A PHASE I/II STUDY OF SUNITINIB IN YOUNG PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR

Compound:	SU011248 L-malate salt
Compound Name:	Sunitinib malate
US IND Number:	62,382
European Clinical Trial Database (Eudra CT) Number:	2011-002008-33
Protocol Number:	A6181196
Phase:	I/II

The name, title, address and telephone number(s) of the sponsor's medical expert for the trial is documented in the study contact list located within the Study Manual.

Document History

Document	Version Date	Summary of Changes and rationale
Amendment 1	11 June 2012	The Schedule of Activities and associated protocol sections were revised to include growth and pubertal maturation assessments for paediatric patients, a reduced mandatory visit schedule after Cycle 3, and clarification of standard tumor analysis requirements. The term "chemotherapy naïve" was removed from the study design and the associated secondary objective to study tolerability in pediatric patients with GIST. Multiple changes were made according the new Pfizer standard safety language for clinical protocols. One significant change in safety language is the following in Section 8.2 Reporting Period: Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported. Previously, this SAE reporting required a potential causal relationship to the study drug. A change in contraception language for the UK was made at the request of the

		UK regulatory authorities. Administrative changes and clarifications made throughout.
Amendment 2	31 July 2017	The number of patients to be enrolled in the study (in the range of age from 6 to < 18) has been reduced from 15 to 6 evaluable patients. The centralized review of imaging (ie, MRI, CT scans etc) aimed to confirm the efficacy endpoint is no longer required. As this study is part of a PIP, both these changes above have been agreed with PDCO and are aligned with the PIP binding elements. Rationale for changes are as follow: The primary objective of the study is the characterization of plasma PK profile of sunitinib and its active metabolite in patients with unresectable GIST. A total of **six pediatric patients** have been included in the study as of today, and the enrollment of additional patient is unlikely due to the rarity of the disease. Recognizing this number is lower than originally planned it still allows the characterization of the pk profile in pediatric patients i.e the analysis of the primary endpoints of the

		study. In regards to the **centralized review of imagine,** this is considered no longer necessary due to the small number of patients enrolled, and in absence of PR or CR. The wording related to the reporting of SAE has been aligned with the current protocol template. New text: SAEs occurring to a patient after the active collection period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are reported to the sponsor.
Original Protocol	11 October 2011	NA

PROTOCOL SUMMARY

Gastrointestinal stromal tumor (GIST) is a tumor of mesenchymal origin occurring in the gastrointestinal tract. GIST is a very rare and newly recognized tumor in children. Pediatric GIST has a different clinical behavior and biology than typical adult GIST. The majority of pediatric GIST occurs in females, and these tumors commonly do not bear the genetic mutations present in adults with GIST.

Sunitinib (SUTENT®) received approval from the US FDA and the European Medicines Agency (EMA) in 2006 for the treatment of GIST after disease progression on or intolerance to imatinib mesylate. Following negotiations with the EMA's Pediatric Committee (PDCO), the sponsor (Pfizer) agreed to conduct this single agent, open-label, single arm, multi-centre trial of sunitinib to investigate the use of sunitinib for the treatment of pediatric GIST, collecting safety, pharmacokinetic (PK) and efficacy data in at least 6 children aged 6 years to less than 18 years with a primary endpoint of PK parameters of sunitinib and its active metabolite SU012662.

The primary objective of this study is to characterize the plasma PK profile of sunitinib and its active metabolite SU012662 in children and young adults with advanced, unresectable GIST. Secondary objectives include evaluation of whether doses greater than the established pediatric maximum tolerated dose (MTD) are tolerated in pediatric patients with GIST, and the safety, tolerability, and anti-tumor activity of sunitinib in children and young patients with GIST. The study will explore PK-pharmacodynamic relationships with respect to safety and efficacy if data allows. The primary endpoint will be the PK parameters of sunitinib and its main active metabolite including total plasma exposure (AUC24) and oral clearance (CL/F). Secondary endpoints will include the definition of adverse events and laboratory abnormalities, the objective response rate (ORR), duration of response, progression-free survival (PFS), and the overall survival (OS) at 2 years after study enrollment. Pharmacokinetic-pharmacodynamic relationships with respect to safety and efficacy in pediatric GIST will be detailed, if data allows.

Study Design: This study is a single arm, multi-center, multi-national, trial evaluating the PK, safety and preliminary anti-tumor efficacy of sunitinib in children and young adults diagnosed with advanced, unresectable GIST. The study aims to enroll 6 evaluable children aged 6 years to less than 18 years. In addition, up to 15 young adults aged 18 years to less than 21 years may be enrolled. The starting dose of sunitinib in children will be approximately 15 mg/m^2/day for 4 weeks followed by 2 weeks with no study drug, using the MTD established during the pediatric Phase 1 clinical trial conducted by the Children's Oncology Group. Intrapatient dose escalation of sunitinib will be allowed, based on tolerability. Investigators will have the option to access real-time PK results to aid in dosing decisions. Sunitinib dosing for the young adults will follow approved guidelines (per current USPI and SmPC). Study treatment for all patients may continue for up to 18 cycles, equaling approximately 2 years of therapy.

Statistical Plan: Descriptive statistics for observed and dose-corrected (where appropriate) pharmacokinetic data will be reported for all patients with at least one pharmacokinetic observation by presenting the population size, arithmetic mean, standard deviation, percent coefficient of variation (CV%), median, minimum, maximum values. In addition, geometric mean and the 95% confidence interval (CI) for the geometric mean, will be reported where appropriate. Other endpoints, including safety and efficacy endpoints, will be collected, analyzed and presented descriptively.

Table 1. SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity	Screen <28 days of first dose	Cycles 1-3 (Days 1-42)[23]				Cycles 4-18 [23]	End of Treatment [4]	Follow-up +/- 7 days
		D1 [2] (D-2 to D2)	D15 Visit[3] D12-D18, inclusive	**D28 Visit[24]** D25-D29, inclusive	**Therapy Break** D29-42	**Day 1 (D-2 to D2)**		
Baseline Documentation								
Informed Consent	X							
Tumor characteristics [1]	X							
Medical/Oncologic History [5]	X							
PE including Wt, Ht, Vital Signs, Lansky/ECOG [6]	X	X	X	X		X	X	X[Per 6.3.1]
Baseline Signs/Symptoms	X							
Laboratory Studies								
Hematology & Chemistry [7]	X	X	X	X		X	X	X[Per 6.3.1]
TSH [8]	X	X				Even Cycles Only	X[8]	
Prothtrombin time (PT or INR) [8]	X	If clinically indicated.						
Urinalysis [9]	X	Cycles 2-3 only				Cycle 4 Only	X	
Urine Pregnancy Test [10]	X	X				X	X	
Pharmacokinetic Sampling [11]		Cycle 1: Pre-dose and 2,4,6,8 hrs post first dose Cycles 2&3: Pre-dose	Pre-dose	Pre-dose				
Sunitinib Dosing [12]		X	X	X		X		
Assessments								
Chest radiograph [13]	X	If clinically indicated.						

Protocol Activity	Screen <28 days of first dose	Cycles 1-3 (Days 1-42)[23]				Cycles 4-18 [23]	End of Treatment [4]	Follow-up +/- 7 days
		D1 [2] (D-2 to D2)	D15 Visit[3] D12-D18, inclusive	**D28 Visit[24]** D25-D29, inclusive	**Therapy Break** D29-42	**Day 1 (D-2 to D2)**		
Tumor assessment(s) [14]	X	X prior to the end of Cycle 2				X prior to the end of each even numbered cycle	X	
FDG-PET [15]	X			Cycle 1 Only				
12-lead ECG [16]	X	Cycle 2 Only					X	
ECHO or MUGA Scan [17]	X	Cycle 3 only				Every 3rd cycle (ie Day 1 of Cycles 6, 9, 12, etc)	X [Per 6.4.1]	
Adverse Events [18]		Throughout study participation						
Study Drug Compliance [19]								
Concomitant Treatments [20]								
Follow-up Survival Monitoring [21]								X
Growth and Pubertal Maturation [22]	X	See footnote [22]					X	

1. **Tumor characteristics:** Tumor *KIT*, *PDGFRA,* and *BRAF* genotype and succinate dehydrogenase (SDH) protein expression by immunohistochemistry. If some or all of these have not been previously done, tumor specimens may be sent for analysis during screening. For patients with no available, previously collected tumor tissue and incomplete testing information covering all of the above tests, a core biopsy is required, unless, in the opinion of the investigator, a biopsy would create an unacceptable risk to the patient. Refer to Section 6.1 for additional details and exceptions.
2. **Day 1 Assessments:** Physical examination, hematology, blood chemistry and urinalysis are not required if acceptable screening assessments are obtained within 7 days prior to the start of study treatment without suggestion of clinical deterioration. Day 1 of subsequent cycles may commence up to two days prior to the scheduled Day 1 visit until one day after the scheduled visit (ie, the washout period can be from 12-15 days).
3. **D15 visit.** Day 15 of Cycle 1 is a mandatory visit, which includes PK, lab tests, and physical exam. For Cycles 2 and 3 a Day 15 visit is required if dose escalation occurs during that cycle, and includes PK, lab tests, and physical exam. Beyond Cycle 3 Day 15 visits will only occur if a dose escalation occurs or as clinically indicated. PK will not be collected at these additional Day 15 visits but lab tests and physical exam will be performed.
4. **End of Treatment/Withdrawal:** Assessments (See Section 6.4.1) not required if performed within 1 week of study withdrawal (within the last 8 weeks for radiological tumor assessments).
5. **Medical/Oncologic History and Demographics:** Includes demographics, oncologic history, history of other diseases (active or resolved), concomitant illnesses, and information on prior cancer treatments including best response observed. Changes in blood pressure medications (new prescriptions, discontinuations, or changes in dose) will also be recorded.

