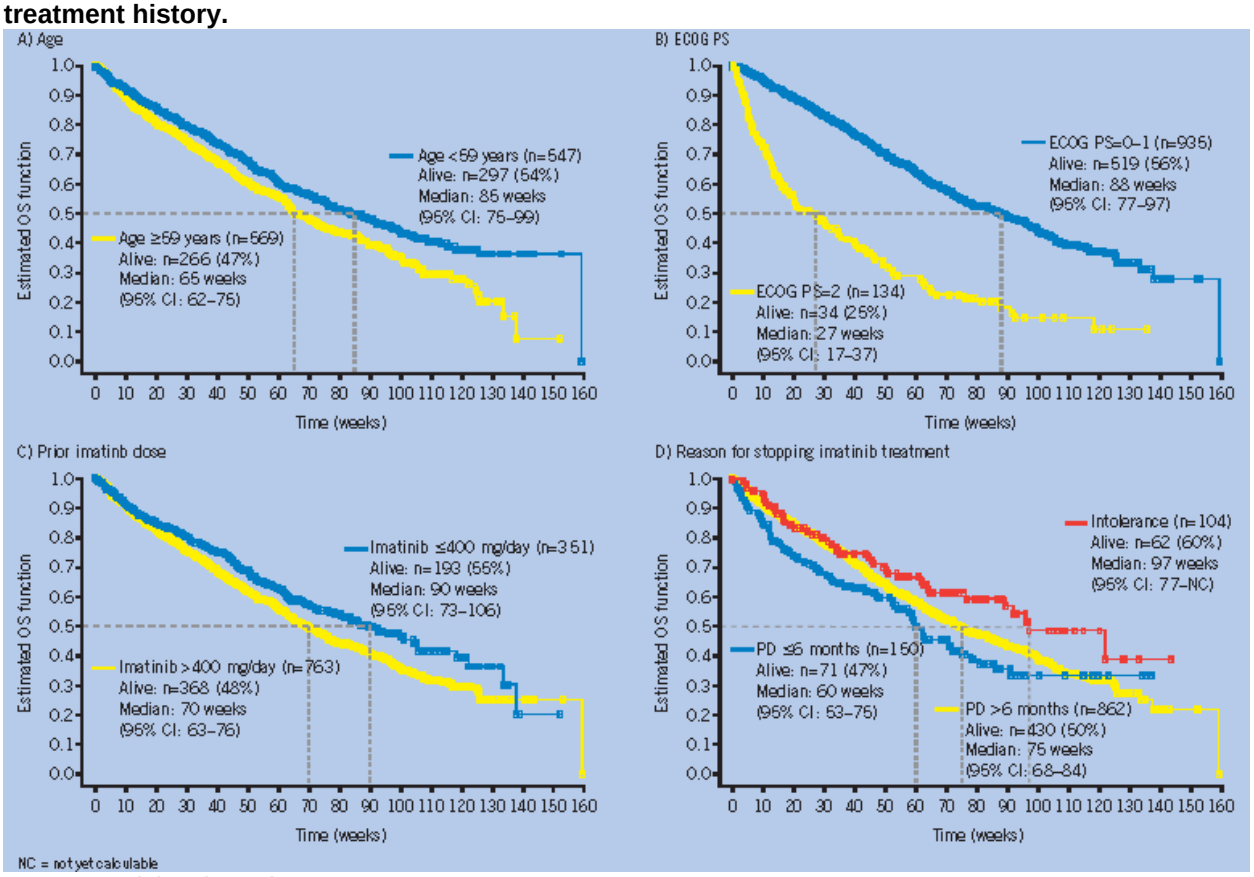


Source: Reichardt et al. 2008

The median estimated TTP was 41 weeks (95% CI: 36–47, Figure 9A). Five hundred and sixty-four patients (50%) in the ITT population were alive at the time of data cut-off. The median estimated OS was 75 weeks (95% CI: 68–84, Figure 9B).

Figure 10 below compares survival data for subgroups based on individual baseline factors and prior imatinib treatment history.

Figure 10: OS for subgroups based on individual baseline factors and prior imatinib treatment history.



Source: Reichardt et al. 2008

Median OS of the subgroup analysis suggested that age (age <59 years, 85 weeks vs. age ≥59 years, 65 weeks), ECOG PS (ECOG PS=0–1, 88 weeks vs. ECOG PS=2, 27 weeks), and prior imatinib dosage (imatinib ≤ 400 mg/day, 90 weeks vs. > 400 mg/day, 70 weeks) may be important prognostic factors affecting the clinical outcome in this patient population, but further studies are required to confirm this.

The overall results of the ongoing study A6181036, demonstrated that sunitinib is effective in the treatment of patients with advanced GIST after imatinib failure with median estimated TTP and OS of 41 and 75 weeks, respectively.

Safety Results

The majority of adverse events observed in this study were mild to moderate and support the results seen with sunitinib in the pivotal phase III RCT.

Fatigue (42%), diarrhoea (39%), and nausea (28%) were the most commonly reported treatment-related non-haematologic AEs (Table 14).

Table 14: Most common (≥ 20%) treatment-related non-haematologic AEs

	Sunitinib (N=1,117)			
AE	**Grades 1–2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Total* n (%)**
Fatigue	374 (33)	88 (8)	3 (0.3)	465 (42)
Diarrhoea	383 (34)	55 (5)	0 (0)	439 (39)
Nausea	291 (26)	23 (2)	0 (0)	315 (28)
Hand–foot syndrome	210 (19)	86 (8)	2 (0.2)	298 (27)

Anorexia	230 (21)	22 (2)	1 (0.1)	253 (23)
Mucosal inflammation	229 (21)	20 (2)	1 (0.1)	250 (22)
Stomatitis	228 (20)	20 (2)	1 (0.1)	249 (22)
Hypertension	188 (17)	58 (5)	2 (0.2)	248 (22)
Vomiting	210 (19)	25 (2)	2 (0.2)	237 (21)

*Twenty-three grade 5 events deemed to be treatment-related have occurred in the study, including one case of diarrhoea and one of nausea
Source: Reichardt et al. 2008

These were mainly grade 1 or 2 in severity. Fatigue (8%), hand–foot syndrome (8%), hypertension (5%), and diarrhoea (5%) were the most commonly reported treatment-related non-haematologic grade 3/4 AEs.

Treatment-related hypothyroidism (all grades) was reported in 10% of patients. Treatment-related haematologic AEs included thrombocytopaenia (19%), neutropaenia (18%), and anaemia (14%; Table 15).

Table 15: Treatment-related haematologic AEs

AE	Sunitinib (N=1,117)			
	Grades 1–2 n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**Total n (%)**
Thrombocytopaenia	156 (14)	44 (4)	13 (1)	213 (19)
Neutropaenia	119 (11)	76 (7)	6 (1)	201 (18)
Anaemia	108 (10)	37 (3)	14 (1)	159 (14)

Source: Reichardt et al. 2008

Most events were grade 1 or 2. Febrile neutropaenia was reported in only three patients. Treatment-related AEs related to cardiac function included heart failure, congestive heart failure, myocardial infarction, reduced ejection fraction, and pulmonary oedema (all ≤ 0.6%; Table 16).

Table 16: Treatment-related AEs related to cardiac function

AE	Sunitinib (N=1,117)				
	Grades 1–2 n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Total n (%)**
Heart failure*	1 (0.1)	4 (0.4)	0 (0)	2 (0.2)	7 (0.6)
Congestive heart failure	2 (0.2)	2 (0.2)	2 (0.2)	0 (0)	6 (0.5)
Myocardial infarction	0 (0)	0 (0)	1 (0.1)	1 (0.1)	2 (0.2)
Ejection fraction†	2 (0.2)	1 (0.1)	0 (0)	0 (0)	3 (0.3)
Pulmonary oedema	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.1)

*Includes acute heart failure. †Includes reduced ejection fraction.
Source: Reichardt et al. 2008

Overall, the safety profile observed in the study A6181036 was acceptable with mild to moderate AEs and similar to that seen with sunitinib in a pivotal phase III RCT.

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Primary and secondary resistance and/or intolerance to imatinib represents a significant problem in the management of unresectable advanced GIST. Prior to sunitinib there was no effective treatment option resulting in an unmet medical need for this patient population.

Based on results from the pivotal phase III RCT (A6181004) and worldwide treatment use study (A6181036), sunitinib demonstrated significant clinical benefit, including disease control and superior survival in patients with advanced gastrointestinal stromal tumour after failure and discontinuation of imatinib. Sunitinib appears to be generally well tolerated in patients with imatinib-resistant or -intolerant advanced GIST.

A worldwide treatment use study in over 1000 patients known as the A6181036 trial was initiated to provide pre-registration access to sunitinib and to obtain safety and efficacy data from a large, broad GIST population, reflective of clinical practice. The trial demonstrated a similar safety profile to that seen with sunitinib in the phase III RCT, with most AEs mild to moderate in severity. In addition, the efficacy including overall survival appeared to be similar in both trials.

The current evidence indicates that sunitinib has a superior therapeutic effect over best supportive care in patients with unresectable and/or metastatic malignant GIST after failure of imatinib treatment due to resistance or, intolerance and therefore represents an important therapeutic option.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

Imatinib 400 mg/d is a recommended dose by NICE for treatment of metastatic/unresectable GISTs. The sunitinib phase III RCT evidence included a median maximum dose and median daily dose of previous imatinib therapy that was higher than this recommended dose. However, the results demonstrated that sunitinib does offer an additional second line choice after resistance or intolerance not only after 400 mg/d of imatinib but also up to and beyond 800 mg/d of imatinib. The results of this trial indicated that patients benefited from sunitinib treatment, irrespective of the prior dose of imatinib.

There is no reason to believe that the study results would not be applicable to patients in routine clinical practice in the United Kingdom.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

Methods
In consultation with a medical librarian a review of the published literature aimed to both identify all relevant published economic evaluations of second-line GIST and to identify the important parameters needed to inform the design of the economic model.

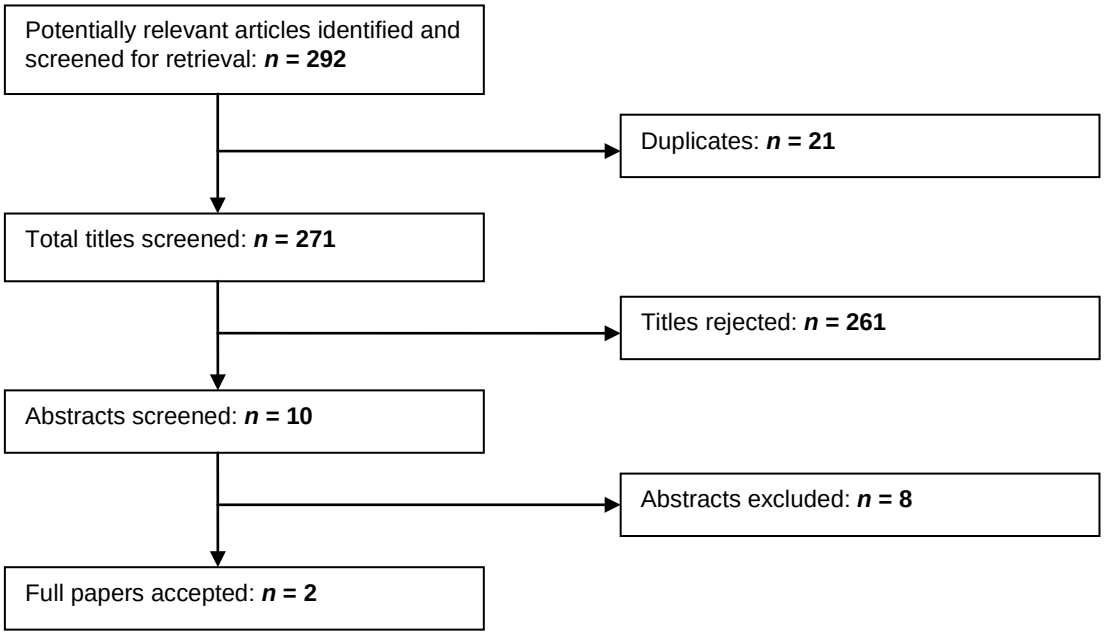
Searches were conducted on the following clinical and health economic databases: Medline and Medline (R) In-process, Embase, NHS Economic Evaluation Database, Health Economic Technology Assessment (HTA) Database. No restrictions were applied to the publication date within the searches. All the searches were accessed and searched in September 2008.

In anticipation of there being a limited amount of data the initial inclusion criteria were left intentionally wide, i.e. any document that included a relevant search term was considered. This resulted in the identification of 292 possible titles. 21 duplicates were removed leaving 271 titles for screening. 261 were then rejected leaving 10 abstracts (Figure 11). Two full papers were accepted for full review.

Inclusion criteria
Studies were included in the economic review if they included a full or partial economic evaluation of patients with GIST receiving second-line treatment AND were original studies describing data that had not been reported elsewhere.

Exclusion criteria
Studies were excluded from the review if they were population-based economic models, studies of first-line treatments, letters to editors and review articles describing data that had been reported elsewhere and editorials. Non-English language papers were excluded.

Figure 11: Summary of cost effectiveness study selection and exclusion



7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

In anticipation of there being a limited amount of data the initial inclusion criteria were left intentionally wide, i.e. any document that included a relevant search term was considered. This resulted in the identification of 292 possible titles. 21 duplicates were removed leaving 271 titles for screening. 261 were then rejected leaving 10 abstracts. Of the 10 abstracts only two papers were considered and accepted for full review. Descriptive summary information relating to each study was extracted, this included the aims (of the study), methods employed and key results, all of which are presented below (Table 17, table 18):

Table 17: Summary of Contrera-Hernandez et al (2008)

Study	**Contrera-Hernandez et al (2008) A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced gastrointestinal stromal tumours**
Aims	To compare the cost and cost-effectiveness of second-line GIST treatments from the perspective of the Mexican healthcare system.
Methods	A Markov model was developed to determine the best therapy for reimbursement, these treatments included, 1) increasing imatinib dose to 800mg per day; 2) switching to sunitinib 50mg per day; 3 regulating symptoms with palliative care. Observational data collated from a Mexican hospital was analysed to provide costs of care associated with imatinib, palliative care and standard oncology procedures in Mexico. The model utilised results from the sunitinib A6181004 trial. Mean Incremental results were presented as progression-free months gained and life years gained.
Results	The incremental effectiveness of therapy as compared to palliative care was 3.1PFM with sunitinib and 0.3PFM with high dose imatinib. The base case results suggests that sunitinib dominates treatment with high dose imatinib and costs

	USD $46,108 per life year gained when compared to palliative care.
Relevance to decision-making in England and Wales	This evaluation has limited relevance to the UK, as costs are based upon treatment pathways in Mexico, the imatinib treatment arm is currently not reimbursed in the UK.

Although the study summarised below is a review of challenges of conducting economic evaluations where cross over occurs; the paper describes in detail the economic model used within this evaluation.