6.	**Physical Examination:** Lansky/ECOG Performance Scale (see Appendix 5) and height for young adults at screening only; Height and weight required at screening and Day 1 of each cycle and at EOT for pediatric patients. Examination of major body systems; vital signs to include temperature, blood pressure (see Section 5.2.11 for guidelines), heart rate and respiratory rate. Abnormal physical examination findings after screening will be reported as adverse events. Patients below the age of 11 who turn 11 while on-study will then require ECOG performance evaluations.
7.	**Hematology & Chemistry:** Required safety tests are also listed in Section 7.2.2. These include white blood count with differential, hemoglobin, and platelets; sodium, potassium, chloride, blood urea nitrogen (BUN), serum creatinine, glucose, uric acid, calcium, magnesium, phosphorous, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total protein, albumin, amylase, and lipase. At any time after initiation of dosing if liver function tests are abnormal refer to Section 8.5.2 for guidelines. On visits that do not include dispensation of study drug, these tests may be performed by labs outside of the study sites in cases where patient travel to the study clinic is not possible.
8.	**TSH** at screen and Day 1 of Cycles 2, 3, and 4, followed by Day 1 of every even cycle (ie, 6, 8, 10 …etc.) thereafter (see also Section 6.2). **Prothrombin time: PT or INR** at screening, then as clinically indicated. When performed, the same test should be used.
9.	**Urinalysis:** During screening and Cycles 2-4, as clinically indicated and at end of treatment. *Only protein will be captured on the CRF*. If the results of the dipstick test indicate a ≥2+ proteinuria, then follow-up should be performed with a quantitative urine protein analysis according to local standard practices, with data captured on the AE CRF if AE criteria are met.
10.	**Pregnancy Test:** Urine test required for all females above age 11 within 7 days prior to administration of the first dose of sunitinib, on Day 1 of each cycle, and at the end of treatment. Patients of less than 11 yrs at study start who turn 11 while on-study will then require pregnancy testing per the Schedule of Activities. Refer to Section 7.2.3 for details.
11.	**PK sampling:** All PK samples collected before and on the Cycle 1 Day 28 Visit should be shipped immediately to BASi Lab for bio-analysis; refer to Section 7.1 for details. Optional Visit Days are C1D7 (D4-D10, inclusive) and C1D21 (D18-D24, inclusive); refer to Section 7.1 for details.
12.	**Sunitinib dosing:** Sunitinib will be dosed Days 1-28 of each cycle followed by a 2 week break in therapy. Dosing will be on an outpatient basis except on days when PK sampling is performed. Capsules should be taken once daily in the morning on the first 28 days of each cycle with the exception of study visit days on which the dose for that day should be withheld until immediately after the completion of all study visit day activities and the investigator's approval for continued dosing. See Section 5.2.3 for details.
13.	**Chest radiograph** at screening and as clinically indicated. Patients who undergo Tumor Imaging (MRI or CT scan) that includes the chest do not need to have a Chest radiograph performed.
14.	**Tumor Imaging:** MRI (or CT scan) of abdomen and pelvis and any other applicable sites of disease at screening, within 14 days prior to the end of each even numbered cycle (Day 28, preferably), whenever disease progression is suspected, to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the End of Treatment/Withdrawal (Refer to Section 7.4).
15.	**FDG-PET** at baseline and at the cycle 1 day 28 visit (if locally available; see Section 7.4).
16.	ECG: Three consecutive 12-lead ECGs approximately 2 minutes apart will be performed at screening, on Cycle 2, Day 1 and at the end of treatment to determine the mean QTc interval. Attempts should be made for the ECGs to be performed in the morning and time-matched (± 1 hour) with screening assessment. ECGs should be done before blood is drawn or 30 minutes afterwards. If the mean QTc interval is prolonged (>500 msec), the ECGs should be read by a cardiologist at the site for confirmation. Additional ECGs may be performed as clinically indicated. ECG should be performed approximately 2 weeks following any sunitinib dose escalation.
17.	**Echocardiogram or MUGA scan** at screening, then on Day 1 of every 3rd cycle (for example, Day 1 Cycle 3, Day 1 Cycle 6 ..etc.). As clinically indicated at the end of treatment/withdrawal per Section 6.3.1 and see suggested dose modifications guidelines for left ventricular systolic dysfunction in Section 5.2.10.

18. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until 28 days after the last dose of study treatment, or until all **serious** or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported from the time that the patient provides informed consent as described in the protocol.
19. **Study Drug Compliance:** Unused sunitinib will be returned to clinic for drug accountability at the beginning of each subsequent cycle.
20. **Concomitant Medications/Treatments** will be recorded from 28 days prior to the start of study treatment, during the study and up to 28 days after the last dose of sunitinib.
21. **Follow-up Survival Monitoring:** Follow-up survival information, including post-study anti-cancer treatment, will be collected by clinic visit or telephone contact every 3 months until death, or either 24 months from patient's first dose of study treatment or completion of 18 cycles. See Section 6.3.2.
22. Growth and Pubertal Maturation Assessments (for pediatric patients only): Bone age assessments must be performed at screening, and then annually with an additional test at End of Treatment or until growth plate closure. Tanner staging must be performed at screening. If patient is Tanner Stage 1-4, then Tanner assessment should be repeated every 6-9 months and at End of Treatment or until patient reaches Tanner Stage 5. Refer to Section 7.3 Growth and Pubertal Maturation Assessments. Tanner staging assessments can only be waived upon agreement by Pfizer. If Tanner staging is initiated it should be continued per Section 7.3.
23. **Reduced Visit Schedule Following Cycle 3:** Following Cycle 3, patients may visit the clinic on Day 1 (within Day 12-15 of the previous sunitinib washout period) of each cycle only or more frequently at the discretion of the investigator. On cycles where there is a dose escalation, a Day 15 visit is required. Labs and physical exam required when visits occur. Sunitinib dosing information will be collected on Day 1 of each cycle and when Day 15 visits occur.
24. **Day 28 Visits:** Day 28 monitoring for labs at discretion of investigator after Cycle 3.

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1. INTRODUCTION

1.1. Indication

Pediatric GIST

Gastrointestinal stromal tumor (GIST) is a tumor of mesenchymal origin occurring in the gastrointestinal tract. GIST is a very rare and newly recognized tumor in children. Pediatric GIST has a different clinical behavior and biology than typical adult GIST.[1-3] In contrast to GIST in adults, the vast majority of pediatric GIST occur in females, lack large scale chromosomal aberrations, and lack the characteristic mutations in *KIT* or *PDGFRA*. Despite multiple recurrences and lack of dramatic responses to tyrosine kinase inhibitor therapy, most pediatric patients survive with active disease for many years, suggesting a more indolent clinical course than observed with adult GIST.[4-7] Further evidence supporting a distinct biology comes from recently published reports of differing gene-expression profiles and genetic progression mechanisms in pediatric GIST versus adult GIST.[8] While most pediatric GIST lack *KIT* mutations, KIT is expressed and activated, suggesting that inhibition of KIT may have clinical efficacy in these tumors.[1] *In vitro* data show that sunitinib's IC50 is 90% lower than imatinib's IC50 for mutation-negative *KIT*. Early clinical studies seem to correspond with the *in vitro* data. Clinical benefit rate (defined as partial response [PR] or stable disease [SD] in *KIT* mutation-negative GIST is 56% versus 34% in adult, *KIT* mutation-positive GIST.[9] Median OS was also significantly longer for adult patients with exon 9 *KIT* mutations (26.9 months) or a mutation-negative genotype (30.5 months) than for those with exon 11 mutations (12.3 months). Neither PFS nor OS differed significantly between patients with exon 9 *KIT* mutations or a mutation-negative genotype. Currently there is no evidence to suggest that pediatric mutation-negative GIST would differ biologically or clinically from adult mutation-negative GIST. A recent study suggests that a proportion of *KIT* mutation-negative GIST tumors have mutations in succinate dehydrogenase (*SDH*).[10] Such mutations result in a loss of SDH expression in these tumors that can be assessed by immunohistochemistry. A loss in SDH expression could potentially result in increases in intra-tumor VEGF expression. Antitumor activity has been reported with sunitinib, which targets the VEGF signaling pathway, in a cohort of pediatric patients with imatinib-resistant, predominantly *KIT* mutation-negative GIST.[5] One of seven of these patients achieved PR, five patients had SD and one patient had PD on sunitinib. In most pediatric patients treated with imatinib followed by sunitinib, the time to progression on sunitinib was longer than on prior imatinib.

1.2. Background and Rationale

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the current version of the Sunitinib (SUTENT®) Investigator Brochure (IB).

1.3. Introduction/Rationale for Development

Receptor tyrosine kinases (RTKs) are transmembrane proteins containing extracellular ligand-binding domains and intracellular catalytic domains. RTKs are activated following binding of their cognate ligands, and many of the processes involved in tumor growth,

progression, and metastases are mediated by signaling molecules acting downstream from these proteins.[11,12] Several members of the split-kinase domain family of RTKs are implicated in deregulated/autocrine proliferation and survival of solid and hematologic cancer cells, including the platelet-derived growth factor receptors (PDGFRα and β); vascular endothelial growth factor receptors (VEGFR) Type 1 and 2 (FLT1 and FLK1/KDR); the stem cell factor (SCF) receptor, KIT; and the FLT3-ligand receptor. In addition, PDGFR and VEGFR are implicated in tumor-dependent angiogenesis.

RTKs play a critical role in embryonic development and are potent mediators of vascular endothelial cell and malignant proliferation.[13] Inhibitors of the RTKs, such as sunitinib, target mediators of tumor-related angiogenesis and cellular survival.

1.3.1. Sunitinib

Sunitinib malate is an orally-bioavailable, small-molecule RTK inhibitor that antagonizes cellular signaling of multiple targets involved in tumor proliferation and angiogenesis, with specific activity against VEGFR, PDGFR, KIT, FLT-3 and RET.[14, 15] Studies have indicated that sunitinib selectively inhibits Class 3 (PDGF) and Class 5 (VEGF) RTKs, and inhibits RTK phosphorylation *in vivo*. Sunitinib has shown *in vivo* activity in decreasing VEGF-induced vascular permeability, RTK phosphorylation and tumor grown in murine xenograft models.[16-20]

In 2006, sunitinib (SUTENT®) was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of GIST after disease progression on or intolerance to imatinib mesylate and for the treatment of advanced renal cell carcinoma.[21,23] SUTENT was also approved by the EMA for treatment of pancreatic neuroendocrine tumor in 2010 and by the US FDA in 2011.

Following negotiations with the EMA's Pediatric Committee (PDCO), the sponsor (Pfizer) agreed to conduct this single agent, open-label, single arm, multi-centre trial of sunitinib to investigate the use of sunitinib for treatment of pediatric GIST, collecting safety, pharmacokinetic (PK) and efficacy data in 6 children aged 6 years to less than 18 years. The PDCO recommended a primary endpoint of PK parameters of sunitinib and its active metabolite SU012662.

1.3.2. Sunitinib Pharmacokinetics and Safety in Adult Clinical Trials

In adults, repeated dosing studies over a range of 25-100 mg daily doses followed by off-treatment periods have identified a 50 mg dose on the Schedule 4/2 (4 weeks of therapy followed by a 2-week off period) as a tolerable, dose dense regimen.[22,24] Steady state levels of sunitinib and its active metabolite SU012662 are reached 7-10 days after repeated daily dosing. Drug accumulation with repeated 4- or 6-week cycles has not been observed. No dose-dependent changes in Tmax or $t_{1/2}$ have been observed. Sunitinib is metabolized primarily by the cytochrome P450 enzyme, 3A4 (CYP3A4). The terminal elimination half-lives of sunitinib and SU012662 are approximately 40 hours and 80 hours, respectively. Fatigue/asthenia is the primary dose limiting toxicity (DLT); adverse events attributed to sunitinib, independent of treatment schedule have been constitutional (eg, fatigue/asthenia),

gastrointestinal (eg, nausea, vomiting, dyspepsia, diarrhea, stomatitis), dermatologic (eg, dermatitis, skin discoloration, hair depigmentation) and hematologic (eg, neutropenia, thrombocytopenia).

1.3.3. Sunitinib and Adult GIST

A multicenter, international, randomized, placebo-controlled Phase 3 clinical trial A6181004 was halted after the planned interim analysis demonstrated efficacy of sunitinib in adult GIST patients following failure of imatinib. Sunitinib, administered at 50 mg once daily for 4 weeks followed by 2 weeks with no drug, demonstrated a significant difference in time to progression (26.6 vs. 6.4 weeks). Table 2 and Table 3 below summarize the efficacy in the GIST phase 3 study and pooled safety results for 440 adult GIST patients receiving sunitinib in multiple clinical studies, respectively.

Table 2. Summary of A6181004 Efficacy Endpoints (ITT Population)

Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment [a]				
	Median (95% CI)		Hazard Ratio		Open-Label
Endpoint	Sunitinib	Placebo	(95% CI)	p	Treatment[b]
Primary					
TTP (weeks)	26.6 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.339 (0.244 to 0.472)	<0.001	10.4 (4.3 to 22.0)
Secondary					
PFS (weeks)	22.9 (10.9 to 28.0)	6.0 (4.4 to 9.7)	0.347 (0.253 to 0.475)	<0.001	-
OS (weeks)	72.7 (61.3 to 83.0)	64.9 (45.7 to 96.0)	0.876 (0.679 to 1.129)	0.306	-
ORR (n)[c]	6.6 (3.8 to 10.5)	0 (-)	6.58 (3.47 to 9.70)	0.004	10.1 (5.0 to 17.8)

a Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.
b Efficacy results for open-label treatment are presented only for the 103 subjects who crossed-over from placebo to sunitinib after unblinding.
c Results for ORR are given as percent of subjects with confirmed response with the 95% CI and treatment difference with 95% CI are also expressed as percent.

Source: A6181004 final Clinical Study Report.

Table 3. Adverse Reactions Reported in GIST Studies with SUTENT

System Organ Class	*Adverse reaction*	*All Grades* n (%)	*Grade 3* n (%)	*Grade 4* n (%)
Blood and lymphatic system disorders	Anaemia	86 (19.5%)	24 (5.5%)	3 (0.7%)
	Neutropoenia	81 (18.4%)	39 (8.9%)	5 (1.1%)
	Thrombocytopoenia	67 (15.2%)	19 (4.3%)	6 (1.4%)
	Leukopoenia	26 (5.9%)	9 (2.0%)	1 (0.2%)
	Lymphopoenia	10 (2.3%)	3 (0.7%)	1 (0.2%)
Endocrine disorders	Hypothyroidism	59 (13.4%)	5 (1.1%)	1 (0.2%)
Metabolism and nutrition disorders	Decreased appetite[a]	117 (26.6%)	8 (1.8%)	0 (0.0%)
Psychiatric disorders	Insomnia	14 (3.2%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Taste disturbance[b]	105 (23.9%)	1 (0.2%)	0 (0.0%)
	Headache	76 (17.3%)	5 (1.1%)	0 (0.0%)
	Paraesthesia	27 (6.1%)	1 (0.2%)	0 (0.0%)
	Dizziness	18 (4.1%)	1 (0.2%)	0 (0.0%)
	Neuropathy peripheral	11 (2.5%)	0 (0.0%)	0 (0.0%)
	Hypoaesthesia	10 (2.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Hypertension	101 (23.0%)	43 (9.8%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Epistaxis	28 (6.4%)	1 (0.2%)	0 (0.0%)
	Dyspnoea	16 (3.6%)	2 (0.5%)	0 (0.0%)
Renal and urinary disorders	Chromaturia	18 (4.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Diarrhoea	187 (42.5%)	24 (5.5%)	0 (0.0%)
	Nausea	161 (36.6%)	15 (3.4%)	0 (0.0%)
	Vomiting	98 (22.2%)	7 (1.6%)	0 (0.0%)
	Stomatitis	90 (20.5%)	7 (1.6%)	0 (0.0%)
	Dyspepsia	80 (18.2%)	4 (0.9%)	0 (0.0%)
	Abdominal pain[c] / distension	77 (17.5%)	15 (3.4%)	2 (0.5%)
	Flatulence	46 (10.5%)	0 (0.0%)	0 (0.0%)
	Oral pain	44 (10.0%)	2 (0.5%)	0 (0.0%)
	Constipation	37 (8.4%)	2 (0.5%)	0 (0.0%)
	Glossodynia	37 (8.4%)	0 (0.0%)	0 (0.0%)
	Dry mouth	31 (7.0%)	0 (0.0%)	0 (0.0%)
	Gastro-oesophageal reflux disease	12 (2.7%)	1 (0.2%)	0 (0.0%)
	Mouth ulceration	11 (2.5%)	0 (0.0%)	0 (0.0%)
	Oral discomfort	11 (2.5%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Yellow skin/ Skin discolouration	146 (33.2%)	0 (0.0%)	0 (0.0%)
	Palmar-plantar erythrodysaesthesia syndrome	106 (24.1%)	27 (6.1%)	0 (0.0%)
	Hair colour changes	67 (15.2%)	0 (0.0%)	0 (0.0%)
	Rash	64 (14.5%)	3 (0.7%)	0 (0.0%)
	Dry skin	41 (9.3%)	0 (0.0%)	0 (0.0%)
	Alopecia	33 (7.5%)	0 (0.0%)	0 (0.0%)
	Dermatitis	29 (6.6%)	1 (0.2%)	0 (0.0%)
	Periorbital oedema	20 (4.5%)	0 (0.0%)	0 (0.0%)
	Skin Reaction	20 (4.5%)	3 (0.7%)	0 (0.0%)