Table 18: Summary of Chabot et al (2008)

Study	**Chabot et al (2008). The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: The example of sunitinib for gastrointestinal stromal tumour.**
Aims	Demonstrate the challenge of conducting economic evaluations presenting the economic evaluation of sunitinib vs best supportive care for the treatment of gastrointestinal stromal tumour in patients intolerant or resistant to imatinib.
Methods	A Markov model was developed to simulate disease progression and death and to estimate QALYs and life years gained over the life-time of patients. The analysis considered only direct medical costs.
Results	The base case cost effectiveness analysis (mean values) reported a cost per life year gained of Can$49,826 and a cost per QALY of Can$79,884. In univariate analysis, cost effectiveness estimates were most sensitive to variation in health state utility values and survival hazard ratio. Based upon these numbers the original decision by the Canadian Common Drug Review was to not recommend sunitinib for reimbursement.
Relevance to decision-making in England and Wales	Best supportive care is relevant comparator arm for the UK. The economic evaluation is based upon the same clinical trial as Contrera-Hernandez 2008 but the perspective was that of the Canadian health care system. The results are consistent with the Mexican scenario of sunitinib vs palliative care.

Summary of the literature

The literature search identified two economic models to consider treatment for GIST, however these were related to first line therapy of GIST and are not relevant for this analysis. Only two economic evaluations report findings for second-line use of sunitinib and report a common analytical approach applied to their specific country setting as summarised above.

Both papers report the use of a decision analytic model to estimate cost-effectiveness with both using a Markov modelling framework. The Contrera-Hernandez paper states that the model is structured around three primary health states of progression free survival, progressed disease and death. Both models use the effectiveness data from the sunitinib clinical trial and the Contera-Hernandez paper uses observational data to provide data upon costs.

While both papers report results in terms of incremental cost per life year gained, only the Chabot paper reports estimates of cost per QALY and provides information on health state utilities.

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case

should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 **How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.**

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

Administration
The drug is administered orally, under the supervision of a physician experienced in the treatment of GIST.

Dose and frequency
50mg orally, taken once daily, with or without food, for 4 consecutive weeks followed by a 2 week rest period, to comprise a complete cycle of 6 weeks.

Duration of use
The model assumes that patients receive sunitinib until disease progression.

Cessation
Within the clinical trial cessation took place on disease progression. Cessation in clinical practice is likely to take place on disease progression or as a result of patient choice.

7.2.1.2 **Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- **the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)**
- **the robustness and plausibility of the endpoint on which the rule is based**
- **whether the 'response' criteria defined in the rule can be reasonably achieved**
- **the appropriateness and robustness of the time at which response is measured**
- **whether the rule can be incorporated into routine clinical practice**
- **whether the rule is likely to predict those patients for whom the technology is particularly cost effective**
- **issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

Within the economic evaluation, sunitinib treatment is assumed to continue until either documented disease progression or death.

7.2.2 Patients

7.2.2.1 **What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?**

The relevant population for the economic evaluation are patients with unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance. This population reflects the population of the A6181004 study and the licensed indication for sunitinib. The populations included in the economic evaluation are believed to relate directly to the specified decision problem.

7.2.2.2 **Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?**

Within the A6181004 trial no formal subgroup analysis was undertaken. Consequently, subgroup analyses were not undertaken within this economic evaluation.

7.2.2.3 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.**

No subgroups were identified.

7.2.2.4 **At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?**

All patients enter and exit the evaluation at the same points. Patients enter at the point where 2nd line treatment is initiated for GIST. The exit of all patients from the model is at death or 6 years, depending on which occurs first. The span of 6 years reflects the maximum life expectancy of the patient population. The time horizon can be adjusted in the electronic version of the economic model.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The GIST model evaluates the cost-utility of sunitinib compared to Best Supportive Care (BSC) which is the standard of care following imatinib failure or resistance.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective adopted followed the NICE reference case. The economic evaluation was considered from the National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs incurred by patients and their relatives, such as direct or indirect productivity losses or out-of-pocket expenses incurred by attending hospital appointments were not estimated.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

The time horizon used was six years. Six years reflects the maximum life expectancy of the patient population within the clinical trials and was validated by expert clinical opinion.

This time horizon can be adjusted in the electronic version of the model to represent shorter time horizons.

7.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 **Please provide the following.**

- **A description of the model type.**

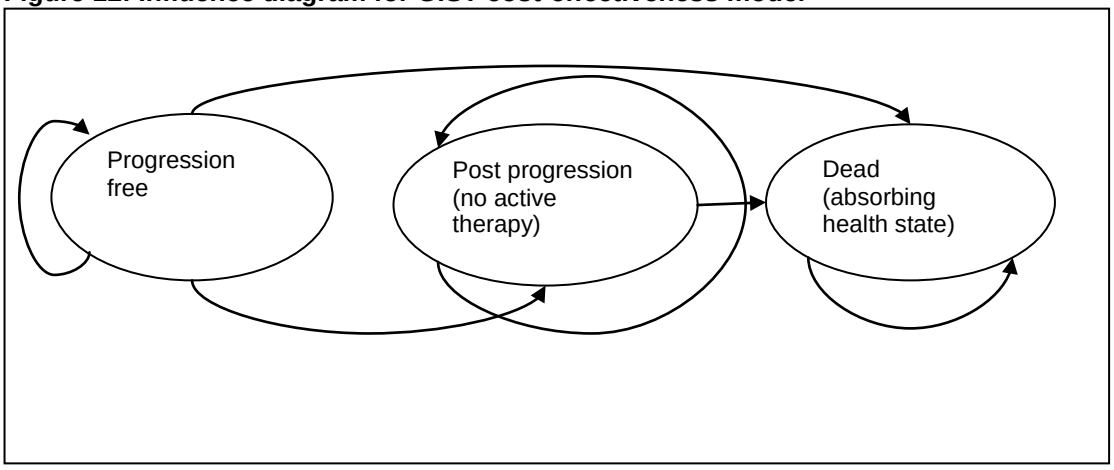
- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**
- **A list of all variables that includes their value, range (distribution) and source.**
- **A separate list of all assumptions and a justification for each assumption.**

Description of the Model

A decision-analytic model has been developed to simulate disease progression in GIST and to estimate the cost-effectiveness of sunitinib as compared to BSC in patients with unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance. The model uses survival analysis to consider progression of GIST in a cohort of patients over time. The model has been written in Microsoft Excel and has been based upon the methodology adopted within the recent assessment of the cost effectiveness of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma.

The model uses three distinct health states: progression-free survival (PFS), progressive disease (PD) and death (figure 12). The model uses estimates of effectiveness, costs and health states values against these health states to model progression of disease and cost-effectiveness over time. The model uses a 6-year time horizon, and a 6-week model cycle. This structure is regarded as appropriate for capturing the health effects, and disease progression in GIST. Future costs and benefits are discounted at 3.5% per annum.

Figure 12: Influence diagram for GIST cost-effectiveness model



All patients enter the model in PFS, having failed imatinib therapy and remain there until they subsequently experience disease progression and/or death. In reality, patients have already experienced disease progression at the point of inception into the model, but on initiation further treatment as they enter the model they are considered to be progression free for this line of treatment. At any moment, a patient is assumed to be in one of the states. Patients move between states once during each cycle. This means that if a patients is in PFS then during the next cycle they can either die, move to progressive or stay in PFS. Patients remain in PFS until they die or until disease progression. Once patients enter the PD state they remain there until death.

In the survival analysis used to structure the model, for each treatment a Weibull curve is derived to describe the number of patients alive over time (overall survival data) and another Weibull curve describes the number of patients in PFS over time. For each treatment the number of patients in the PD health state at any time is calculated as the number alive minus the number in PFS health state, at that time.

Model parameters

Modelling health outcomes for BSC

Effectiveness outcomes for patients receiving sunitinib were based on empirical time-to-event data (progression-free survival and overall survival) collected within study A6181004 (final unpublished analysis). As discussed in section 6.3.5, the empirical time-to-event for overall survival used within the economic model is the post-hoc analysis performed using RPSFT methods. The impact of using the ITT KM data for OS is presented in the sensitivity analysis.

As the empirical survival curves for progression-free survival and overall survival outcomes are subjected to a degree of censoring, regression analysis was used to fit Weibull curves to the empirical patient level data. The Weibull curve was fitted to one data point per month. The Weibull survivor functions, S(t), used within the cost-effectiveness model are based upon the formulation as shown below:

$S(t) = \exp\{\lambda t^{\gamma}\}$

where λ describes the Weibull scale parameter, γ describes the Weibull shape parameter, and t is time.

Modelling the relative effectiveness of sunitinib

Two options were considered for the extrapolation of the sunitinib PFS and OS curves when developing the economic model:

a. extrapolation based on the empirical data
b. extrapolation based on application of the hazard ratio from the trial to the BSC curve

As can be seen in figures 13 and 14 the extrapolation based on the application of the hazard ratio does not give a good fit to the empirical evidence. Therefore, in the base case analysis the sunitinib curves have been extrapolated based on the empirical data using the estimates of λ and γ, show in table 19. The impact of using the extrapolation based on application of the hazard ratio from the trial to the BSC curves is presented in the sensitivity analysis.

Figure 13: Progression free survival curves

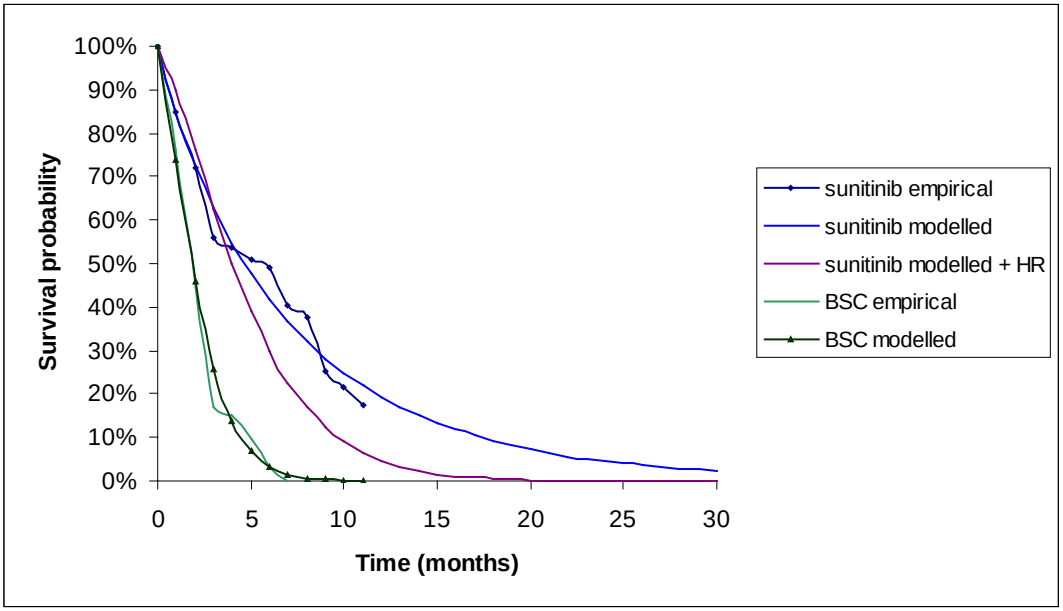


Figure 14: Overall survival curves

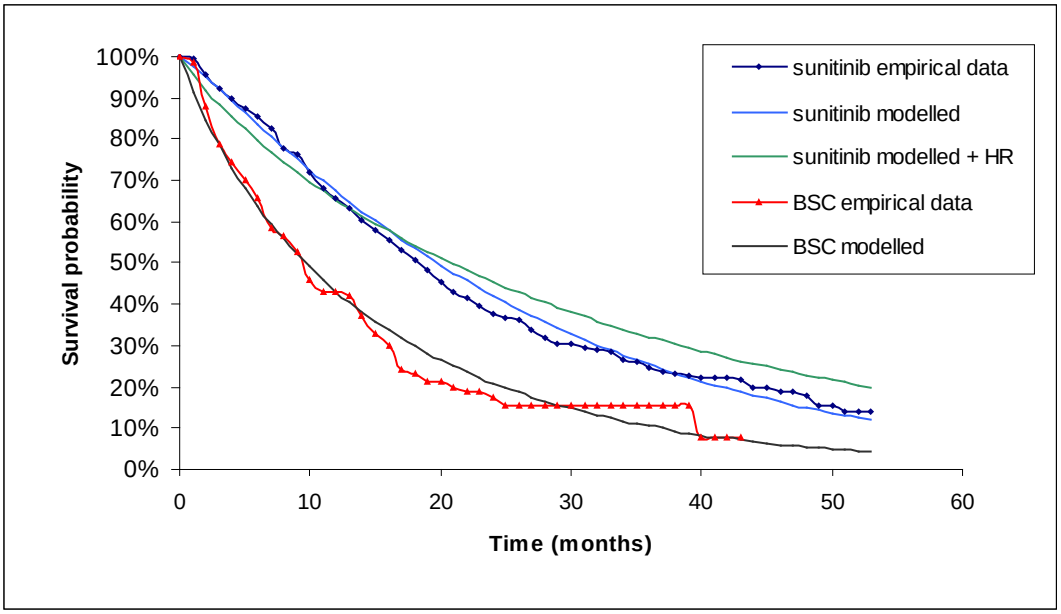


Table 19: Parameters of Weibull distribution

	PFS		OS	
	λ	γ	λ	γ
sunitinib	0.171	0.91	0.024	1.13
BSC	0.303	1.36	0.090	0.899

Modelling health-related utility values

The cost effectiveness model assumes that a patient's level of health related quality of life is dependent on whether they have experienced disease progression, or whether they are progression free. Within the base case analysis, the model assumes that a patient has a higher level of health related quality of life (HRQoL) prior to disease progression and that health utilities differ by treatment received. For the pre-progression health state, a health utility score was derived directly from the A6181004 trial.

Health utilities were assessed with study A6181004 using the EQ-5D health classification questionnaire. EQ-5D utility scores were valued using the UK tariff reported by Dolan (Dolan 1997). The results of the EQ-5D values within trial A6181004 showed that the mean baseline scores between sunitinib and the placebo arm were only slightly different, consequently all subsequent changes in utility were calculated as changes from the baseline. Within this economic analysis all patients (both in the sunitinib and the BSC arm) were assumed to start with a baseline utility of 0.785 (the baseline values reported in trial A6181004 for the sunitinib arm).
The sunitinib mean utility value is weighted over the 6 week treatment cycle, within trial A6181004 utility values were taken at day 28 of each cycle (after four weeks of treatment) and at the first day of each cycle (after two weeks rest). The average of these two measurements were assumed to present the utility during these treatment phases. These two values were then weighted to give one value for the 6 week cycle. The pre-progression utility value for sunitinib is 0.73.
The utility for the patients with no progression in the BSC arm were calculated from the average changes in the EQ-5D scores in the placebo arm of trial A6181004. The pre-progression utility value for BSC is 0.78.

Patients after progression were assumed to have the same utility, regardless of previous treatment type. Their utility was calculated from the average EQ-5D score (both sunitinib and placebo arm) measured at the termination of the double-blind phase of trial A6181004.

Modelling costs and resource use
The cost effectiveness model distinguished between the costs of care incurred whilst patients are free from disease progression (and receiving active treatment), and the costs associated with those resources consumed following disease progression. To determine patterns of treatment and resource use in the absence of direct observational data, a cancer physician panel was consulted.