Table 3. Adverse Reactions Reported in GIST Studies with SUTENT

System Organ Class	*Adverse reaction*	*All Grades* n (%)	*Grade 3* n (%)	*Grade 4* n (%)
	Erythema	18 (4.1%)	0 (0.0%)	0 (0.0%)
	Eczema	16 (3.6%)	1 (0.2%)	0 (0.0%)
	Pruritus	16 (3.6%)	0 (0.0%)	0 (0.0%)
	Hyperpigmentation	15 (3.4%)	0 (0.0%)	0 (0.0%)
	Skin exfoliation	12 (2.7%)	0 (0.0%)	0 (0.0%)
	Blister	10 (2.3%)	1 (0.2%)	0 (0.0%)
	Skin lesion	10 (2.3%)	1 (0.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Pain in extremity/limb	54 (12.3%)	5 (1.1%)	0 (0.0%)
	Arthralgia	39 (8.9%)	3 (0.7%)	0 (0.0%)
	Myalgia	29 (6.6%)	0 (0.0%)	0 (0.0%)
	Muscle spasm	21 (4.8%)	1 (0.2%)	0 (0.0%)
	Back pain	11 (2.5%)	2 (0.5%)	0 (0.0%)
	Muscular weakness	10 (2.3%)	1 (0.2%)	0 (0.0%)
General disorders and administration site conditions	Fatigue/Asthenia	287 (65.2%)	64 (14.5%)	5 (1.1%)
	Mucosal inflammation	70 (15.9%)	6 (1.4%)	1 (0.2%)
	Oedema[d]	59 (13.4%)	1 (0.2%)	0 (0.0%)
	Pyrexia	26 (5.9%)	2 (0.5%)	0 (0.0%)
Investigations	Lipase increase	35 (8.0%)	12 (2.7%)	7 (1.6%)
	White blood cell count decreased[e]	33 (7.5%)	15 (3.4%)	0 (0.0%)
	Ejection fraction decreased	27 (6.1%)	5 (1.2%)	0 (0.0%)
	Haemoglobin decreased	27 (6.1%)	6 (1.4%)	0 (0.0%)
	Platelet count decreased	25 (5.7%)	4 (0.9%)	1 (0.2%)
	Weight decreased	23 (5.2%)	1 (0.2%)	0 (0.0%)
	Blood creatinine phosphokinase increased	22 (5.0%)	1 (0.2%)	1 (0.2%)
	Amylase increased	21 (4.8%)	8 (1.8%)	0 (0.0%)
	Aspartate aminotransferase increased	18 (4.1%)	2 (0.5%)	1 (0.2%)
	Alanine aminotransferase increased	12 (2.7%)	1 (0.2%)	0 (0.0%)

Includes all adverse reactions occurring in ≥2% (all grades) of adult patients in GIST studies during treatment with SUTENT) Source: Adapted from the EU SUMMARY OF PRODUCT CHARACTERISTICS version approved on 4 January 2011.

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.

1.3.4. Pediatric Phase I Clinical Trial (ADVL0612)

A Phase I study conducted by the Children's Oncology Group (COG), ADVL0612, was designed to evaluate the safety and tolerability of sunitinib in patients aged 2-21 years with advanced solid tumors. This study has determined the MTD associated with sunitinib in this Phase 1 oncology population, and has characterized its safety profile and pharmacokinetics. Patients received sunitinib once daily for 4 weeks, followed by a 2 week break between each cycle. Doses were rounded to the closest 12.5 mg.

Twenty-three patients were treated on Amendments A and B (protocol amendment explained below). The median age was 13.9 years; (range, 3.9 – 20.6 years). Table 4 summarizes the DLTs. At the starting dose of 20 mg/m^2 (approximately 80% of the approved adult dose), DLTs included grade 2 systolic dysfunction, grade 3 anorexia and grade 4 neutropenia. The sunitinib dose was then de-escalated to 15 mg/m^2. DLTs in this cohort included prolonged grade 3 ALT elevation in 1 patient, and grade 3 diastolic plus grade 2 systolic dysfunction in a patient who had received maximal anthracycline therapy in addition to cardiac radiation exposure. A detailed evaluation of both cases of reversible cardiac dysfunction indicated that these patients had received cumulative doxorubicin doses of either 157 mg/m^2 (grade 2 systolic dysfunction) or 347 mg/m^2 (grade 2 systolic dysfunction) prior to entering the Phase I study. There were also 8 additional patients in this study who had received prior anthracycline exposure where no cardiac dysfunction was detected. However, it was felt that the cardiotoxicity might have been due in part to anthracycline exposure and in one case compounded by prior cardiac radiation exposure. Therefore, the protocol was amended (Part B) to exclude patients with prior anthracycline or cardiac radiation exposure in addition to those with known bone marrow metastasis.

Table 4. Dose Limiting Toxicities from ADVL0612

Dose Level	Dose Limiting Toxicity
Part A	
20 mg/m^2	1) Grade 2 systolic dysfunction 2) Grade 3 anorexia 3) Grade 4 neutropenia
15 mg/m^2	1) Grade 3 ALT elevation 2) Grade 3 diastolic + Grade 2 systolic dysfunction
Part B (patients with prior anthracycline or cardiac radiation exposure and those with known bone marrow metastasis excluded)	
15 mg/m^2	0/6 evaluable patients
20 mg/m^2	1) Grade 4 hyperuricemia in setting of Grade 2 diarrhea/dehydration 2) Grade 5 aspiration pneumonia in the setting of Grade 4 punctate hemorrhage into a progressive diffuse pontine glioma

Eight patients were enrolled on Part B of the study at a starting dose of 15 mg/m^2. Two patients suffered early disease progression, therefore were not evaluable for DLT. None of the 6 evaluable patients treated at this dose level experienced DLT. Subsequently, 2 of 3 patients treated at 20 mg/m^2 experienced DLT, including grade 4 hyperuricemia in the

setting of grade 2 diarrhea and dehydration, and grade 5 aspiration pneumonia in the setting of grade 4 punctate hemorrhage into a progressive diffuse pontine glioma. While this episode may have been related to the natural history of disease,[25] a possible attribution to study therapy could not be excluded. These results established 15 mg/m^2/day as the MTD for patients without prior cardiac radiation or anthracycline exposure. No cardiac dysfunction was observed in Part B of the trial.

Patient characteristics and other safety results are summarized in Appendix 2. Neutropenia, thrombocytopenia, and transaminase elevation were the most commonly reported toxicities. Gastrointestinal symptoms and fatigue were the most commonly reported symptoms.

1.3.5. ADVL0612 Sunitinib Pharmacokinetic Profile

In the pediatric Phase 1 study, steady state concentrations of sunitinib, the active metabolite SU012662, and total drug (sunitinib + SU012662) were reached by Day 7. Five of 14 patients (36%) at the 15 mg/m^2 dose level and five of nine patients (56%) at the 20 mg/m^2 dose level had steady-state total drug trough concentrations >50 ng/mL, the target total drug concentration for RTK inhibition based on preclinical studies.[11] Nine patients participated in the extended PK sampling study. A median peak sunitinib plasma concentration of 16.8 ng/mL (range 9.5 – 61.4) was achieved 7 hours after the first dose. Median values of the sunitinib and SU012662 half-life, based on the accumulation ratios calculated from the steady-state data were 38.7 (range 23.9 – 61.7) and 93.4 (range 47.4 – 176) hours, respectively.

1.3.6. Application of ADVL0612 PK Results to Young Patients with GIST

ADVL0612 has several features limiting its applicability to the pediatric GIST population. Many patients enrolled on ADVL0612 were heavily pre-treated with chemotherapy and/or radiation therapy while pediatric GIST patients will not have received multiple cycles of cytotoxic chemotherapy prior to sunitinib.

At the established pediatric MTD, the C_{max} and AUC_{48} are both below the levels observed in adult patients with GIST during sunitinib therapy. The adult daily dose of 50 mg is equal to a body surface area (BSA)-corrected dose of approximately 30 mg/m^2 (ie, 50 mg / 1.73 m^2 ≅ 30 mg/m^2). In adults who require a dose reduction, the daily dose of 37.5 mg is equal to a BSA-corrected dose of approximately 22 mg/m^2 (ie, 37.5 mg / 1.73 m^2 ≅ 22 mg/m^2). A recent meta-analysis indicates that increased steady-state AUC of sunitinib and response probability, with AUC significantly associated with improved stable disease in patients with GIST.[26]

Based on the preliminary population PK analysis from ADVL0612, the oral clearance and volume of distribution in pediatric patients appeared to correlate with BSA. When corrected for BSA, the oral clearance of sunitinib in children appeared to be similar to that in adult patients (analysis data in house). However, since the MTD from this study was lower than that observed in adult patients (ie, 15 mg/m^2 versus 30 mg/m^2), the steady state trough total drug concentrations fell below target concentrations (50 ng/mL, based on preclinical data) in 9 of 14 (64%) patients. While peak concentrations would be predicted to exceed this target

concentration, it is likely that tyrosine kinase inhibition may be intermittent for most patients treated at the 15 mg/m^2 dose. Therefore, to achieve the optimal plasma concentrations, intra-patient dose escalation up to the adult MTD of 30 mg/m^2 per day has been incorporated into the study design based on individual patient tolerability. Since the incidence of DLT at 15 mg/m^2 in children is lower than those seen at the adult MTD of 30 mg/m^2, it would be expected that the majority of pediatric patients would qualify for intra-patient dose escalation.

To ensure that the plasma concentrations of sunitinib and its active metabolite in pediatric GIST patients are comparable to that in adult GIST patients, the PK samples collected in Cycle 1 (after collection of Day 28 of Cycle 1) will be batched together and sent immediately to the designated lab (ie, BASi) for bio-analysis. Following the preliminary quantification of sunitinib and its active metabolite in plasma samples, the preliminary concentration data will be sent to Pfizer Inc. for PK analysis. Following the PK analysis using NONMEM or other approaches, the steady state plasma total exposures will be estimated for that individual patient and compared to the plasma total exposures observed in adults GIST patients from historical data. The PK analysis results, in addition to the comparative analysis, will be provided to the investigator as soon as possible, hopefully prior to starting Cycle 2 therapy. In addition to the patient's safety and tolerability data from Cycle 1, the PK data will be available to the treating investigator to guide a decision on the patient's dose for Cycle 2 or later cycles. Therefore, the required PK samples collected from each pediatric patient during Cycle 1 may be used to facilitate the dose optimization process in that individual patient.

We propose to evaluate the PK, safety and preliminary efficacy of sunitinib in 6 pediatric and up to 15 young adult patients diagnosed with GIST. The characterization of the PK profile of sunitinib and its active metabolite has been selected as the primary endpoint of this study for the following reasons: 1) PK data for sunitinib and its active metabolite in pediatric GIST patients are lacking, 2) additional sunitinib PK data are needed to combine with the Phase 1 pediatric data to more accurately describe the PK profile of sunitinib and its active metabolite in children, and to identify the fixed effect sources of variability in children, 3) the PK data will be used to perform PK-PD modeling for both safety and potentially efficacy endpoints to improve our understanding of the relationship between safety and efficacy and plasma drug concentrations, and 4) the PK samples may be used to facilitate the dose-optimization process in each individual pediatric patient.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To characterize the plasma PK profile of sunitinib and its active metabolite SU012662 in children and young adults with advanced, unresectable GIST.

Secondary Objectives:

- To investigate whether doses greater than the established pediatric MTD are tolerated in pediatric patients with GIST;
- To investigate the safety and tolerability of sunitinib in children and young adults with GIST;
- To investigate the anti-tumor activity of sunitinib in children and young adults with GIST;
- To explore PK-pharmacodynamic relationships with respect to safety and efficacy in children and young adults with GIST, if data allows.

2.2. Endpoints

Primary Endpoint:

- Pharmacokinetic parameters of sunitinib and its main active metabolite (SU012662) including total plasma exposure (AUC_{24}) and oral clearance (CL/F).

Secondary Endpoints:

- Type, incidence, severity (graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0 [v4.0]), timing, seriousness, and relatedness of adverse events and laboratory abnormalities;
- Objective response rate, duration of response, PFS and OS at 2 years after study enrollment;
- Pharmacokinetic-pharmacodynamic relationships with respect to safety and efficacy in pediatric GIST, if data allows.

3. STUDY DESIGN

This study is a single arm, multi-center, multi-national, clinical trial evaluating the PK, safety and preliminary anti-tumor efficacy of sunitinib in children and young adults diagnosed with advanced, unresectable GIST. The study aims to enroll 6 evaluable patients aged 6 years to less than 18 years. In addition, up to 15 young adults aged 18 - <21 years diagnosed with GIST may be enrolled.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team and confirmed with Pfizer before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for to commence study drug treatment into the study:

1. Histological diagnosis of GIST (refer to Section 6.1);

2. Tumor tissue must be available to assess *KIT*, *PDGFRA,* and *BRAF* genotypes (for any of these genes where genotyping was not previously performed) and to assess succinate dehydrogenase (SDH) protein expression by immunohistochemistry. For exceptions see Section 6.1;

3. Patients must have demonstrated disease progression or intolerance to imatinib mesylate; have GIST with non-mutant *KIT* (tumor genotyping may be performed prior to or during screening; patients with an indeterminate *KIT* genotype are eligible if genotyping performed during screening); or cannot obtain imatinib in their country.

4. Age 6 to <21 years;

5. Advanced, unresectable GIST for which there are no available options for treatment with curative intent as assessed by the investigator;

6. Measurable (per Response Evaluation Criteria in Solid Tumors; RECIST version 1.1; or evaluable disease (Refer to Appendix 4);

7. Resolution of all acute toxic effects of prior cancer treatment, radiotherapy or surgical procedure to NCI CTCAE v4.0 grade ≤1;

8. ECOG Performance Status 0 -2 (for patients ≥11 years of age) or Lansky ≥50% (for patients <11 years);

9. Adequate organ function determined within 14 days prior to enrollment, defined by:

    - Peripheral absolute neutrophil count (ANC) ≥1500/μL;
    - Platelet count ≥100,000/μL;
    - Hemoglobin ≥10 g/dL;
    - Total bilirubin ≤1.5 x upper limit of normal (ULN) for age;
    - ALT (SGPT) or AST (SGOT) ≤ 3 x ULN for age;
    - Serum albumin ≥2.0 g/dL;

- Serum amylase and lipase <1.5 x ULN;

- Serum creatinine based on age/gender as follows:

Age	**Maximum Serum** Creatinine (mg/dL)	
	Male	Female
6 to <10 years	1	1
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985)[27] utilizing child length and stature data published by the CDC.

- Blood Pressure (BP) < the 95th percentile for age, height and gender (refer to Appendix 3 for pediatric ranges);

- Cardiac shortening fraction or ejection fraction greater than the lower limit of normal (LLN).

10. Evidence of a personally signed and dated informed consent (and where applicable, assent) document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study;

11. Patients (including legal guardian for minors where applicable) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures, including anticipated ability to swallow capsules;

12. Male and female patients of childbearing potential who are sexually active must agree to use a highly effective method of contraception throughout the study and for 30 days after the last sunitinib treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active (refer to Section 4.3).

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Current treatment with another investigational agent and/or systemic anti-cancer therapy within 4 weeks before starting sunitinib treatment.

2. Prior sunitinib treatment;

3. Prior therapy with known risk for cardiovascular complications, eg, high intensity anthracycline therapy (ie, total equivalent cumulative dose > 100 mg/m^2 of doxorubicin) or prior radiation therapy that included the heart (cardiac silhouette) and/or craniospinal radiation;

4. Concomitant treatment with any drug having proarrhythmic potential (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide);

5. Prior diagnosis of cardiac disease, including, but not limited to:

   - Ongoing cardiac dysrhythmias of NCI CTCAE v4.0 ≥ grade 2, atrial fibrillation of any grade;
   - QTc interval >450 msec for males or >470 msec for females;
   - Hypertension that cannot be controlled by medications;
   - Any of the following within the 12 months prior to starting study treatment: congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolism.

6. Grade ≥3 hemorrhage within 4 weeks prior to first dose of study drug

7. Current treatment with therapeutic doses of coumarin-derivative anticoagulants such as warfarin or anti-vitamin K agents;

8. Concurrent administration of strong cytochrome P450-3A (CYP3A4) inhibitor(s) and/or inducer(s) within 7 and 12 days prior to first dose of study drug, respectively (see Section 5.5.2);

9. Prior radiation to >25% of the bone marrow.

10. Patients with history of allergic reaction attributed to any component of sunitinib capsules;

11. Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for 30 days after last dose of investigational product; in the UK, males and females of childbearing potential not using two (2) methods of highly effective contraception or not agreeing to continue two (2) methods of highly effective contraception for 30 days after last dose of investigational product (refer to Section 4.3);

12. Active infection with HIV, or receiving antiretroviral therapy for HIV disease;

13. Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial;

14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

4.3. Life Style Guidelines

All patients (male and female) with reproductive potential, including females above age 11 must agree to practice simultaneously 2 effective contraception methods or abstinence for at least 14 days prior to the first dose of study drug and for 30 days following the last dose of study drug. At each study visit, the investigator must confirm and document in the patient notes that the patient continues to practice effective contraception consistently and correctly as noted above.