When patients are in the health state of PFS and irrespective of treatment, there is a resource use/cost associated with out patient monitoring, scans and tests. It was assumed, based upon clinical opinion, that patients would have one outpatient appointment every month at £112 per visit (DoH, 2008), one CT scan every 3-months at a cost of £141 per scan (DoH, 2006) and standard blood tests once every month at a cost of £3 per test (DoH, 2008). The total cost of medical management for a 6-week cycle used within the model is £224. When patients are in the progressive disease (PD) health state our clinical panel suggested that patients would continue to receive regular monitoring as in the PFS health state and that some patients would receive imatinib. However, clinical opinion differed regarding the proportion of patients who would suitable for imatinib 400mg daily as a palliative treatment. Given this uncertainty, our base case analysis excludes the costs of imatinib 400mg daily, the sensitivity analysis includes the cost of giving 50%-70% of patients imatinib therapy in the BSC arm and the PD health state. The cost of imatinib therapy is assumed to be £2,246 per cycle (BNF 56).

Given the terminal nature of this condition, a cost associated with death was included within the analysis, this cost was based on an estimate from the literature (Coyle et al, 1999). This cost of £3,923 was averaged over hospital and hospice stays. As a sensitivity analysis no cost of death was assumed.

Modelling costs of adverse events
Within the base case analysis, only costs associated with Grade 3 or 4 adverse events (AEs) reported in study A6181004 are included, since these are expected to be those that incur additional NHS costs. The adverse event judged to require cost estimate was hypertension; the ongoing treatment of hypertension was assumed to include two GP visits per year (cost per visit = £36)[Curtis, 2007], two district nurse visits per year (cost per visit = £25)[Curtis 2007], and medication for hypertension (cost per year = £246)[NICE clinical guideline 34], with a total cost estimate of £367 per year. The duration a patient would experience hypertension for was unclear and therefore it was assumed treatment would continue for the duration of PFS.

Although not an adverse event reported within the A6181004 study, our clinical panel suggested that sunitinib treated patients would be monitored for hypothyroidism and where necessary given a thyroxin. We assumed that 10% of patients would need to receive a thyroxin at a cost of £2.28 per cycle (based upon the retail price of Levothyroxine, BNF 56).

The following tables give a list of all model assumptions along with relevant justifications

Table 20: Methodological Assumptions

Assumption	Assumption description	Justification
Time horizon	Six years in base case. Varied within sensitivity analysis.	Clinical experts endorsed that this time horizon was a suitable length for 2nd line GIST patients in the UK. At this time point only 5% of patients treated with sunitinib and 2% of patients receiving BSC remain alive.
Choice of inflation indices	The unit costs for all resource items, other than drugs, were inflated to present values (2008).	Inflation indices were taken from the Unit Costs of Health and Social Care Publication (2008), University of Kent. This increases the validity of the model to reflect the current economic case.
Sources of unit cost data	The BNF prices 56 (September 2008) for medications used within the model. The hospitalisation costs were based on the most up to date NHS Reference Costs and inflated to present values. The most up to date NHS Reference Costs were used for laboratory and radiology tests.	This is standard practice in economic evaluation and reflects the NICE reference case.
Sources of BSC costs/resource costs	BSC costs were sourced from clinical opinion. Varied within sensitivity analysis.	No specific costs for BSC in GIST have been identified for the UK setting. This was considered best available source of BSC costs as these are poorly defined. As a sensitivity analysis the costs used for BSC in the mRCC NICE submission were used.
Sequencing of health states	It was assumed that once the progressed health state has been entered, patients either remain in this state of move to the death state.	This assumption was endorsed by expert clinical opinion.

Table 21: Dose reductions

Assumptions	Assumption description	Justification
Dose reductions	The model uses reported RDI values for sunitinib to alter the drug acquisition costs. In sensitivity analysis this assumption is removed.	The impact of dose reduction is included in the phase III clinical trial survival estimates. However, efficacy has not been reported by dose. The sensitivity analysis assumes full dose sunitinib is given because the extent to which reductions occur in clinical practice is unknown.

Table 22: Assumptions relating to treatment-related adverse events

Assumptions	Assumption description	Justification
Study of adverse events	It was decided to include only Grade 3/ 4 toxicities.	This assumption was made on the bases that AE grades 1/ 2 have minimal impact on patients' quality of life and costs of treatment. The exclusion of grade 1/ 2 adverse events was endorsed by expert clinical opinion.
Coverage of	The following adverse event was	This assumption was included as on-going

adverse events (AEs)	reflected in the model: Grade 3/ 4 hypertension	treatment has direct cost to NHS. The other Grade 3/ 4 AEs were seen to have no direct cost to the NHS as could be managed by either dose reduction or over the counter therapies. This assumption was endorsed by expert clinical opinion.
	All patients receiving sunitinib were monitored for hyperthyroidism for the duration of their treatment.	Clinical opinion endorsed the inclusion of monitoring for this side effect.
Utility decrement associated with the occurrence of serious adverse events	A utility decrement associated with experiencing an AE was not incorporated into the model.	Utility differences between placebo arm of the trial and sunitinib indicated a disutility to being treated with sunitinib. Clinical opinion suggested this disutility was a consequence of treatment related side effects.
Frequency of adverse events by health state	It was assumed that patients will not experience any adverse events once they progress.	This assumption was endorsed by expert clinical opinion.

Table 23: Treatment-related assumptions

Assumptions	Assumption description	Justification
Number of treatment cycles in the model	The model assumes the duration of therapy is linked to time to disease progression which is drawn from the A6181004 trial. No further treatment stopping rule has been used within the model.	To incorporate a treatment stopping rule into the model would introduce uncertainty, as it is difficult to estimate the impact on efficacy of reduced duration of therapy.
Best supportive care	It was assumed that patients randomised to the placebo arm of the A6181004 trial would receive BSC until death.	Those given placebo therapy in the trial would not have received active therapy. Clinical opinion endorsed that the survival seen with the placebo arm is that expected by patients who receive palliative care in clinical practice.
Costs of best supportive care	In the base case analysis, patients who receive best supportive care are assumed to be managed in the same way as patients receiving active therapy, thus the costs are set to equal. This assumption was tested in the sensitivity analysis in two ways: 1) Management costs remained the same as active treatment and the cost of imatinib 400mg daily was included for a proportion of patients receiving BSC; 2) costs were differed according to treatment received, the costs attributed to each arm were based upon those used by the Assessment Group in the mRCC model (PenTAG, 2008).	The base case assumption was made to reflect the clinical experience of UK patients as set out by expert clinical opinion. As there is uncertainty around the costs of BSC, the sensitivity analysis was used to test this assumption. The sensitivity analysis explored including Imatinib 400mg daily for a proportion of patients as expert clinical opinion suggested some patients gain symptom relief despite earlier progression.

7.2.6.2 Why was this particular type of model used?

A Markov type model was chosen to simulate the transitions of a hypothetical cohort of GIST patients from the point at which they receive a second line treatment until death. This model represents a convenient way of modelling a condition where patients pass through a series of well defined and mutually exclusive health states.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The use of a model structure based on progression-free and post-progression health states was selected as this is consistent with the clinical outcomes used within oncology trials, specifically study A6181004. As patients typically remain on treatment until disease progresses, there are clears cost differences for pre- and post-progression health states.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The structure of the model and the methodology used to evaluate the cost-effectiveness of sunitinib compared to BSC was based closely on the approach employed within the sunitinib modelled identified within the literature.
The structure of the model was further developed through consultation with clinical experts.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model was designed to include all the relevant aspects of the disease progression from start of treatment until death. These aspects were validated with expert clinical opinion.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The cycle length for the model is 6 weeks, this represents one cycle of sunitinib treatment as specified within the summary of product characteristics.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction is applied in the modelling.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The costs and outcomes are extrapolated beyond the duration of the trial follow-up.

The A6181004 trial data were used to populate the second line in the model. Data were available from A6181004 on when patients progressed or subsequently died. In the survival analysis used to structure the model, for each treatment a Weibull curve is derived to describe the number of patients alive over time (overall survival data) and another Weibull curve describes the number of patients in PFS over time.

b) Non-model-based economic evaluations

7.2.6.9 **Was the evaluation based on patient-level economic data from a clinical trial or trials?**

The analysis takes the form of a mathematical model rather than a trial-based economic evaluation, and as such sections 7.2.6.9 to 7.2.6.13 are not applicable

7.2.6.10 **Provide details of the clinical trial, including the rationale for its selection**.

7.2.6.11 **Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?**

7.2.6.12 **Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?**

7.2.6.13 **Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?**

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

7.2.7.1 **How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.**

Best supportive care was the baseline treatment strategy, and was compared with sunitinib therapy. To estimate baseline disease progression data are taken from the placebo arm of the A6181004 trial. The overall survival and progression free survival (PFS) data (RPSFT and Kaplan Meier survival data) are used to model disease progression over time. PFS and OS data for BSC were read directly from the published survival curves in the A6181004 RCT and Weibull curves were then fitted to the date for use in the model.

7.2.7.2 **How were the relative risks of disease progression estimated?**

In the base case analysis, we have estimated disease progression for sunitinib by fitting Weibull curves to the sunitinib data within trial A6181004 (Kaplan Meier curves for PFS and OS(final analysis)). Alternatively, using the BSC disease progression data, the disease progression for sunitinib could have been estimated using the relative measures of treatment effect (hazard ratios) for PFS (0.333 95%CI:0.238 - 0.467) and OS (0.505 95%CI: 0.388 – 0.658) reported in Section 6.4. However the curves modelled with the hazard ratio do not give a good fit to the existing data and consequently overestimate the survival benefit of sunitinib. However, the structural assumption is considered in the sensitivity analysis by using the PFS and OS curves

modelled with the hazard ratios. See figures 13 and 14 in Section 7.2.6.1 for the fit of the Weibull curves to the empirical data used in sensitivity analysis

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Yes. Intermediate economic outcomes measures linked to final outcomes are included. The linked clinical/health outcome measures are listed below:

- quality-adjusted life year
- life year gained

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

In the cost effectiveness analysis the mean cost for treatment of adverse events (AEs) is included. At a cohort level these costs are very small, given the relatively rare incidence of events regarded as serious and associated with NHS resource use. Only Grade 3 and 4 adverse events (AEs) were included, since these are expected to be those that incur additional NHS costs.

Clinical opinion suggested that most AEs would be resolved through dose modification and over the counter medicine. The adverse events that required cost estimates were hypertension and hypothyroidism. The cost estimate for ongoing hypertension treatment used within this review was £367 per year which incorporated two GP visits per year (cost per visit = £36)[Curtis, 2007], two district nurse visits per year (cost per visit = £25)[Curtis 2007], and medication for hypertension (cost per year = £246)[NICE clinical guideline 34]. It was assumed that hypertension would continue for the duration of PFS.
The cost estimate for ongoing hypothyroidism assumed that patients would be treated until death with a thyroxin at a cost of £2.28 per cycle.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Phase III clinical trial data was predominantly the source used to provide values for clinical parameters.

Expert opinion was used to:

- validate the overall structure of the model ensuring that it reflected the natural course of the disease in the UK
- identify the algorithms used with the treatment of adverse events
- the follow-up schedule for patients receiving best supportive care

The method of elicitation was to use a round table discussion with practising oncologists. In instances where alignment was not immediate, discussion followed to obtain consensus.

The clinical experts identified were consultant oncologists currently treating GIST patients in the UK.

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

See previous question and section 7.2.6.1 regarding assumptions and justification.

7.2.8 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.8.1 **If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?**

Health benefits were expressed in QALYs.

7.2.8.2 **Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.**

The model estimates progression-free survival, life years gained, and QALYs gained. Progression-free survival and overall survival were measured for BSC and sunitinib groups directly within study A6181004.

Post-progression survival (the number of patients in the PD health state at any time) was calculated as the number alive minus the number in the PFS health state at that time. QALYs were estimated by applying the treatment and health state specific utilities to the number of patients in each health state at that time.

7.2.8.3 **How were health effects measured and valued? Consideration should be given to all of the following:**

- **State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.**
- **Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.**
- **Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.**
- **How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?**
- **Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.**
- **Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who**

produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

In the base case analysis treatment specific health state values are used. The health states values are derived from a within-trial assessment of patients across the two treatment groups using the EQ-5D health questionnaire, valued using the tariffs reported by Dolan et al (Dolan 1997).

The results of the EQ-5D values within trial A6181004 showed that the mean baseline scores between sunitinib and the placebo arm were only slightly different, consequently all subsequent changes in utility were calculated as changes from the baseline. Within this economic analysis all patients (both in the sunitinib and the BSC arm) were assumed to start with a baseline utility of 0.785 (the baseline values reported in trial A6181004 for the sunitinib arm).
The sunitinib mean utility value is weighted over the 6 week treatment cycle, within trial A6181004 utility values were taken at day 28 of each cycle (after four weeks of treatment) and at the first day of each cycle (after two weeks rest). The average of these two measurements were assumed to present the utility during these treatment phases. These two values were then weighted to give one value for the 6 week cycle. The utility for the patients with no progression in the BSC arm were calculated from the average changes in the EQ-5D scores in the placebo arm of trial A6181004. Patients after progression were assumed to have the same utility, regardless of previous treatment type. Their utility was calculated from the average EQ-5D score (both sunitinib and placebo arm) measured at the termination of the double-blind phase of trial A6181004. The calculated utilities within the model are shown in Table 24.

Table 24. Model utilities

Health state	Mean Utility	SD
Sunitinib – progression free (4 week on treatment)	0.712	0.2
Progression free (2 week rest)	0.793	0.02
Weighted value	0.731	
BSC – progression free	0.781	0.2
Progression	0.577	0.3

The modelling of utilities in this evaluation is consistent with the methods used in the economic evaluation of sunitinib reported by Chabot (2008).

7.2.8.4 **Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).**

No other preference based measures were included in the A6181004 trial.

7.2.8.5 **Were any health effects excluded from the analysis? If so, why were they excluded?**

Disutility associated with adverse events are not included within the analysis. Utility decrements relating to specific adverse events were not available from the A6181004 trial. The inclusion of such effects would require numerous assumptions concerning the durations for which the patient experiences the adverse events, and the

independence of interdependence of events. Further assumptions would be required concerning the multiplicative or additive impact of such events. These events are potentially already captured within the sunitinib pre-progression utility estimate, further inclusion would therefore lead to a downward biasing of resulting utility estimates due to double counting.

7.2.9 Resource identification, measurement and valuation

For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are bpossible. These resources should be valued using the prices relevant to the NHS and PSS. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The cost components included in this evaluation are:

Drug costs
Drug used: cycles and dose given

Monitoring
Laboratory tests, CT scans, out patient visits

Resource usage of treatment related adverse events
Occurrence; Treatment (drugs/ visits/ setting/ tests)

BSC in PD health state
Hospital contacts; investigation and medications related to GIST after the end of treatment; cost associated with death

7.2.9.2 How were the resources measured?

Resource use was not measured directly within the A6181004 trial. Assumptions concerning monitoring schedules for managing GIST and adverse events have been based upon information provided by clinicians in an advisory board. As a sensitivity analysis the costs reported in the imatinib review have been used.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Efficacy data has been obtained from the A6181004 trial. Drug usage and relative dose intensity estimates were derived from the data collected within this study. Other resources were measured using alternative external sources as above.

7.2.9.4 **Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).**

As far as the available evidence would allow, all relevant resources were included for the entire time horizon.

7.2.9.5 **What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.**

Drug acquisition costs
The acquisition costs were obtained from the BNF (56 September 2008)

Medical management costs
The unit costs associated with medical management i.e cost of consultant outpatient visit have been sourced from the UK Department of Health's National Reference Costs.
The costs associated with death have also been included, this cost was based upon an estimate from the literature (Coyle et al, 1999).