Examples of effective contraception methods may include:

- Barrier (condoms, diaphragm or cervical cap) with spermicide.
- Oral or other acceptable contraceptives which may include but is not limited to: injectable, implanted or patch hormone therapy, IUD, or documented surgical sterilization.
- Absolute sexual abstinence, without a second method.
- For patients enrolled in the United Kingdom, effective contraception is defined as double barrier contraception (ie, male condom OR female condom used WITH a spermicide, diaphragm, cervical cap, or intrauterine device). Note: male and female condoms should NOT be used in tandem as friction may result in product failure.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Following completion of the screening assessments and confirmation of eligibility, sites will be instructed to use the next available patient ID in RDC-Onsite (database). The first patient would be XXXX[PPD] where XXXX is the site number. The next patient ID would be XXXX[PPD], XXXX[PPD], etc. For example, Site [PPD] would have patient IDs [PPD], [PPD], and [PPD] even if Site [PPD] enrolled patients during the same timeframe.

5.2. Drug Supplies

Sunitinib malate is formulated in 6.25 mg, 12.5 mg and 25 mg capsules. The latter two strengths listed are authorized products; however, the 6.25 mg strength is only available for investigational purposes.

5.2.1. Formulation and Packaging

Sunitinib malate study medication will be supplied to the clinic pharmacy by the Sponsor (Pfizer Inc) as hard gelatin capsules in HDPE bottles containing 28 or 30 capsules for oral administration. Sunitinib malate capsules will contain 6.25 mg, 12.5 mg and 25 mg equivalents of sunitinib free-base.

Capsule Strength	Description
6.25 mg	#3 gray/gray capsule
12.5 mg	Swedish Orange, Size 4 hard gelatin capsule
25 mg	Swedish Orange/Caramel, Size 3 hard gelatin capsule

5.2.2. Preparation and Dispensing

Sunitinib capsules will be dispensed at the beginning of each treatment cycle. New drug supply will be supplied at the start of each cycle. In the event of dose modification (and in consultation with study team) where the patient has sufficient drug of the appropriate strengths to finish that current cycle, new drug may not be dispensed.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of anti-cancer agents.

5.2.3. Sunitinib Administration

A cycle of therapy is considered to be 42 days, with the reporting period for each cycle being Day 1 to Day 42. For all patients, sunitinib will be dosed intermittently [4 weeks on study drug followed by 2 weeks off therapy (Schedule 4/2)].

Sunitinib can be taken without regard to meals, but the incidence of drug-associated nausea may be less when taken with food. Therefore, it is recommended that sunitinib be taken with at least a small amount of food.

Self-administration of sunitinib capsules will take place on an outpatient basis (under parent/legal guardian supervision as appropriate) except on days when PK sampling is performed. Capsules should be taken once daily in the morning on the first 28 days of each cycle with the exception of study visit days on which the dose for that day should be withheld until immediately after the completion of all study visit day activities and the investigator's approval for continued dosing. Capsules must be administered whole, not opened, or manipulated prior to administration.

In the absence of progressive disease, patients may receive up to 18 cycles of sunitinib therapy for up to 24 months.

5.2.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosate strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AEpage and, if applicable, any associated AE(s) are captured on an AE CRF page.

Patients should take a missed dose as soon as they remember. However, patients should not take the dose if it is close to the next dose. Instead, patients should take the next dose at the regular time. Patients should not take more than one dose of study drug at a time. The study drug may be re-administered (after 1hr) in the case of vomiting if this event occurs within 15 min after administration or if all intact study drug capsules are observed in the vomitus.

5.2.5. For Children (age less than 18 years at enrollment)

Dosing for all cycles will be based on the BSA obtained at the start of each cycle.

BSA for dosing should be calculated using the Mosteller formula.[28]

$$\text{BSA in } m^2 = [(\text{height in cm} \times \text{weight in kg})/3600]^{1/2}$$

http://www.halls.md/body-surface-area/bsa.htm

The sunitinib intended starting dose will be 15 mg/m^2/day (not to exceed 50 mg/day) on Schedule 4/2. (See Appendix 6).

Intra-patient dose escalation of sunitinib will be allowed after completion of Cycle 1 based on dose modification guidelines detailed in Section 5.2.8. Dose escalation will be in increments of 7.5 mg/m^2, up to a maximum dose of 30 mg/m^2 (not to exceed 50 mg/day). The dose and the dose change increments will be rounded to the nearest number which is a multiple of 6.25 mg, the lowest dose strength available. After Cycle 1, when the minimum frequency of clinic visits is reduced, an additional Day 15 visit is required if the sunitinib dose is escalated during that cycle.

At each dose level (mg/m^2), based on each individual patient body surface area (BSA) the calculated total dose in mg is rounded to the nearest number which is a multiple of 6.25 mg, the lowest dose strength available (See Table 5 for the available doses). The rounded doses considering an individual patient's BSA for daily Dose Levels of 15 mg/m^2, 22.5 mg/m^2 and 30 mg/m^2 have been provided in Appendix 6.

Table 5. Available Sunitinib Doses (Using 6.25 mg, 12.5 mg and 25 mg capsules)

Daily Dose	May Be Dispensed As
6.25 mg	1 x 6.25-mg capsule
12.5 mg	1 x 12.5-mg capsule **or** 2 x 6.25 mg capsules
18.75 mg	1 x 6.25-mg capsule **plus** 1 x 12.5-mg capsule
25 mg	1 x 25-mg capsule **or** 2 x 12.5-mg capsules
31.25 mg	1 x 25-mg capsule **plus** 1 x 6.25 mg capsule
37.5 mg	3 x 12.5-mg capsule **or** 1 x 25-mg capsule **plus** 1 x 12.5-mg capsule
43.75 mg	1 x 25 mg capsule **plus** 1 x 12.5 mg capsule **plus** 1 x 6.25 mg capsule **or** 3 x 12.5 mg **plus** 1 x 6.25 mg
50 mg	2 x 25 mg capsules

5.2.6. For Young Adults (age ≥18 years)

Young adults of age ≥18 years will be dosed according to the approved adult dosing regimen, 50 mg once daily for 4 weeks, followed by a 2 week break in dosing (Schedule 4/2). For patients who turn 18 during the treatment phase of this study, a young adult consent may be required per local regulation, and dose modifications will be at the discretion of the investigator based on tolerability.

5.2.7. Criteria for Starting Subsequent Cycles

1. A cycle may be repeated every 42 days if the patient has met laboratory parameters as defined below (if the treatment is delayed more than 28 days to meet the following criteria the patient may be considered for withdrawal from the study):

2. Adequate organ function defined by:

   - Peripheral absolute neutrophil count (ANC) ≥1500/μL with or without growth factor support;
   - Platelet count ≥75,000/μL;
   - Hemoglobin ≥10 g/dL;
   - Total bilirubin ≤ 2 x upper limit of normal (ULN) for age;

- ALT (SGPT) or AST ≤ 3 x ULN for age;
- Serum albumin ≥2.0 g/dL;
- Serum amylase and lipase < 2 x ULN;
- Serum creatinine based on age/gender as follows:

Age	**Maximum Serum** Creatinine (mg/dL)	
	Male	Female
6 to <10 years	1	1
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985)[27] utilizing child length and stature data published by the CDC.

- Blood Pressure (BP) < the 95th percentile for age, height and gender (refer to Appendix 3 for pediatric ranges);
- Ejection fraction below the lower limit of normal (LLN) (institutional norm).

5.2.8. Dose Modifications

Patients will be monitored for toxicity, and the sunitinib dose may be adjusted according to individual patient tolerance at the discretion of the investigator. The available doses were presented in Table 5 above. After Cycle 3, when the frequency of clinic visits may be reduced to a minimum of once per cycle, investigators may wish to include more frequent visits for assessment of blood pressure and/or to perform clinically indicated laboratory tests if sunitinib related toxicities are expected or observed. The following are suggested guidelines that investigators may use as a reference.

For patients <18 yrs, intra-patient dose escalation of sunitinib will be allowed after completion of Cycle 1 and/or later cycles, and in the absence of toxicity greater than Grade 1 in the prior cycle, with exceptions listed in the footnotes to Table 6. Dose escalation will be in increments of 7.5 mg/m^2, up to a maximum dose of 30 mg/m^2 (not to exceed 50 mg/day). The sunitinib dose may be reduced in response to toxicities based on investigator discretion, with general guidelines listed in Table 6. Dose reductions in patients <18yrs will be in decrements of 7.5mg/m^2. For young adults aged 18-<21 years, inclusive, the intra-patient dose modification will be in 12.5 mg increments or decrements, consistent with Sutent® drug label recommendation.