7.2.9.6 **What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.**

The unit cost of sunitinib used in this evaluation does not differ from the acquisition cost reported in section 1.

Sunitinib malate is available in two pack sizes a 28 capsule pack and 30 capsule pack

12.5mg 28-capsule pack = £784.70
25mg 28-capsule pack = £1,569.40
50mg 28-capsule pack = £3,138.80

12.5mg 30-capsule pack = £840.75
25mg 30-capsule pack = £1,681.50
50mg 30-capsule pack = £3,363

7.2.9.7 **Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.**

Additional infrastructure does not need to be put in place.

7.2.9.8 **Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?**

The costs included in the model were direct costs to the NHS and consistent with the reference case.

7.2.9.9 **Were resource values indexed to the current price year?**

BNF 56 current list prices were used for drug pricing, and all other costs are inflated to 2008 values. Where 2008 prices were not available, these have been uplifted using the Hospital and Community Services Prices Index (Curtis 2007).

7.2.9.10 **Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.**

A detailed list of assumptions concerning the measurement and valuation of resources is presented in Section 7.2.6.1.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

An annual discount rate of 3.5% is applied for both costs and benefits, which is based on the rates specified within the NICE reference.

7.2.11 Sensitivity analysis

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.2.11.1 **Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.**

The impact of assuming a proportional hazard rather than assuming independent hazard to extrapolate the sunitinib Weibull curves has been explored. The results of this analysis are presented in Section 7.3.3.1

7.2.11.2 **Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?**

A range of one-way sensitivity analyses were run using the economic model to consider the variation in the incremental cost, incremental benefit and ICER outcomes when viable ranges of parameter values were independently considered.

The list of sensitivity scenarios are summarised below.

Time horizon

- This was varied between 1 and 10 years to investigate the impact on results.

Costs

- Discount rates were varied from the baseline to between 0% and 6%
- **Cost associated with death**: This was set to £0 for both treatments
- **Cost estimated for BSC in PD health state:** Inclusion of imatinib 400mg daily to treat palliative symptoms regardless of PFS treatment. BSC costs for within PFS and PD health state were set to those used within the Assessment Group mRCC cost effectiveness model.
- **Cost of monitoring, out patients:** These costs were set to both £0 and doubled from the baseline estimate.
- **Adverse event costs:** Set to £0 for both treatments.
- **Dose intensity:** Sunitinib dose intensity increased to 100%

Effectiveness
- **Survival curves:** sunitinib PFS and OS curve extrapolation based on application of the hazard ratio from the trial to BSC curves.
- **Overall survival:** baseline BSC data taken from the ITT analysis
- **Discount rates:** varied between 0-6%

Utilities
- **Utility estimates**: The same estimates of health state value for PFS were applied to BSC and sunitinib, setting both to 0.78 and 0.73.

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

A probabilistic sensitivity analysis was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values.

For each treatment the two parameters of the Weibull distribution, In(λ) and γ, for PFS and separately for OS were drawn from bivariate normal distributions, using the cholesky matrix decomposition. The variance-covariance matrices used in the matrix decomposition were estimated from linear regression of In(-(InS(t)) against In(t), described in section 7.2.12.1, where S(t) is the survival function at time t.

In the PSA the uncertainties in the parameter values for the key clinical and cost variables in the model were considered simultaneously by repeatedly sampling mean parameters from a series of assigned distribution types, based on point estimates and the standard error statistics for each average parameter values. The means, standard errors and statistical distributions for these parameters are given in Table 25.

Table 25: Parameters used in the PSA

Parameter type	Parameter	Mean value per 6-weeks	Statistical distribution
Effectiveness	Weibull: λ, γ	Sunitinib PFS λ = 0.193; γ = 0.906 Sunitinib OS λ =0.022; γ =1.154 BSC PFS λ =0.215; γ =1.543 BSC OS λ =0.126 ; γ =0.922	Bivariate normal
Health state utilities	All utilities	Sunitinib PFS = 0.73 PD = 0.58	beta

		BSC PFS = 0.78 PD = 0.58	
Costs	Drug acquisition Adverse events Medical management	Not stochastic Not stochastic PFS both treatments: £223 PD both treatments: £435	n/a n/a gamma gamma

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

A cohort analysis was undertaken in the model to simulate the prognosis of a hypothetical cohort of 1,000 individuals on each treatment. For each cycle in the model, the number of patients alive (overall survival data) and the number of patients in PFS are derived from Weibull curves. For each treatment, the number of patients in the PD health state at any time is calculated as the number alive minus the number in the PFS health state.

Weibull curves for the best supportive care arm of the model were fitted separately to the PFS and OS Kaplan-Meier curves using data from trial A6181004. The Weibull curves were fitted to one data point per month to improve the fit to the actual data by reducing the influencing of the first few data points in the trial data. This is consistent to the methodology used to fit the curves to data used by the assessment group in the mRCC economic model. The Weibull survival function used is:

$S(t) = \exp(- \lambda t^{\gamma})$

at time t, with scale parameter λ, shape parameter γ and hazard:

$h(t) = \gamma\lambda\, t^{\gamma-1}$

if $\gamma > 1$, the hazard increases with time, and if $0 < \gamma < 1$, it decreases with time. Parametric curves can be fitted to empirical Kaplan-Meier data using simple regression by transforming the survivor function to a linear function. The parameters γ and λ are estimated from the linearising equation:

$\log (- \log(S(t))) = \log (\lambda) + \gamma \log (t)$

Two options have been considered for the extrapolation of the sunitinib curve:

1) extrapolation based on the empirical data
2) extrapolation based on application of the hazard ratio from the trial to the BSC curve

In the base case analysis, sunitinib disease progression has been calculated by extrapolating from the sunitinib empirical data using the methodology as explained above for the extrapolation of BSC curves.

In sensitivity analysis the sunitinib curve was obtained by application of the hazard ratio to the BSC survival curve. The γ for sunitinib was set to equal γ for BSC, and λ for sunitinib was calculated as λ for BSC multiplied buy the hazard ratio between the two treatments.

7.2.12.2 **Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.**

Using the methods described in section 7.2.12.1 for each treatment the number of patients in each health state at each model cycle. The probabilities of transition between the three health states does depend on time. However, it is not possible to calculate these time dependent transition probabilities because at each time, there are three unknown transition probabilities, but only two independent equations containing these three probabilities. It is unknown whether the number of patients who die in each cycle come from PFS or PD.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

A variety of steps were undertaken to validate and check the model:

- Expert clinical opinion was sought to comment on the:
  - decision problem
  - validate the model structure
  - agree on sensitivity analysis
- Cell by cell verification of the model has also been undertaken
- A new version of the model was built in Excel independently of the original model. Empirical validation was conducted comparing the costs and effects estimated by the validation model to the estimates obtained in the original model. The costs and effect estimates produced but the original model were the same as those produced by the validation model when all parameters were set to those in the original model.

Methods for cell by cell verification

- Both treatments were set to be the same (e.g. sunitinib vs sunitinib) and checked for to ensure there were no differences between final results, and intermediate values/totals.
  - Ensure that all values in every cell of 'Data entry' and 'Parameter' sheets are identical, using a comparison sheet.
  - Ensure differences in totals in 'Data entry' and 'Parameter' sheets are zero
  - Ensure all in differences in CE calculations are zero, and CE ratios are n/a.

This test demonstrates that the two treatment arms have the same logic and calculations, and hence will come to the same results with the same data.

- Check sum of three health states = 1000 at all times
  - Check that the sum of each years patient flow (in 'sunitinib' and 'BSC without X-over' sheets) sum to 1,000

This test ensures that patients are neither entering nor leaving the model – only changing from one state to another.

- Set all sunitinib PFS/OS γ and λ values to equal the PFS/OS γ and λ for BSC
  - Set sunitinib PFS γ and λ to equal the as those for BSC
  - Set sunitinib OS γ and λ to equal the as those for BSC

- Check the numbers of patients in each of the three health states are the same for each treatment

This test demonstrates that differences in patients numbers in each of the three health states between treatments are due to differences in progression free and overall survival.

- Set all utility to 1.00
  - Set all utilities values to 1.00 by overtyping the values in the 'Data entry' sheet.
  - Set outcomes discounting to 0%
  - Check that the number of life years each year is the same as the number of QALYs.

This test demonstrates that all patients alive are being counted in the LYG and QALY calculations.

- Set each of the cost parameters to £0
  - Set the treatment and associated costs for sunitinib and BSC to £0 by overtyping the values in the 'Data entry' sheet.
  - Set outcomes discounting to 0%
  - Check that the total costs for both treatment arms are 0 for every year
  - Check that the total cost (in the results table found on 'Model options & key results' sheet) is £0 for both treatment arms

This test demonstrates that all the costs are derived from the values in the 'Data entry' sheet and that without these (i.e with them set to £0) the cost of each treatment strategy is £0.

7.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves including a representation of the cost-effectiveness acceptability frontier
- scatterplots on cost-effectiveness quadrants
- a tabulation of the mean results (costs, QALYs, ICERs) the probability that the treatment is cost-effectiveness a thresholds of £20,000-£30,000 per QALY gained and the error probability.

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

Table 28 presents the mean estimates of costs and benefits for sunitinib and best supportive care (BSC), and the incremental benefits associated with sunitinib compared to BSC, in patients suitable for second line therapy.

For sunitinib compared to BSC, the incremental life years and QALYs gained are 0.77 and 0.50 respectively, and the incremental cost is £13,699. Table 26 reports the breakdown of the main components of the total cost estimates, with drug costs making up the difference in mean total costs. Time on treatment (in the PFS health

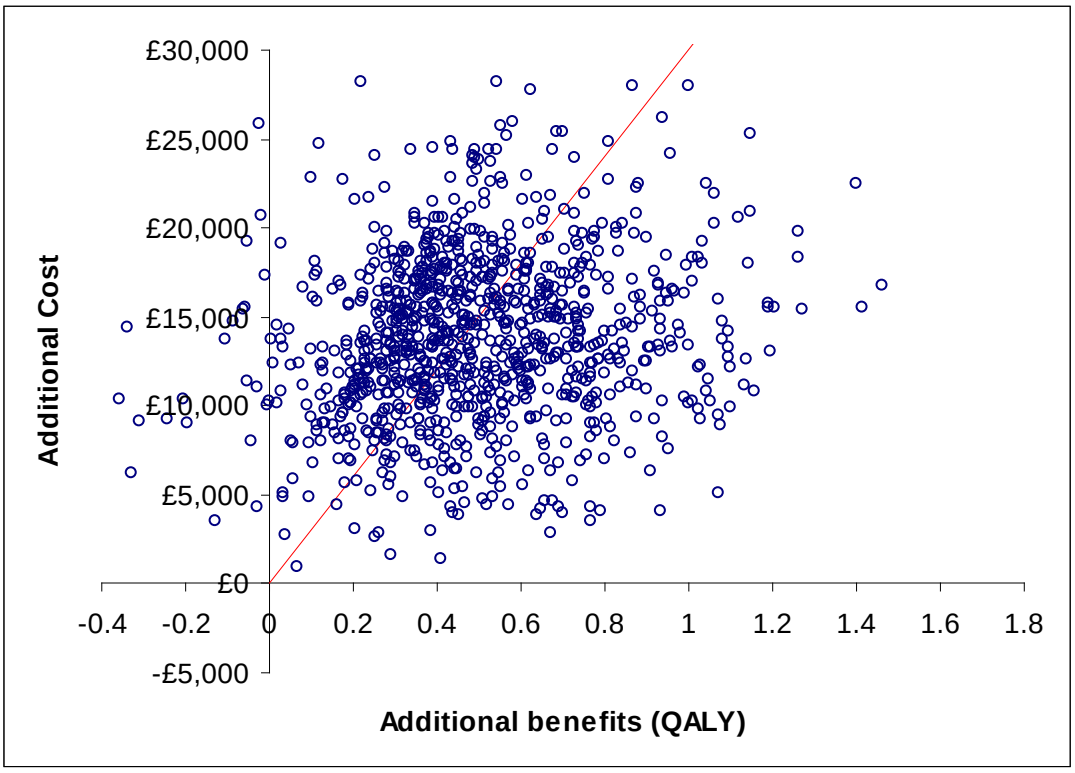
state) for sunitinib is 7.3 months. When compared to BSC sunitinib has an ICER of £17,695 per LYG and £27,365 per QALY gained.

Table 26: Costs, benefits and ICERS of sunitinib compared to BSC

	sunitinib	BSC	sunitinib vs. BSC
Time on treatment (months)	7.3	n/a	7.3
Life years	1.98	1.21	0.77
QALYs	1.23	0.73	0.50
Drug cost	£12,391	£0	£12,391
Monitoring	£799	£249	£551
Blood tests	£22	£7	£15
CT scans	£336	£105	£232
AEs	£11	£0	£11
BSC in PD	£2,692	£1,985	£708
Death	£3,515	£3,724	-£208
Total costs	£19,767	£6,315	£13,699
ICERs			
Cost/LYG			£17,695
Cost/QALY			£27,365

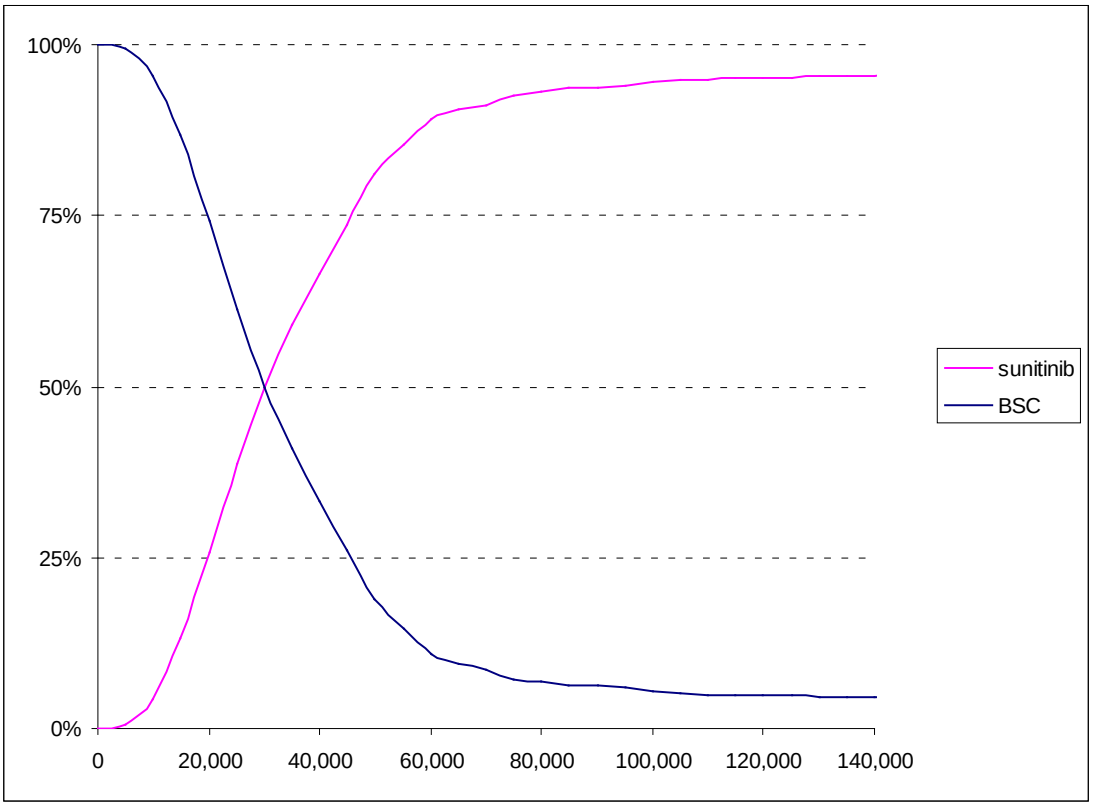
PSA analysis was conducted using 1000 iterations, the results of which can be seen below (figure 15). The scatter plot data demonstrates that the majority of simulation resulted in additional costs and benefits for sunitinib over BSC (the top right quadrant), This suggests that there is only a small probability of sunitinib having a worse outcome than BSC (top and bottom left hand quadrants of the CE plane).