Sunitinib will be held for Grade 3 and 4 toxicities until the toxicity decreases to Grade 1 (≤Grade 2 for hematologic toxicities) or baseline, at which point sunitinib will be resumed as detailed in Table 6 below. Re-escalation will be permitted with appropriate supportive care and monitoring at the discretion of the investigator.

Recurrence of Grade 3 or greater toxicity will require dose reduction until toxicity has resolved to baseline.

Any patient requiring >4 weeks of dose interruption for toxicity should be considered for study withdrawal.

Table 6. Dose Modifications for Toxicity Attributed to Sunitinib for Patients <18 Years of Age

Toxicity	Grade 0-1	Grade 2	Grade 3	Grade 4
Non-hematologic[4]	May escalate 1 dose level[1] or, if escalation previously attempted and reversed, continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then resume treatment at the same dose level (assuming non-recurrent) or reduce the dose by 1 level at the discretion of the investigator.[2]	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.[2]
Hematologic	May escalate 1 dose level or, if escalation previously attempted and reversed, continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2 or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.[3]	Withhold dose until toxicity is grade ≤2 or has returned to baseline, then reduce the dose by 1 level and resume treatment.[3]

1. A dose level will be considered 7.5 mg/m^2 increase or decrease from current dose.
3. Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting and/or diarrhea should persist at Grade 3 or 4 despite maximal medical therapy before reducing the sunitinib dose.
4. Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.
5. For hypertension guidelines reference Section 5.2.11.

5.2.9. Minimum Sunitinib Dose Allowed

For Children

Pediatric patients already receiving an absolute dose of 6.25 mg at the time of an indicated dose reduction must be removed from protocol therapy.

For Young Adults

For young adults, dose interruption and/or modification in 12.5 mg increments or decrements are recommended, based on individual safety and tolerability. The adult minimum acceptable dose for the purpose of this study is 25 mg/day.

5.2.10. Dose Modifications for Left Ventricular Systolic Dysfunction

- Left ventricular systolic dysfunction will be graded according to NCI CTCAE v4.0 criteria, but will also take into account absolute changes in ejection fraction.

- If LVEF decreases by more than 8 percentage points and decreases below an ejection fraction of 45%, hold study drug and repeat echocardiogram in 7 days. If LVEF remains below 45%, patient will be taken off-protocol therapy and referred to a cardiologist. If repeat ECHO does not confirm toxicity, patient may start next cycle of therapy on schedule with repeat ECHO 14 days and 28 days after start of next cycle. If any two ECHO demonstrate >8 absolute percentage point decrease in ejection fraction, the patient will be taken off-protocol therapy.

- If patient develops ≥Grade 3 left ventricular systolic dysfunction, patient should be withdrawn from the study and referred to a cardiologist.

5.2.11. Management of Sunitinib-induced Hypertension

Baseline blood pressure (BP) is defined as the BP obtained at the examination used for study enrollment as follows:

1. Measurements should begin after at least 5 minutes of rest and before invasive procedures, such as phlebotomy. Avoid using the lower extremity if possible. The appropriate cuff size must be used, with the bladder cuff encircling at least 80% of the arm.

2. Obtain 3 serial BPs from the same extremity with the patient in the same position, separated by approximately 2 minutes. These measurements should be recorded in the source document.

3. Average the systolic BP from the 2nd and 3rd measurements.

4. Average the diastolic BP from the 2nd and 3rd measurements.

5. The baseline BP is the average of the systolic over the average of the diastolic BP measurements. This average BP should be recorded in the CRF as the baseline BP.

Hypertension, defined as elevation of either the systolic or diastolic BP, should be considered per the following criteria:

- For children and adolescents, hypertension is defined as a systolic and/or diastolic BP that on repeated measurement is ≥95th percentile for age, height and gender. Refer to Appendix 3.

- Utilize NCI CTCAE v4.0 to determine the grade of hypertension for both pediatric patients and young adults.

- Elevated BP measurements should be confirmed on the same day. Patients with elevated BP should have BP measurements performed at least twice weekly until BP is consistently <95th percentile for age, height and gender.

Suggested Hypertension Management Guidelines for Pediatric Patients

1. Suggested hypertension management guidelines for pediatric patients are provided below; alternatively, hypertension may be managed according to investigator discretion. However, **In case of Grade 4 hypertension**, the patient should be permanently discontinued from the trial and anti-hypertensive therapy should be administered as clinically indicated.

2. If the average systolic and/or diastolic BP is <95th percentile for age, height and gender, continue sunitinib at the same dose.

3. If the average systolic and/or diastolic BP is greater than the 95th percentile and ≤10 mmHg higher than the 95th percentile, continue sunitinib at the same dose and recheck BP twice weekly. BP can be measured at a study site-approved local clinic as long as protocol guidelines are followed closely, and study site is involved with clinical decisions.

    a. Upon recheck, if the average BP is <95th percentile, continue sunitinib at the same dose;

    b. If the BP continues to be ≥95th percentile, when measured at least twice over a two week period, start anti-hypertensive therapy, continue sunitinib at the same dose, and monitor BP twice weekly.

4. If the average systolic and/or diastolic BP is 11-25 mmHg above the 95th percentile recheck BP twice weekly. If the BP continues to be >11 mmHg above the 95th percentile over a two week period (in at least 2 out of 3 average BP measurements) start anti-hypertensive therapy, continue sunitinib at the same dose and monitor BP twice weekly;

    a. If the average BP returns to <95th percentile within 14 days, continue sunitinib at the same dose and continue anti-hypertensive therapy;

    b. If the average BP remains elevated ≤25 mmHg above the 95th percentile for more than two weeks after the institution of antihypertensive therapy, hold sunitinib, monitor BP at least twice weekly;

        - If the average BP returns to <95th percentile within two weeks, restart sunitinib at a reduced dose (reduce by 7.5 mg/m^2);

        - If the average BP remains ≥95th percentile for more than two weeks, patient should be removed from study.

5. **If the average systolic and/or diastolic BP is >25 mmHg above the 95th percentile,** hold sunitinib, start or continue anti-hypertensive agent(s) per institutional guidelines. Monitor the BP at least twice weekly. (See 4b. above for guidance on restarting dosing).

Antihypertensive therapy should be continued until the BP is consistently <95th percentile.

If anti-hypertensive therapy is required, single agent therapy (eg, a calcium channel blocker such as amlodipine or nifedipine) should be started and the BP should be monitored at least twice weekly until within normal limits.

Hypertension Management Guidelines for Young Adults

For young adults aged 18 - <21 years there are no specific dose modification guidelines for hypertension. However, investigators may wish to refer to Section 5.2.8 above for suggested dose modification guidelines for toxicity by grade of severity.

5.2.12. Management of Hypothyroidism or Adrenal Insufficiency

Patients who develop hypothyroidism while on study should be evaluated and managed by an endocrinologist. Similarly, upon consultation with an endocrinologist, patients on this trial may be supported with appropriate hormone replacement therapy in the event they develop adrenal insufficiency in the absence of disease progression or unacceptable treatment-associated toxicity.

5.2.13. Compliance

A patient dosing diary will be used to track compliance, recording the date and time of each dose as well as any observed side effects, supportive treatments and/or medication errors. In the case of a sunitinib dosing error, documentation of the error in the dosing diary in addition to capturing the error on the dosing page of the associated CRF should be provided. This diary should be reviewed with the treating physician at each clinic appointment while on study.

Patients will be required to return all bottles of sunitinib at the beginning of each cycle. The number of capsules remaining will be documented.

5.2.14. Study Drug Overdose Instructions

In the event of an overdose of sunitinib, study drug should be withheld, symptomatic treatment should be instituted, and the Sponsor should be contacted to discuss the details of the overdose to formulate a clinical management plan.

5.3. Drug Storage and Drug Accountability

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked, limited access room. Capsules should be stored at controlled room temperature (15 ºC to 30ºC) and protected from light.

Storage conditions stated in the SRSD [ie, Investigator Brochure (IB), Core Data Sheet (CDS), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD)] may be superseded by the sunitinib label.

Investigators and site staff are reminded to check temperatures daily and ensure that room storage thermometers are working correctly as required for proper storage of investigational products. Any temperature excursions should be reported immediately.

The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor.

The investigator must maintain adequate records documenting the receipt, use, loss, or other deposition of the investigational product. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug and copies must be provided to Pfizer. The prescribed dose should also be recorded in the patient's medical records.

All bottles of study drug must be returned to the investigator by the patient. At the end of the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented. Otherwise, all bottles should be returned to Pfizer for appropriate destruction. Only appropriate, commercially labeled materials will be eligible for donation and will require explicit Pfizer pre-authorization.