Figure 15: Incremental costs and outcomes per 1,000 patients sunitinib compared to BSC



The cost effectiveness acceptability curves (CEAC) show the likelihood of sunitinib being cost effective compared to BSC when considered across a range of thresholds for the cost per QALY. Below (figure 16) is the CEAC for the incremental cost per QALY per for sunitinib compared to BSC. The CEAC plots shows that sunitinib has a 50% likelihood of having a cost per QALY value below £30,000.

Figure 16: Cost-effectiveness acceptability curve



7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

Subgroup analyses were not undertaken within the health economic analysis.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

The results of the deterministic sensitivity analyses are presented below in table 27.

Table 27: Sensitivity analysis: sunitinib vs BSC

	Base case	Sensitivity analysis	ICER Sunitinib vs BSC
Base case	n/a	n/a	£27,365
General			
Time horizon	6 years	1 year 10 years	£59,002 £26,483
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£26,425

		6% p.a. costs and benefits	£28,021
Cost Cost associated with death	£3,923	£0	£27,781
Cost for BSC to include imatinib 400mg daily (per 6 week cycle)	£224 for BSC in PFS £224 for BSC in PD	£1,796 for BSC in PFS £1,796 for BSC in PD	£32,234
Costs for BSC using PenTAG mRCC assumption	£224 for both treatments and both health states	£81 for BSC in PFS £224 for sunitinib in PFS £435 for BSC in PD for both treatments	£29,033
Cost of monitoring, outpatient costs (per 6 week cycle)	£155 sunitinib, £155 BSC	£0 for both treatments £310 for both treatments	£26,265 £28,466
AE cost	£11 sunitinib £0 BSC	£0 both treatments	£27,365
Dose intensity	97% sunitinib	100% sunitinib	£30,550
Effectiveness Survival curves for PFS and OS	Sunitinib curve extrapolated independently	Sunitinib PFS curve extrapolated using hazard ratio	£19,434
		Sunitinib OS curve extrapolated using hazard ratio	£22,003
		Sunitinib PFS and OS curves extrapolated using hazard ratio	£15,536
Baseline progression data: statistical data used BSC overall survival	RPSFT method used to account for cross-over	KM data used with cross-over patients included (Final ITT)	£34,649
Health state utilities Utility estimates for PFS	0.73 sunitinib 0.78 BSC	0.73 for both treatments 0.78 for both treatments	£26,868 £25,830

7.3.3.2 What are the key drivers of the cost effectiveness results?

The results shown in Table 27 suggest that the incremental cost effectiveness of sunitinib is stable to changes in most of the model parameters. Within the sensitivity analysis, the incremental cost effectiveness of sunitinib compared to BSC ranged from approximately £15,536 to £59,002 per QALY gained. The key determinants of cost effectiveness for this comparison concern the statistical data used for the BSC overall survival curve; assumptions concerning the method used to extrapolate the PFS and OS curves for sunitinib; and the time horizon selected for the analysis.

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this

evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Only two published economic evaluations were identified that reported on the cost-effectiveness of sunitinib as a second-line therapy for the treatment of GIST. In both publications sunitinib was shown to result in an increase in survival but at an increased cost, which is consistent with our findings. However, the effectiveness data used in both of these evaluations was based upon the interim data and not the final trial results. In addition, the Mexican study had collated resource use data from within a Mexican hospital. Consequently it is difficult to drawn more meaningful comparisons between these evaluations and the current appraisal.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation is based on the efficacy data from the A6181004 study. The licence for sunitinib reflects the population of patients eligible for the A6181004 trial and therefore the economic evaluation based on this trial data is broadly representative of those patients who could use the technology.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The key strengths and weaknesses of the economic analysis of sunitinib compared to BSC is presented below.

Key strengths

- The scope of the economic analysis is comprehensive and includes all relevant treatment options
- The structure of the model is clinically appropriate and makes the most of the available data from the A6181004 study
- Data for this intervention is scares with only one phase III trial used to support its use in this setting. Consequently, attention has been placed to fitting the most appropriate survival curves to best extrapolate the available data
- The use of EQ-5D utilities valued using the tariffs reported by Dolan (Dolan 1997) is consistent with NICE's reference case
- The sensitivity analysis is comprehensive in scope and allows for all uncertainty surrounding the incremental cost-effectiveness of sunitinib

Key weaknesses

- The model does not capture the disutility associated with adverse events as utility decrements relating to specific adverse events were not available from the A6181004 trial. The inclusion of such effects would require numerous assumptions concerning the durations for which the patient experiences the adverse events, and the independence of interdependence of events. Further assumptions would be required concerning the multiplicative or additive impact of such events. These events are potentially already captured within the sunitinib pre-progression utility estimate, further inclusion would therefore lead to a downward biasing of resulting utility estimates due to double counting
- There may be potential difference between trial and clinical practice dosages, if sunitinib dose reduction is more prevalent in clinical practice than in clinical trials then the achievable survival outcomes at the license dose could be lower than those supported in trial protocol context

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The sensitivity analyses presented within this submission is broad in scope and covers all key areas of uncertainty. As is always the case, conducting further clinical trials (particularly in subgroups) and collecting/evaluating real work data would provide information that could be used in future economic evaluations that may results in changes in the magnitude of the effects seen in the current evaluation.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The per patient annual costs for sunitinib and BSC were calculated using the cost effectiveness model described in Section 7. These costs were then multiplied by the number or patients assumed to receive sunitinib or BSC in England and Wales to given an overall estimate of the budget impact (see Table 28)

Table 28: Projected total costs of treating unresectable and/or metastatic malignant GIST refractory to imatinib.

Patients treated with sunitinib					
Year of diagnosis	**2009**	**2010**	**2011**	**2012**	**2013**
2009	£346,692	£73,711	£26,894	£9,178	£3,064
2010		£1,160,364	£246,514	£89,943	£30,696
2011			£1,166,258	£247,342	£90,245
2012				£1,168,155	£248,169
2013					£1,171,984
Total undiscounted	£346,962	£1,234,075	£1,437,667	£1,514,618	£1,544,158
Total discounted	£346,733	£1,232,443	£1,434,816	£1,513,616	£1,540,077
Patients treated with BSC					
Year of diagnosis	**2009**	**2010**	**2011**	**2012**	**2013**
2009	£99,766	£16,889	£5,647	£1,611	£442
2010		£333,651	£56,484	£18,884	£5,386
2011			£334,771	£56,673	£18,948
2012				£335,891	£56,863
2013					£336,992
Total undiscounted	£99,766	£350,540	£62,130	£413,059	£418,631
Total discounted	£99,700	£350,077	£62,007	£411,968	£417,525

The estimated budget impact for the NHS in England and Wales is projected to be £247,033 in 2009 rising to £1,122,553 in 2013 (see Table 29).

Table 29: Estimated net budget impact of introducing sunitinib

	2009	**2010**	**2011**	**2012**	**2013**
Net budget impact undiscounted	£247,197	£883,534	£1,375,536	£1,101,559	£1,125,527
Net budget impact discounted	£247,033	£882,366	£1,372,809	£1,101,649	£1,122,553

8.2 What number of patients were assumed to be eligible? How was this figure derived?

Estimating the number of patients eligible for treatment with sunitinib involves identifying the following:

1) the English and Welsh population with diagnosed GIST
2) the incidence of GIST
3) population with GIST who have unresectable and/or metastatic GIST
4) the number of patients treated with imatinib that have primary resistance

5) the number of patients treated with imatinib that develop a reduced response

The English and Welsh population estimates by five-year age groups and gender between 2006 and 2014 (Government Actuary's Department) were combined to give a total an estimate of the total population for England and Wales.

The estimates of the annual incidence of GIST of 15 per million was based upon figures from the manufacturers of imatinib (quoted in final scope for this appraisal). It is reported that between 10 to 30% of GIST are malignant (Bucher, 2004) and require targeted therapy with imatinib. The figure of 30% has been used within this budget impact analysis.

Of the number of patients treated with imatinib approximately 21% of patients were assumed to experience primary resistance and 30% were assumed to develop a reduced response. Using these figures the maximum eligible patient population for sunitinib is 109 in 2009 rising to 110 in 2013 as shown in table 30.

Table 30: Patients eligible for sunitinib in England and Wales.

	2009	2010	2011	2012	2013
Population of England and Wales	54,259,858	54,443,768	54,627,820	54,808,039	54,981,418
Number of patients with GIST	814	817	819	822	825
Number of patients with metastatic and/or unresectable GIST	244	245	246	247	247
Number of patients with primary resistance	51	51	52	52	52
Number of patients developing a reduced response to imatinib	57	58	58	58	58
Number of patients eligible for sunitinib	109	109	109	110	110

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

The proportions of patients receiving imatinib and then consequently experiencing primary resistance and reduced response were based upon the figures supplied by the manufacturers of imatinib quoted within the final scope for this appraisal. The maximum numbers of patients quoted in the final scoping document as being treated with imatinib was 240 people per year. The number of patients quoted as experiencing primary resistance (approx 50) and developing a reduced response (60-100) were then converted into percentages, 21% and 30% respectively. These percentages were then used to project future uptake of imatinib.
The budget impact analysis has used the upper estimates of reduced response and assumes a that patients experience a reduced response after two years of imatinib treatment.

8.4 What assumption(s) were made about market share (where relevant)?

It is assumed that the market share for 2009 will be 24% and will remain at 80% for the years 2010-2013.

Two factors account for the relatively low second line market share projection for 2009. Primarily, access to funding for the majority of the year will preclude most eligible patients from having access to the drug. Secondly, advice from clinical experts suggests that in practice a significant group of eligible patients will receive 800mg imatinib as second line therapy and will then not go on to receive further lines of treatment.

Assuming a positive decision by NICE, we project an 80% second line market share for GIST in the following years. Expert clinical opinion suggests that the Sunitinib penetration wouldn't be absolute due to patient willingness to receive further lines of therapy, physician reluctance to prescribe drug to those with poor performance status and the inability of some patients to tolerate Sunitinib.

8.5 What unit costs were assumed? How were these calculated?

The budget impact model includes estimates of lifetime costs for sunitinib and BSC included in the cost effectiveness model. A detailed description of the cost components and calculations used to estimate each one is presented in Section 7. The price of sunitinib assumed for the budget impact modelling is that used in the economic modelling.

The expected cost per patient, as shown in table 31, was calculated by combining the cost for each cycle with the probability of being alive during that cycle and summed over each year. The decreasing cost for each subsequent year reflects the decreasing probability that patients are alive as time passes. The number of patients in each year were combined with the expected cost for each year to calculate the total direct costs of treatment for the two treatment options. Costs were discounted at a 3.5 % annual rate.

Table 31: Expected direct costs per patient

	Year 1	Year 2	Year 3	Year 4	Year 5
sunitinib	£13,279	£3,749	£1,847	£905	£441
BSC	£3,815	£1,234	£680	£331	£152

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Sunitinib is administered orally and therefore does not requires hospital day case or outpatient administration costs.

The use of resources is dependent on treatment duration which is determined by time to disease progression or death. Both the cost effectiveness model and the budget impact analysis include cost adjustments to account for reductions in doses, this is handled using relative dose intensity from study A6181004. Costs associated with adverse events (irrespective of treatment) are included in both the cost effectiveness model and the budget impact analysis.

8.7 Were there any estimates of resource savings? If so, what were they?

The introduction of sunitinib is not estimated to provide any resource savings.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The introduction of sunitinib is not estimated to provide any resources savings.

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10 Appendices

10.1 Appendix 1

Summary of Product Characteristics or Technical Manual or drafts

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUTENT® 12.5 mg hard capsules

SUTENT® 25 mg hard capsules

SUTENT® 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUTENT® 12.5 mg hard capsules
Each capsule contains sunitinib malate, equivalent to 12.5 mg of sunitinib.
Excipient(s): 80.0 mg of mannitol

SUTENT® 25 mg hard capsules
Each capsule contains sunitinib malate, equivalent to 25.0 mg of sunitinib
Excipient(s): 39.663 mg of mannitol.

SUTENT® 50 mg hard capsules
Each capsule contains sunitinib malate equivalent to 50 mg of sunitinib
Excipient(s): 79.326 mg of mannitol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SUTENT® 12.5 mg
Hard capsules.
Gelatin capsules with orange cap and orange body, printed with white ink “Pfizer” on the cap, “STN 12.5 mg” on the body, and containing yellow to orange granules.

SUTENT® 25 mg
Hard Capsules
Gelatin capsule with caramel cap and orange body, printed with white ink “Pfizer” on the cap and “STN 25 mg ” on the body and containing yellow to orange granules.

SUTENT® 50 mg
Hard capsules
Gelatin capsules with caramel cap and caramel body, printed with white ink “Pfizer” on the cap and “STN 50 mg” on the body and containing yellow to orange granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the treatment of renal cell carcinoma or GIST.

The recommended dose of SUTENT is one 50 mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Dose adjustments

Safety and Tolerability

Dose modifications in 12.5-mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg nor be decreased below 25 mg.

CYP3A4 Inhibitors/Inducers

Co-administration of potent CYP3A4 inducers such as rifampin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg increments (up to 87.5 mg per day) based on careful monitoring of tolerability.

Co-administration of SUTENT with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible the doses of SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability.

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

Paediatric use**:** The safety and efficacy of SUTENT in paediatric patients have not been established.

SUTENT should not be used in paediatric population until further data become available.

Elderly patients use: 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.

Hepatic Insufficiency: No dose adjustment is recommended 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 Child-Pugh Class C hepatic impairment (see section 5.2).

Renal Insufficiency: No clinical studies have been performed in patients with impaired renal function.(see section 5.2).

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.

4.3 Contraindications

Hypersensitivity to sunitinib malate or to any of the excipients.

4.4 Special warnings and precautions for use

Co-administration of potent CYP3A4 inducers such as rifampin, may **decrease** sunitinib plasma concentrations. Combination with inducers should therefore be avoided. If this is not possible, the dosage of SUTENT may need to be increased (see sections 4.2 and 4.5)

Co-administration of strong CYP3A4 inhibitor such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If this is not possible, the dosage of SUTENT may need to be reduced (see sections 4.2 and 4.5).

*Skin and tissue*s
Skin discolouration, possibly due to the active substance colour (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.
Mouth pain/irritation was reported in approximately 14% of patients. Dysgeusia (taste disturbance) was reported in approximately 28% of patients.
The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Haemorrhage
Haemorrhagic events, some of which were fatal, reported through post-marketing experience, 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 on 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 SUTENT in a phase 3 GIST Study compared to 17% of patients receiving placebo. In patients receiving SUTENT for treatment-naïve MRCC, 28% had bleeding events compared to 7% of patients receiving IFN- α. Seven (1.9%) patients on sunitinib malate versus 0% of patients on IFN-α experienced Grade 3 or greater treatment-related bleeding events. Of patients receiving sunitinib malate for cytokine-refractory MRCC, 26% experienced bleeding. Routine assessment of this event should include complete blood counts and physical examination.
Epistaxis was the most common treatment-related haemorrhagic adverse event, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. Some of these events were severe, but very rarely fatal.

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. Treatment-related fatal gastrointestinal bleeding occurred in 0.5% of patients receiving placebo in the GIST Phase 3 study.

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 were 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 malate for treatment-naïve MRCC compared to 1% of patients receiving IFN-α. Severe hypertension occurred in 5% of treatment-naïve patients on sunitinib malate and 1% of patients on IFN-α. 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.

Haematological
Decreased absolute neutrophil counts of grade 3 and 4 severity were reported in 13.1% and 0.9% patients, respectively. Decreased platelet counts of grade 3 and 4 severity were reported in 4% and 0.5% patients respectively. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Cardiovascular
Cardiovascular events, some of which were fatal, reported through post-marketing experience, have included left ventricular ejection fraction (LVEF) decrease and cardiac failure. In clinical trials, decreases in LVEF of $\geq$ 20% and below the lower limit of normal occurred in approximately 2% of SUTENT-treated GIST patients, 4% of cytokine-refractory MRCC patients, 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% patients on SUTENT and 12% of patients on interferon-α (IFN-α), had an LVEF value below the lower limit of normal. One (<1%) patient who received SUTENT was diagnosed with congestive heart failure (CHF).
Treatment-related adverse events of 'cardiac failure', 'cardiac failure congestive' or 'left ventricular failure' were reported in 0.7% of patients with solid tumours and 1% of patients treated with placebo. All patients had GIST. In the phase 3 GIST study (n=312), treatment-related fatal cardiac events occurred in 1% of patients on each arm of the study (i.e. SUTENT and placebo arms). In a phase II 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 SUTENT arm experienced fatal cardiac events. 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 ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies.
Close monitoring for clinical signs and symptoms of CHF should be performed, especially in patients with cardiac risk factors and/or history of coronary artery disease.
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
Data from non-clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process (e.g. prolongation of QT interval).
Increases in the QTc interval to over 500 msec occurred in 0.5% and changes from baseline in excess of 60 msec occurred in 1.1% of the 450 solid tumours patients; both these parameters are recognized as potentially significant changes. At approximately twice therapeutic concentrations, SUTENT has been shown to prolong the QTcF Inteval (Frederica's Correction).

QT interval prolongation was investigated in a trial in 24 patients, aged 20-87 years, with advanced malignancies. The results of this study demonstrated that sunitinib had an effect on QTc (defined as a mean placebo-adjusted change of > 10 msec with a 90% CI upper limit > 15 msec) at therapeutic concentration (day 3) using the within-day baseline correction method, and at greater than therapeutic concentration (Day 9) using both baseline correction methods. No patients had a QTc value >500 msec. Although an effect on QTcF was observed on Day 3 at 24 hours post-dose (i.e. at therapeutic plasma concentration expected after the recommended starting dose of 50 mg) with the within-day baseline correction method, the clinical significance of this finding is unclear.
Using comprehensive serial ECG assessments at times corresponding to either therapeutic or greater than therapeutic exposures, none of the patients in the evaluable or ITT populations were observed to develop QTc prolongation considered as “severe” (i.e. equal to or greater than Grade 3 by CTCAE version 3.0).

At therapeutic plasma concentrations, the maximum QTcF (Frederica’s correction) mean change from baseline was 9.6 msec (90% CI 15.1msec). At approximately twice therapeutic concentrations, the maximum QTcF change from baseline was 15.4 msec (90% CI 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF change from baseline. No subjects experienced an effect on the QTc inteval greater than Grade 2 (CTCAE version 3.0). No patient presented with a cardiac arrhythmia.

QT interval prolongation may lead to an increased risk of ventricular arrhythmias including *Torsade de pointes*. *Torsade de pointes* has been observed in <0.1% of SUTENT-exposed patients. SUTENT should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of SUTENT reduced (see Section 4.2 and 4.5).

Venous Thromboembolic Events
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 (2%) patients receiving SUTENT for treatment-naïve MRCC and four patients (2%) on the two cytokine-refractory MRCC studies had venous thromboembolic events reported. Six of these patients had pulmonary embolism, one was Grade 3 and five were Grade 4, and five patients had DVT, one each with Grade 1 and 2, and three with Grade 3. Dose interruption occurred in one.
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 embolism, one Grade 1 and four with Grade 4.

Pulmonary Events
Treatment-related pulmonary embolism was reported in approximately 1.1% patients with solid tumours who received SUTENT. None of these events resulted in a patient discontinuing treatment with SUTENT; however a dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these patients after treatment was resumed.

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.

Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two cytokine-refractory MRCC studies in nine patients (2%) on SUTENT and one patient (<1%) in the IFN-α arm in the treatment-naïve MRCC study. Additionally, TSH elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT *versus* 1 (1%) on placebo.
Rare cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Pancreatitis
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received SUTENT. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours. Pancreatitis has been observed rarely (<1%) in patients receiving SUTENT for GIST or MRCC.
Cases of serious pancreatic events, some with fatal outcome, have been reported. If symptoms of pancreatitis are present, patients should have SUTENT discontinued and be provided with appropriate supportive care.

Hepatic Function
Serious cases of SUTENT-related hepatobiliary events have been reported in patients with solid tumours; hepatic failure was observed in <1% of these patients. Cases of hepatobiliary events some with fatal outcome, have been reported. If signs or symptoms of hepatic failure are present, SUTENT should be discontinued and appropriate supportive care should be provided.

Seizures
In clinical studies of SUTENT and from post-marketing experience, seizures have been observed in subjects with or without 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). 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.

4.5 Interaction with other medicinal products and other forms of interaction

*Drugs that may **increase** sunitinib plasma concentrations.*
Concomitant administration of sunitinib malate with the potent CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers.
Administration of SUTENT with potent inhibitors of the CYP3A4 family (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations
Combination with inhibitors should therefore be avoided, or the selection of an alternate concomitant medication with no, or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dosage of SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability (see section 4.2)

*Drugs that may **decrease** sunitinib plasma concentrations:*
Concomitant use of SUTENT with the CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers.
Administration of SUTENT with potent inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* known also as

St. John's Wort) may decrease sunitinib concentrations. Combination with inducers should therefore be avoided, or selection of an alternate concomitant medication with no, or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of SUTENT may need to be increased in 12.5 mg increments (up to 87.5 mg per day) based on careful monitoring of tolerability (see section 4.2).
To maintain sunitinib target concentrations, selection of co-medications with less enzyme induction potential, should be considered. If this is not possible, dose-adjustments of SUTENT may be necessary (see section 4.2).

Haemorrhage has been observed rarely in patients treated with SUTENT (see section 4.4). Patients receiving concomitant treatment with anti-coagulants (e.g. warfarin; acenocumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR), and physical examination

4.6 Pregnancy and lactation

PREGNANCY

There are no studies in pregnant women using SUTENT. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus.
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Based on non-clinical findings, male and female fertility may be compromised by treatment with SUTENT (see section 5.3)

Lactation
Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breast feed while taking SUTENT.

4.7 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 dizziness during treatment with SUTENT.

4.8 Undesirable effects

The most important treatment-related serious adverse events associated with SUTENT treatment of patients with solid tumours were pulmonary embolism (1%), thrombocytopoenia (1%), tumour haemorrhage (0.9%), febrile neutropoenia (0.4%), and hypertension (0.4%). The most common treatment-related adverse events (experienced by at least 20% of the patients) of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; dysgeusia and anorexia. Fatigue, hypertension and neutropoenia were the most common treatment-related adverse events of Grade 3 maximum severity and increased lipase was the most frequently occurring treatment-related adverse event of Grade 4 maximum severity in patients with solid tumours. Hepatitis and hepatic failure occurred in <1% of patients and prolonged QT interval in < 0.1% (see section 4.4).

Fatal events other than those listed in section 4.4 above or section 4.8 below that were considered possibly related to SUTENT included multi-system organ failure, disseminated intravascular coagulation, peritonoeal haemorrhage, rhabdomyolysis, cerebrovascular accident, dehydration, adrenal insufficiency, renal failure, respiratory failure, pleural effusion, pneumothorax, shock, and sudden death.

Treatment-related adverse reactions that were reported in >2% of solid tumour patients are listed below, by system organ class, frequency and grade of severity. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequencies are defined as: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to <1//100), rare (≥1/10,000 to 1/1,000), very rare (< 1/10,000).

Treatment-Related Adverse Reactions reported in GIST studies

System Organ Class	*Frequency*	*Adverse Reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Blood and the lymphatic system disorders	Very common	Anaemia	86 (19.5%)	24 (5.5%)	3 (0.7%)
	Very common	Neutropoenia	81 (18.4%)	39 (8.9%)	5 (1.1%)
	Very common	Thrombocytopoenia	67 (15.2%)	19 (4.3%)	6 (1.4%)
	Common	Leukopoenia	26 (5.9%)	9 (2.0%)	1 (0.2%)
	Common	Lymphopoenia	10 (2.3%)	3 (0.7%)	1 (0.2%)
Endocrine disorders	Very common	Hypothyroidism	59 (13.4%)	5 (1.1%)	1 (0.2%)
Metabolism and nutrition disorders	Very common	Decreased appetite[a]	117 (26.6%)	8 (1.8%)	0 (0.0%)
Nervous system disorders	Very common	Taste disturbance[b]	105 (23.9%)	1 (0.2%)	0 (0.0%)
	Very common	Headache	76 (17.3%)	5 (1.1%)	0 (0.0%)
	Common	Paraesthesia	27 (6.1%)	1 (0.2%)	0 (0.0%)
	Common	Dizziness	18 (4.1%)	1 (0.2%)	0 (0.0%)
	Common	Neuropathy peripheral	11 (2.5%)	0 (0.0%)	0 (0.0%)
	Common	Hypoaesthesia	10 (2.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	101 (23.0%)	43 (9.8%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	28 (6.4%)	1 (0.2%)	0 (0.0%)
	Common	Dyspnoea	16 (3.6%)	2 (0.5%)	0 (0.0%)
Renal and urinary disorders	Common	Chromaturia	18 (4.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	187 (42.5%)	24 (5.5%)	0 (0.0%)
	Very common	Nausea	161 (36.6%)	15 (3.4%)	0 (0.0%)
	Very common	Vomiting	98 (22.2%)	7 (1.6%)	0 (0.0%)
	Very common	Stomatitis	90 (20.5%)	7 (1.6%)	0 (0.0%)
	Very common	Dyspepsia	80 (18.2%)	4 (0.9%)	0 (0.0%)
	Very common	Abdominal pain[c] / distension	77 (17.5%)	15 (3.4%)	2 (0.5%)
	Very common	Flatulence	46 (10.5%)	0 (0.0%)	0 (0.0%)
	Very common	Oral pain	44 (10.0%)	2 (0.5%)	0 (0.0%)
	Common	Constipation	37 (8.4%)	2 (0.5%)	0 (0.0%)
	Common	Glossodynia	37 (8.4%)	0 (0.0%)	0 (0.0%)
	Common	Dry mouth	31 (7.0%)	0 (0.0%)	0 (0.0%)
	Common	Gastro-oesophageal reflux disease	12 (2.7%)	1 (0.2%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse Reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Common	Mouth ulceration	11 (2.5%)	0 (0.0%)	0 (0.0%)
	Common	Oral discomfort	11 (2.5%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Yellow skin/ Skin discolouration	146 (33.2%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	106 (24.1%)	27 (6.1%)	0 (0.0%)
	Very common	Hair colour changes	67 (15.2%)	0 (0.0%)	0 (0.0%)
	Very common	Rash	64 (14.5%)	3 (0.7%)	0 (0.0%)
	Common	Dry skin	41 (9.3%)	0 (0.0%)	0 (0.0%)
	Common	Alopecia	33 (7.5%)	0 (0.0%)	0 (0.0%)
	Common	Dermatitis	29 (6.6%)	1 (0.2%)	0 (0.0%)
	Common	Periorbital oedema	20 (4.5%)	0 (0.0%)	0 (0.0%)
	Common	Skin Reaction	20 (4.5%)	3 (0.7%)	0 (0.0%)
	Common	Erythema	18 (4.1%)	0 (0.0%)	0 (0.0%)
	Common	Eczema	16 (3.6%)	1 (0.2%)	0 (0.0%)
	Common	Pruritus	16 (3.6%)	0 (0.0%)	0 (0.0%)
	Common	Skin hyperpigmentation	15 (3.4%)	0 (0.0%)	0 (0.0%)
	Common	Skin exfoliation	12 (2.7%)	0 (0.0%)	0 (0.0%)
	Common	Blister	10 (2.3%)	1 (0.2%)	0 (0.0%)
	Common	Skin lesion	10 (2.3%)	1 (0.2%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Very Common	Pain in extremity/limb	54 (12.3%)	5 (1.1%)	0 (0.0%)
	Common	Arthralgia	39 (8.9%)	3 (0.7%)	0 (0.0%)
	Common	Myalgia	29 (6.6%)	0 (0.0%)	0 (0.0%)
	Common	Muscle spasm	21 (4.8%)	1 (0.2%)	0 (0.0%)
	Common	Back pain	11 (2.5%)	2 (0.5%)	0 (0.0%)
	Common	Muscular weakness	10 (2.3%)	1 (0.2%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	287 (65.2%)	64 (14.5%)	5 (1.1%)
	Very common	Mucosal inflammation	70 (15.9%)	6 (1.4%)	1 (0.2%)
	Very common	Oedema[d]	59 (13.4%)	1 (0.2%)	0 (0.0%)
	Common	Pyrexia	26 (5.9%)	2 (0.5%)	0 (0.0%)
Psychiatric disorders	Common	Insomnia	14 (3.2%)	0 (0.0%)	0 (0.0%)
Investigations	Common	Lipase increase	35 (8.0%)	12 (2.7%)	7 (1.6%)
	Common	White blood cell count decreased[e]	33 (7.5%)	15 (3.4%)	0 (0.0%)
	Common	Ejection fraction decreased	27 (6.1%)	5 (1.2%)	0 (0.0%)
	Common	Haemoglobin decreased	27 (6.1%)	6 (1.4%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	22 (5.0%)	1 (0.2%)	1 (0.2%)
	Common	Platelet count decrease	25 (5.7%)	4 (0.9%)	1 (0.2%)
	Common	Weight decreased	23 (5.2%)	1 (0.2%)	0 (0.0%)
	Common	Amylase increased	21 (4.8%)	8 (1.8%)	0 (0.0%)
	Common	Aspartate aminotransferase increased	18 (4.1%)	2 (0.5%)	1 (0.2%)
	Common	Alanine aminotransferase	12 (2.7%)	1 (0.2%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse Reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
		increased			
		Any adverse event	414 (94.1%)	204 (46.4%)	53 (12.0%)

The following terms have been combined:

[a] Anorexia and decreased appetite

[b] Dysgeusia, ageusia and taste disturbance

[c] Abdominal pain and abdominal pain upper

[d] Oedema, oedema peripheral and oedema face

[e] White blood cell count decreased, neutrophil count decreased, and leukocyte count decreased

Treatment-Related Adverse Reactions reported in cytokine-refractory and treatment-naïve MRCC studies

System Organ Class	*Frequency*	*Adverse Reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Blood and lymphatic system disorders	Very common	Neutropoenia	89 (16.4%)	46 (8.5%)	5 (0.9%)
	Very common	Thrombocytopoenia	86 (15.8%)	37 (6.8%)	5 (0.9%)
	Very common	Anaemia	67 (12.3%)	20 (3.7%)	3 (0.6%)
	Common	Leukopoenia	45 (8.3%)	16 (2.9%)	0 (0%)
	Common	Lymphopenia	21 (3.9%)	12 (2.2%)	1 (0.2%)
Endocrine disorders	Very common	Hypothyroidism	67 (12.3%)	7 (1.3%)	0 (0%)
Eye disorders	Common	Lacrimation increased	39 (7.2%)	0 (0%)	0 (0%)
	Common	Eyelid oedema	12 (2.2%)	0 (0%)	0 (0%)
Metabolism and nutrition disorders	Common	Decreased appetite [a]	205 (37.7%)	9 (1.7%)	0 (0%)
	Common	Dehydration	33 (6.1%)	7 (1.3%)	1 (0.2%)
Nervous system disorders	Very common	Taste disturbance [b]	250 (46.0%)	1 (0.2%)	0 (0%)
	Very common	Headache	82 (15.1%)	3 (0.6%)	0 (0%)
	Common	Dizziness	38 (7.0%)	2 (0.4%)	0 (0%)
	Common	Paraesthesia	36 (5.9%)	0 (0%)	0 (0%)
	Common	Neuropathy peripheral	33 (6.1%)	1 (0.2%)	0 (0%)
	Common	Hypoaesthesia	20 (3.7%)	0 (0%)	0 (0%)
	Common	Hyperaesthesia	17 (3.1%)	0 (0%)	0 (0%)
Vascular disorders	Very common	Hypertension	143 (26.3%)	55 (10.1%)	0 (0%)
	Common	Flushing	17 (3.1%)	0 (0%)	0 (0%)
	Common	Hot flush	12 (2.2%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis	86 (15.8%)	3 (0.6%)	0 (0%)
	Common	Dyspnoea	45 (8.3%)	6 (1.1%)	0 (0%)
	Common	Pharyngolaryngeal pain	29 (5.3%)	2 (0.4%)	0 (0%)
	Common	Cough	23 (4.2%)	0 (0%)	0 (0%)
	Common	Dysphonia	16 (2.9%)	0 (0%)	0 (0%)

System Organ Class	*Frequency*	*Adverse Reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Common	Nasal dryness	14 (2.6%)	0 (0%)	0 (0%)
	Common	Dyspnoea exertional	12 (2.2%)	0 (0%)	0 (0%)
	Common	Nasal congestion	12 (2.2%)	0 (0%)	0 (0%)
	Common	Pleural effusion	12 (2.2%)	3 (0.6%)	0 (0%)
Gastrointestinal disorders	Very common	Diarrhoea	326 (59.9%)	38 (7.0%)	0 (0%)
	Very common	Nausea	290 (53.3%)	19 (3.5%)	0 (0%)
	Very common	Dyspepsia	189 (34.7%)	8 (1.5%)	0 (0%)
	Very common	Stomatitis	185 (34.0%)	13 (2.4%)	0 (0%)
	Very common	Vomiting	178 (32.7%)	17 (3.1%)	0 (0%)
	Very common	Abdominal pain [c] / distension	106 (19.5%)	10 (1.8%)	0 (0%)
	Very common	Constipation	83 (15.3%)	1 (0.2%)	0 (0%)
	Very common	Glossodynia	63 (11.6%)	0 (0%)	0 (0%)
	Very common	Flatulence	60 (11.0%)	0 (0%)	0 (0%)
	Very common	Oral pain	60 (11.0%)	2 (0.4%)	0 (0%)
	Very common	Dry mouth	56 (10.3%)	0 (0%)	0 (0%)
	Common	Gastroesophageal reflux disease	50 (9.2%)	2 (0.4%)	0 (0%)
	Common	Dysphagia	20 (3.7%)	2 (0.4%)	1 (0.2%)
	Common	Cheilitis	19 (3.5%)	1 (0.2%)	1 (0.2%)
	Common	Gingival bleeding	18 (3.3%)	0 (0%)	0 (0%)
	Common	Haemorrhoids	18 (3.3%)	0 (0%)	0 (0%)
	Common	Proctalgia	17 (3.1%)	1 (0.2%)	0 (0%)
	Common	Mouth ulceration	16 (2.9%)	0 (0%)	1 (0.2%)
	Common	Stomach discomfort	15 (2.8%)	0 (0%)	0 (0%)
	Common	Rectal haemorrhage	13 (2.4%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	Very common	Palmar-plantar erythrodysaesthesia syndrome	144 (26.5%)	46 (8.5%)	0 (0%)
	Very common	Yellow discolouration/ Skin discolouration	144 (26.5%)	1 (0.2%)	0 (0%)
	Very common	Rash	121 (22.2%)	2 (0.4%)	1 (0.2%)
	Very common	Dry skin	108 (19.9%)	1 (0.2%)	0 (0%)
	Very common	Hair colour changes	103 (18.9%)	0 (0%)	0 (0%)
	Very common	Alopecia	64 (11.8%)	0 (0%)	0 (0%)
	Common	Erythema	51 (9.4%)	2 (0.4%)	0 (0%)
	Common	Skin exfoliation	47 (8.6%)	4 (0.7%)	0 (0%)
	Common	Pruritus	40 (7.4%)	1 (0.2%)	0 (0%)
	Common	Periorbital oedema	31 (5.7%)	1 (0.2%)	0 (0%)
	Common	Dermatitis	27 (5.0%)	4 (0.7%)	0 (0%)
	Common	Skin lesion	26 (4.8%)	1 (0.2%)	0 (0%)
	Common	Nail disorder/ discolouration	25 (4.6%)	0 (0%)	0 (0%)
	Common	Blister	23 (4.2%)	1 (0.2%)	0 (0%)
	Common	Skin reaction	23 (4.2%)	6 (1.1%)	0 (0%)
	Common	Hyperkeratosis	22 (4.0%)	4 (0.7%)	0 (0%)
	Common	Acne	19 (3.5%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity	96 (17.6%)	6 (1.1%)	0 (0%)
	Common	Arthralgia	49 (9.0%)	1 (0.2%)	0 (0%)
	Common	Myalgia	48 (8.8%)	2 (0.4%)	0 (0%)
	Common	Muscle Spasm	26 (4.8%)	0 (0%)	0 (0%)
	Common	Back pain	17 (3.1%)	2 (0.4%)	0 (0%)

System Organ Class	*Frequency*	*Adverse Reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
General disorders and administration site conditions	Very common	Fatigue/asthenia	397 (73.0%)	95 (17.5%)	1 (0.2%)
	Very common	Mucosal inflammation	127 (23.3%)	8 (1.5%)	0 (0%)
	Very common	Oedema [d]	99 (18.2%)	5 (0.9%)	0 (0%)
	Common	Pyrexia	37 (6.8%)	3 (0.6%)	0 (0%)
	Common	Chills	35 (6.4%)	2 (0.4%)	0 (0%)
	Common	Pain	20 (3.7%)	0 (0%)	0 (0%)
	Common	Chest pain	13 (2.4%)	2 (0.4%)	0 (0%)
Psychiatric disorders	Common	Insomnia	22 (4.0%)	0 (0%)	0 (0%)
	Common	Depression	15 (2.8%)	1 (0.2%)	0 (0%)
Investigations	Very common	Ejection fraction decreased	84 (15.4%)	16 (2.9%)	0 (0%)
	Very common	Weight decreased	57 (10.5%)	1 (0.2%)	0 (0%)
	Common	Platelet count decreased	41 (7.5%)	15 (2.8%)	2 (0.4%)
	Common	White blood cell count decreased [e]	37 (6.8%)	16 (2.9%)	0 (0%)
	Common	Lipase increased	36 (6.6%)	19 (3.5%)	11 (2%)
	Common	Haemoglobin decreased	25 (4.6%)	8 (1.5%)	0 (0%)
	Common	Blood creatine phosphokinase increased	19 (3.5%)	7 (1.3%)	2 (0.4%)
	Common	Aspartate aminotransferase increased	18 (3.3%)	7 (1.3%)	0 (0%)
	Common	Blood amylase increased	18 (3.3%)	11 (2.0%)	2 (0.4%)
	Common	Blood creatinine increased	15 (2.8%)	2 (0.4%)	0 (0%)
	Common	Blood pressure increased	15 (2.8%)	2 (0.4%)	0 (0%)
	Common	Alanine aminotransferase increased	14 (2.6%)	7 (1.3%)	2 (0.4%)
		Any adverse event	524 (96.3%)	296 (54.4%)	57 (10.5%)

The following terms have been combined:

[a] Anorexia and decreased appetite

[b] Dysgeusia, ageusia and taste disturbance

[c] Abdominal pain and abdominal pain upper

[d] Oedema, oedema peripheral and oedema face

[e] White blood cell count decreased, neutrophil count decreased, and leukocyte count decreased

Adverse reactions from post-marketing experience

The following adverse reactions have been identified during post-approval use of SUTENT. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications.

Cardiac disorders:

Uncommon: Cardiac failure, cardiac failure congestive, left ventricular

failure
Rare: **Prolonged QT interval, Torsade de pointes**
Gastrointestinal disorders:
Uncommon: **Pancreatitis**
Rare: **Gastrointestinal perforation**
Hepatobiliary disorders:
Uncommon: **Hepatic failure**
Investigations:
Common: **Elevated thyroid stimulating hormone (TSH)**
Infections and Infestations
Non known **Infections (with or without neutropoenia)**
Muscoloskeletal and connective tissue disorders
Not known **Myopathy and/or rhabdomyolysis**
Pulmonary disorders
Not known: **Pleural effusion**
Not known: **Pulmonary embolism and respiratory failure**

Infection and infestations: Cases of serious infection (with or without neutropoenia), in some cases with fatal outcome, have been reported.

Musculoskeletal and connective tissue disorders: Rare cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice

Blood and lymphatic system disorders: Rare cases of thrombotic microangiopathy have been reported. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Endocrine Disorders: Rare cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (See also section 4.4).

Renal and urinary disorders: 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 SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitor,
ATC Code :LO1XE04

Sunitinib malate inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and 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 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

CLINICAL STUDIES
The clinical safety and efficacy of SUTENT has been studied in the treatment of patients with malignant gastrointestinal stromal tumour (GIST) who were resistant to imatinib (i.e. those who experienced disease progression during or following treatment with imatinib) or intolerant to imatinib (i.e. those who experienced significant toxicity during treatment with imatinib that precluded further treatment) and the treatment of patients with metastatic renal cell carcinoma (MRCC).
Efficacy is based on time to tumour progression and an increase in survival in GIST and on progression free survival and objective response rates for treatment-naïve and cytokine-refractory MRCC respectively.

Gastrointestinal Stromal Tumours
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 50 mg at the recommended treatment schedule 4 weeks on /2 weeks off ("schedule 4/2").
In this study the median Time To Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).

A phase 3, randomised, double-blind, placebo-controlled 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 50 mg SUTENT 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 primary efficacy endpoint of the study was TTP, defined as the time from randomization to first documentation of objective tumour progression.
The median TTP on SUTENT was 28.9 weeks (95% CI = 21.3-34.1 weeks) and was statistically significantly longer than the TTP of 5.1 weeks (95% CI = 4.4-10.1 weeks) on placebo. The difference in overall survival was statistically in favour of SUTENT [hazard ratio: 0.491 (95% C.I. 0.290- 0.831)]; the risk of death was 2 times higher in patients in the placebo arm compared to the SUTENT arm. The percentages of deaths were 14% for SUTENT *vs* 25% for placebo. Median overall survival had not yet been reached in either treatment arm at the time of analysis.

Treatment-naïve Metastatic Renal cell Carcinoma (MRCC)
A phase 3 randomised, multicenter, international, study evaluating the efficacy and safety of sunitinib compared with IFN-α in patients with treatment-naïve metastatic RCC was conducted. Seven hundred and fifty patients were randomised 1:1 to the treatment arms; they received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily oral administration followed by 2 weeks of rest (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.

The primary efficacy endpoint was progression free survival (PFS). In this study 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-value <0.001).

Cytokine-Refractory Metastatic Renal Cell Carcinoma.
A phase II study of SUTENT was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or interferon-α. Sixty three patients received a starting dose of 50 mg of SUTENT orally, once daily for 4 consecutive weeks followed by a 2-week rest period, to comprise a complete cycle of 6 weeks (schedule 4/2). The primary efficacy endpoint was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST).

In this study the objective response rate was 36.5% (95% C.I. 24.7% - 49.6%) and the median time to progression (TTP) was 37.7 weeks (95% C.I. 24.0 - 46.4 weeks).

A confirmatory, open-label, single-arm, multi-centre study evaluating the efficacy and safety of SUTENT was conducted in patients with MRCC who were refractory to prior cytokine therapy. One hundred and six patients received at least one 50 mg dose of SUTENT on schedule 4/2.

The primary efficacy endpoint of this study was Objective Response Rate (ORR). Secondary endpoints included TTP, duration of response (DR) and overall survival (OS).
In this study the ORR was 35.8% (95% C.I. 26.8% – 47.5 %) The median DR and OS had not yet been reached.

5.2 Pharmacokinetic properties

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

Absorption
After oral administration of sunitinib, maximum concentrations (C_{max}) are generally observed from 6 to 12 hours (T_{max}) post-dose.
Food has no effect on the bioavailability of sunitinib.

Distribution
Binding of sunitinib and its primary active metabolite to human plasma protein in *in vitro* assays was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (V/F) for sunitinib was large - 2230 l -, indicating distribution into the tissues.

Metabolism
The calculated *in vitro* Ki values for all CYP isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 AND CYP4A9/11) indicated that sunitinib and its primary active metabolite are unlikely to inhibit metabolism, to any clinically relevant extent, of drugs that may be metabolized by these enzymes.
In-vitro studies also indicate that SUTENT neither induces nor inhibits major CYP enzymes, including CYP3A4.

Biotransformation
Sunitinib is metabolized primarily by CYP3A4, the cytochrome P450 enzyme, which produces its primary active metabolite, which is then further metabolized by CYP3A4.
Concurrent administration of SUTENT with the potent CYP3A4 inducer, rifampin, resulted approximately in 56% and 78% reduction in sunitinib C_{max} and $AUC_{0-\infty}$, values respectively, after a single dose of SUTENT in healthy volunteers. Administration of SUTENT with other inducers of the CYP3A4 family /(e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or *Hypericum perforatum*, known also as St. John's Wort) may decrease sunitinib concentrations.

Elimination
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.

Organ Functions impairment
Hepatic insufficiency: Sunitinib and its primary metabolite are mainly metabolized 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.

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.

Renal insufficiency: No clinical studies have been performed in patients with impaired renal function
Studies excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42-347 ml/min).

Plasma Pharmacokinetics
Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary active 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 is 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*. The primary active metabolite comprises 23 to 37% of the total exposure. 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. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for weight or ECOG score.
Available data indicate that females could have about 30% lower apparent clearance (CL/F) of sunitinib than males: this difference however does not necessitate dose adjustments.

5.3 Preclinical safety data

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

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

Carcinogenicity
Carcinogenicity studies with sunitinib malate have not been performed.

Reproductive and Developmental toxicity.
No effects on male or female fertility were observed in reproductive toxicity studies . However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea, endometrial changes in the uterus and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididimes and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than is observed in clinic.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SUTENT® 12.5 mg, 25 mg, 50 mg hard capsules
Capsule content
- Mannitol
- Croscarmellose Sodium
- Povidone
- Magnesium Stearate

SUTENT® 12.5 mg, 25 mg hard capsules
Orange Capsule Shell
- Gelatin
- Red Iron Oxide (E172)
- Titanium dioxide (E171)

SUTENT® 25 mg, 50 mg hard capsules
Caramel Capsule Shell
- Gelatin
- Titanium dioxide (E171)
- Yellow Iron Oxide (E172)
- Red Iron Oxide (E172)
- Black Iron Oxide (E172)

SUTENT® 12.5 mg, 25 mg, 50 mg hard capsules
Printing ink.
- Shellac
- Propylene glycol
- Sodium hydroxide
- Povidone

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with a polypropylene closure, containing 30 capsules.
Aclar/PVC transparent blister with aluminium foil coated with heat seal lacquer containing 28 (4 x 7) hard capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/347/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: July 19, 2006
Due-date for next renewal: July 19, 2011

10. DATE OF REVISION OF THE TEXT

22 August 2008

LEGAL CATEGORY

POM

10.2 Appendix 2: search strategy for section 6

Service provider: DataStar

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

10.3.2 The date on which the search was conducted.

16 September 2008

10.3.3 The date span of the search.

Embase & Medline 1996 – 2008
Medline in progress (24th July - 16th September 2008)

10.3.4 The complete search strategies used, including all the search terms: textwords (free text),

Medline 1996 - 2008-09-16

No. 3, Database MEDL; Search term: "Gastrointestinal-Neoplasms.DE." (Info added since: unrestricted, Results 5078)
No. 5, Database MEDL; Search term: "GASTROINTESTINAL-STROMAL-TUMORS.DE." (Info added since: unrestricted, Results 1391)
No. 6, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 953)
No. 7, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumors" (Info added since: unrestricted, Results 2227)
No. 9, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumours" (Info added since: unrestricted, Results 306)
No. 10, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumour" (Info added since: unrestricted, Results 188)
No. 11, Database MEDL; Search term: "3 OR 5 OR 6 OR 7 OR 9 OR 10" (Info added since: unrestricted, Results 7250)
No. 12, Database MEDL; Search term: "sutent" (Info added since: unrestricted, Results 45)
No. 13, Database MEDL; Search term: "sunitinib" (Info added since: unrestricted, Results 506)
No. 16, Database MEDL; Search term: "11 AND (12 OR 13)" (Info added since: unrestricted, Results 110)
No. 20, Database MEDL; Search term: "PT=META-ANALYSIS" (Info added since: unrestricted, Results 16708)
No. 21, Database MEDL; Search term: "CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#" (Info added since: unrestricted, Results 354215)
No. 22, Database MEDL; Search term: "REVIEW=YES" (Info added since: unrestricted, Results 915661)
No. 23, Database MEDL; Search term: "20 OR 21 OR 22" (Info added since: unrestricted, Results 1267128)
No. 24, Database MEDL; Search term: "16 AND 23" (Info added since: unrestricted, Results 55)

Medline in progress (24th July - 16th September 2008)

No. 25, Database MEIP; Search term: "Gastrointestinal-Neoplasms.DE." (Info added since: unrestricted, Results 0)
No. 26, Database MEIP; Search term: "GASTROINTESTINAL-STROMAL-TUMORS.DE." (Info added since: unrestricted, Results 0)

No. 27, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 59)
No. 28, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumors" (Info added since: unrestricted, Results 82)
No. 29, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumours" (Info added since: unrestricted, Results 17)
No. 30, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumour" (Info added since: unrestricted, Results 8)
No. 31, Database MEIP; Search term: "25 OR 26 OR 27 OR 28 OR 29 OR 30" (Info added since: unrestricted, Results 141)
No. 32, Database MEIP; Search term: "sutent" (Info added since: unrestricted, Results 8)
No. 33, Database MEIP; Search term: "sunitinib" (Info added since: unrestricted, Results 78)
No. 34, Database MEIP; Search term: "31 AND (32 OR 33)" (Info added since: unrestricted, Results 14)

Embase 1996 - 2008

No. 42, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 3108)
No. 43, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumors" (Info added since: unrestricted, Results 1329)
No. 44, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumours" (Info added since: unrestricted, Results 291)
No. 45, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumour" (Info added since: unrestricted, Results 174)
No. 47, Database EMED; Search term: "sutent" (Info added since: unrestricted, Results 550)
No. 48, Database EMED; Search term: "sunitinib" (Info added since: unrestricted, Results 2019)
No. 62, Database EMED; Search term: "GASTROINTESTINAL-TUMOR.DE." (Info added since: unrestricted, Results 2294)
No. 64, Database EMED; Search term: "GASTROINTESTINAL-STROMAL-TUMOR.DE." (Info added since: unrestricted, Results 2895)
No. 66, Database EMED; Search term: "SUNITINIB.W..DE." (Info added since: unrestricted, Results 2006)
No. 67, Database EMED; Search term: "(42 OR 43 OR 44 OR 45 OR 62 OR 64) AND (47 OR 48 OR 66)" (Info added since: unrestricted, Results 471)
No. 68, Database EMED; Search term: "CLINICAL-TRIAL#" (Info added since: unrestricted, Results 425323)
No. 69, Database EMED; Search term: "META-ANALYSIS.DE." (Info added since: unrestricted, Results 30780)
No. 70, Database EMED; Search term: "REVIEW=YES" (Info added since: unrestricted, Results 681945)
No. 71, Database EMED; Search term: "67 AND (68 OR 69 OR 70)" (Info added since: unrestricted, Results 375)
No. 74, Database EMED MEDL MEIP; Search term: "combined sets 24, 34, 71" (Info added since: unrestricted, Results 444)
No. 76, Database EMED MEDL MEIP; Search term: "unique records from 74" (Info added since: unrestricted, Results 402)

Cochrane

Simple search: GASTROINTESTINAL-STROMAL-TUMORS or "gastrointestinal stromal tumor" or "gastrointestinal stromal tumors" or "gastrointestinal stromal tumours" or "gastrointestinal stromal tumour"

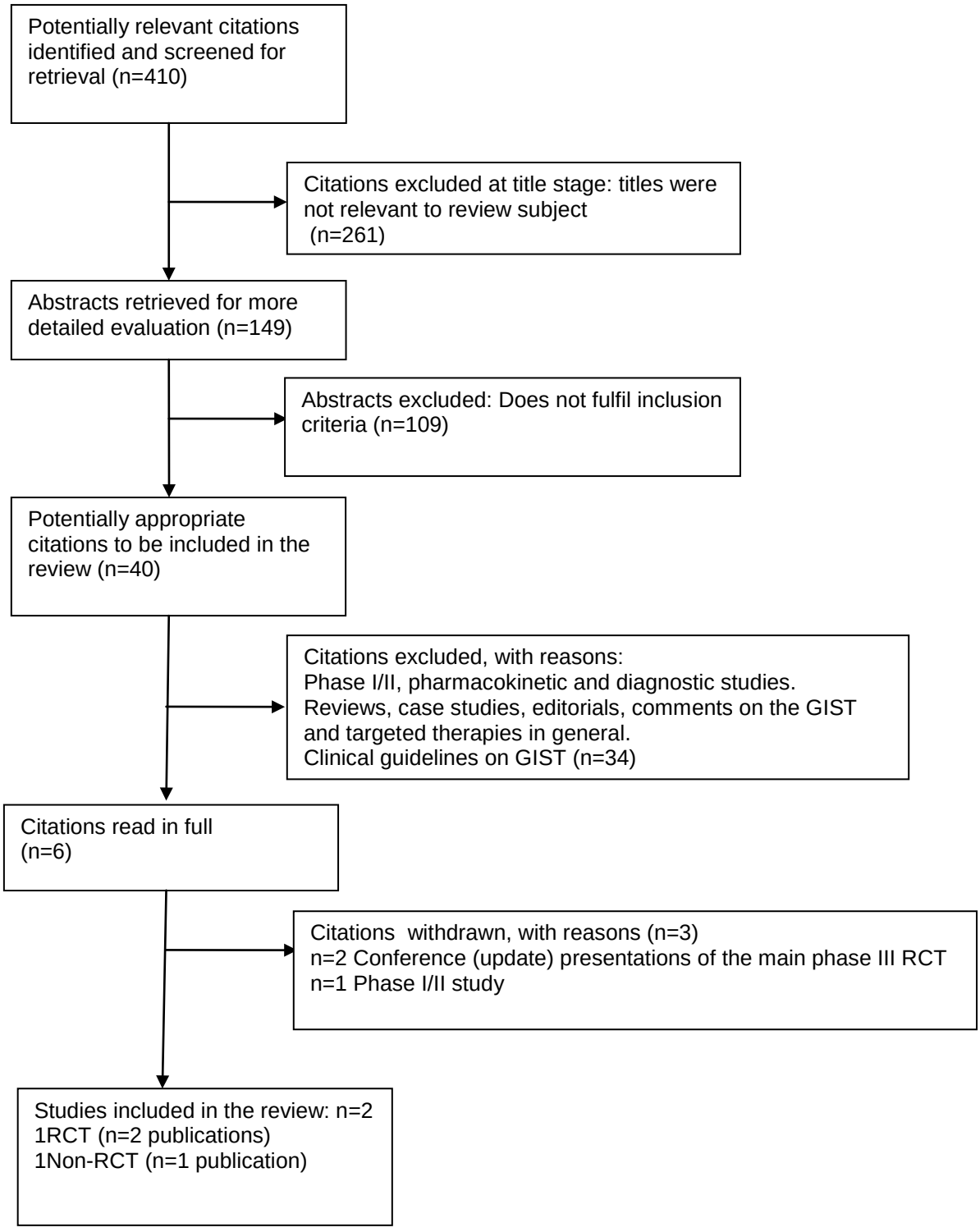
10.3 Details of any additional searches, for example searches of company databases (include a description of each database).

- ASCO website (2000-2008) was manually hand searched for relevant presentations.
- The Pfizer clinical trials database, Documentum, was searched (23 September, 2008).

Of 410 (after removal of duplicates) citations identified by the literature search, 261 citations were not relevant by title and remaining 149 citations were reviewed in the abstract form. After examining the full manuscripts (n=109) of all potentially relevant abstracts, those (n=40) deemed to be potential RCTs relating directly to the scope question were obtained (Figure 1).

One phase 3 RCT and one open label EAP are fulfilled the inclusion criteria.

Figure 1: QUORUM statement flow diagram of study retrieval



10.3 Appendix 3: search strategy for section 7

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **Health Economic Evaluation Database**
- **NHS Economic Evaluation Database (NHS EED).**

The search strategy was translated and run in the following databases:
MEDLINE via DataStar
MEDLINE in progress July-September 2008 via DataStar
EMBASE via DataStar
NHS EED
HTA section of Centre for Reviews and Dissemination database
Conferences searched on the internet, ECCO 14, ASCO and ISPOR

10.3.2 The date on which the search was conducted.

16th September 2008

10.3.3 The date span of the search.

Database inception to 16th September 2008

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline
1, Database MEDL; Search term: "Gastrointestinal-Neoplasms.DE." (Info added since: unrestricted, Results 5078)
2, Database MEDL; Search term: "GASTROINTESTINAL-STROMAL-TUMORS.DE." (Info added since: unrestricted, Results 1391)
3, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 953)
4, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumors" (Info added since: unrestricted, Results 2227)
5, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumours" (Info added since: unrestricted, Results 306)
6, Database MEDL; Search term: "gastrointestinal ADJ stromal ADJ tumour" (Info added since: unrestricted, Results 188)
7, Database MEDL; Search term: "1 OR 2 OR 3 OR 4 OR 5 OR 6" (Info added since: unrestricted, Results 7250)
8, Database MEDL; Search term: "economics" (Info added since: unrestricted, Results 170778)
9, Database MEDL; Search term: "ECONOMICS-MEDICAL#.DE." (Info added since: unrestricted, Results 2455)
10, Database MEDL; Search term: "HEALTH-CARE-COSTS#.DE." (Info added since: unrestricted, Results 25366)
11, Database MEDL; Search term: "COST-OF-ILLNESS#.DE." (Info added since: unrestricted, Results 9767)
12, Database MEDL; Search term: "ECONOMICS-HOSPITAL#.DE. OR HOSPITAL-COSTS#.DE." (Info added since: unrestricted, Results 7418)

13, Database MEDL; Search term: "cost ADJ effectiveness" (Info added since: unrestricted, Results 16904)
14, Database MEDL; Search term: "8 OR 9 OR 10 OR 11 OR 12 OR 13" (Info added since: unrestricted, Results 184725)
15, Database MEDL; Search term: "7 AND 14" (Info added since: unrestricted, Results 66)

MEDLINE in progress July – September 2008
1, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 59)
2, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumors" (Info added since: unrestricted, Results 82)
3, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumours" (Info added since: unrestricted, Results 17)
4, Database MEIP; Search term: "gastrointestinal ADJ stromal ADJ tumour" (Info added since: unrestricted, Results 8)
5, Database MEIP; Search term: "economic OR economics OR pricing OR price OR cost OR costs OR costing OR costings" (Info added since: unrestricted, Results 7479)
6, Database MEIP; Search term: "1 OR 2 OR 3 OR 4" (Info added since: unrestricted, Results 141)
7, Database MEIP; Search term: "5 AND 6" (Info added since: unrestricted, Results 3)

EMBASE
1, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 3108)
2, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumors" (Info added since: unrestricted, Results 1329)
3, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumours" (Info added since: unrestricted, Results 291)
4, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumour" (Info added since: unrestricted, Results 174)
5, Database EMED; Search term: "gastrointestinal ADJ neoplasms" (Info added since: unrestricted, Results 99)
6, Database EMED; Search term: "GASTROINTESTINAL-TUMOR.DE." (Info added since: unrestricted, Results 2294)
7, Database EMED; Search term: "gastrointestinal ADJ stromal ADJ tumor" (Info added since: unrestricted, Results 3108)
8, Database EMED; Search term: "GASTROINTESTINAL-STROMAL-TUMOR.DE." (Info added since: unrestricted, Results 2895)
9, Database EMED; Search term: "economic OR economics OR pricing OR price OR cost OR costs OR costing OR costings" (Info added since: unrestricted, Results 346762)
10, Database EMED; Search term: "1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8" (Info added since: unrestricted, Results 5411)
11, Database EMED; Search term: "HEALTH-CARE-COST.DE. OR COST-EFFECTIVENESS-ANALYSIS.DE. OR HEALTH-ECONOMICS.DE. OR COST-UTILITY-ANALYSIS.DE." (Info added since: unrestricted, Results 95494)
12, Database EMED; Search term: "10 AND (9 OR 11)" (Info added since: unrestricted, Results 213)

10.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Conferences searched on the internet, ECCO 14, ASCO and ISPOR