5.4. Concomitant Medication(s) and/or Therapy

Patients must be instructed not to take any additional medications (including over-the-counter products) during the study without prior consultation with the Investigator. Commercially available palliative and supportive care for disease-related symptoms should be offered to all treated patients. The Sponsor will not supply palliative and supportive care agents. All concomitant medications and blood products, as well as interventions (eg, paracentesis) received by patients from screening until the end of follow up will be recorded on the relevant e-CRF.

Every medication including herbal supplements (specifically St. John's wort) or treatment taken by the patient during the trial and the reason for its administration must be recorded on the relevant e-CRF.

Supportive care may include premedication with antiemetics to limit treatment-related nausea and vomiting. During the first cycle of treatment patients should be closely monitored for diarrhea and treated with anti-diarrheals (eg, loperamide) at the first sign of loose or frequent stools. Patients may receive secondary prophylaxis for treatment-induced diarrhea.

Blood product transfusions should be administered as clinically indicated.

Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the investigator. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

Anti-inflammatory or narcotic analgesics may be offered as needed. Steroids are to be avoided whenever possible since they are metabolized by CYP3A4 and may interfere with sunitinib metabolism.

Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician.

Sunitinib should be interrupted during palliative radiotherapy – stopping 1 day before and resuming treatment 1 day after. Treatment with palliative radiotherapy should be recorded on the appropriate CRFs.

Surgery is permitted after documentation of response as defined in Appendix 4 (RECIST v1.1). This is to allow for resection of disease in patients whose tumors become resectable following treatment with sunitinib.

The appropriate interval of time between surgery and sunitinib treatment required to minimize the risk of impaired wound healing and bleeding has not been determined. Based upon PK considerations of sunitinib, stopping sunitinib is recommended at least 7 to 10 days prior to major elective surgery and at least 3 to 4 days before minor surgery. Patients who require surgery less than 14 days from treatment with sunitinib should be monitored closely for wound complications. The decision to reinitiate sunitinib should be based upon a clinical assessment of satisfactory wound healing and recovery from surgery.

5.5. Contraindicated Medications

5.5.1. Drugs with Proarrhythmic Potential

Concomitant treatment with any drug having proarrhythmic potential (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide) is not permitted during the study.

5.5.2. Inhibitors and Inducers of CYP3A4

Sunitinib is primarily metabolized by liver enzymes, in particular CYP3A4. There was a mean 1.8-fold increase in exposure of sunitinib when co-administered with ketoconazole, a strong inhibitor of CYP3A4 and a mean 4-fold decreased in exposure of sunitinib when co-administered with rifampin, a strong inducer of CYP3A4.

Therefore, co-administration with strong inhibitors (ketoconazole, itraconazole, clarithromycin, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir, nefazodone, voriconazole, telithromycin) and inducers (dexamethasone, rifampin, rifabutin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort) of CYP3A4 may result in significant increases/decreases in exposure of sunitinib and may alter the safety/efficacy of the drug (See the Study Manual for further information).

Strong CYP3A4 inhibitors and inducers are not permitted during the 7 and 12 days before dosing, respectively. During study participation, strong CYP3A4 inhibitors and inducers are not recommended. Alternative therapies should be used when available. If usage of a strong CYP3A4 inhibitor or inducer is necessary, this must be in agreement with the Sponsor.

5.5.3. Anticoagulants

Therapeutic doses of coumarin-derivative anticoagulants such as warfarin (Coumadin®) are not recommended, though doses up to 2 mg daily are permitted for prophylaxis of thrombosis, ie, PT and/or INR are targeted to <1.5 times the ULN.

6. STUDY PROCEDURES

Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB)-approved informed consent form and assent form as per local guidelines. All on-study procedures are permitted within the window frame indicated in Table 1.

6.1. Screening

The following screening procedures must be performed within 28 days prior to treatment on-study unless otherwise stated:

- Patient, parental or legal guardian (for patients <18 years of age) signature on current IRB-approved informed consent form and assent form per local guidelines; Tumor tissue must be available from all patients to assess *KIT*, *PDGFRA,* and *BRAF* genotyping (for any of these genes where genotyping was not previously performed) and to assess succinate dehydrogenase (SDH) protein expression by immunohistochemistry. For patients with no available, previously collected tumor tissue and incomplete testing information covering all of the above tests, a core biopsy is required, unless, in the opinion of the investigator, a biopsy would create an unacceptable risk to the patient. For such patients with incomplete genotype/SDH information, where a tumor biopsy cannot be obtained, patients may commence treatment with sunitinib if there is previous confirmation of GIST diagnosis (see below). Similarly, if tumor tissue is obtained from patients during screening but the results of testing are inconclusive, it will not be necessary to collect additional biopsies from patients before initiating treatment with sunitinib. However, if archived tumor tissue is available it may be requested for repeat analyses on a case by case basis, prior to treatment with sunitinib.

- In cases where any of the tumor analyses listed above have not previously been obtained, it is acceptable to obtain a paraffin block or 25 unstained slides (charged slides) representative of the tumor, along with the original pathology report. Tumor samples negative for SDH staining may be further subjected to *SDH* genotyping. It is suggested that for patients negative for SDH that patients/families be referred for genetic counseling. (See the Introduction for background on these tests).

- Confirmation of GIST diagnosis (requires documentation from a reference pathology laboratory); Medical history including oncologic history, history of other disease processes (active or resolved), concomitant illnesses, and demographics;
- Tanner Staging for patients < 18 yrs (this can only be waived upon agreement by Pfizer);
- Physical examination including examination of major body systems, ECOG (or Lansky) performance status, body weight, height and vital signs (temperature, blood pressure in triplicate, heart rate, respiratory rate);
- Hematology and Chemistry: See Section 7.2.2 for specific tests;
- Thyroid stimulating hormone (TSH);
- Urinalysis (dipstick test). (If the results of the dipstick test indicate a ≥2+ proteinuria, then follow-up should be performed with a quantitative urine protein analysis according to local standard practices);
- Prothrombin time or INR (The same test should be used throughout the study);
- Pregnancy test (urine), if applicable, within 7 days before initiation of study therapy (refer to Section 7.2.3);
- Three 12-lead ECGs approximately 2 minutes apart, preferably in the morning;
- ECHO or MUGA scan;
- MRI (or CT) scan of abdomen and pelvis, in addition to any other applicable sites of disease;
- Chest radiograph if tumor imaging (with MRI or CT scan) does not include the chest;
- Bone age determination for patients < 18yrs;
- FDG-PET, if locally available;
- Assessment of concomitant medications and treatments;
- Assessment of ongoing symptoms/events (serious adverse events must be recorded from time of signed consent);
- Study registration.

6.2. Study Period

The following will be performed according to the schedule outlined in the Schedule of Activities Table 1:

- Physical examination; follow baseline BP measurement guidelines provided in Section 5.2.8; Height and weight for pediatric patients at day 1 of each cycle (see Appendix 3 for reference; local standards may vary);
- Tanner Stage every 6-9 months for patients assessed at screen who were < Tanner Stage 5;
- Bone age at 1yr from treatment initiation for patients <18 yrs who had open growth plates at the last assessment;
- Hematology and blood chemistry labs: Same as Screening;
- TSH, Day 1 of Cycles 2, 3, and 4 and every even cycle number thereafter;
- PT or INR, as clinically indicated (The same test should be used throughout the study);
- Urinalysis, and 24-hour urine protein if urinalysis shows 2+ protein;
- Pregnancy test (urine) if applicable, prior to each cycle and as indicated (refer to Section 7.2.3);
- Three 12-lead ECGs: approximately 2 minutes apart in the morning (preferred) at Cycle 2, Day 1. Additional ECGs should be performed approximately 2 weeks following intra-patient sunitinib dose adjustments and as clinically indicated;
- ECHO or MUGA scan every 3rd cycle on Day 1;
- Tumor reassessment(s) before the end of the even number cycles (Day 28 of the even numbered cycles if feasible). Evidence of tumor response will be confirmed with repeated imaging studies at ≥4 weeks;
- FDG-PET at Cycle 1 day 28 only, if locally available;
- Treatment with sunitinib (refer to Section 5.2.3);
- Collection of blood for sunitinib PK profiling at the following timepoints:

  Mandatory samples:

  Cycle 1: Post-dose samples at 2, 4, 6, 8 hours on Day 1;

Cycle 1: Pre-dose samples: Day 1, Day 15 (between Days 12-18), and Day 28 (between Days 25-29);

Cycle 2: Pre-dose samples: Day 1, Day 15 (between Days 12-18) [only if a study visit is required due to dose escalation], and Day 28 (between Days 25-29);

Cycle 3: Pre-dose samples: Day 1, Day 15 (between Days 12-18) [only if a study visit is required due to dose escalation], and Day 28 (between Days 25-29);

Recording of exact actual time of draw and last dose prior to sampling is crucial.

NOTE: ALL PK SAMPLES COLLECTED BEFORE AND ON CYCLE 1 DAY 28 WILL BE BATCHED FOR THAT PATIENT AND SENT IMMEDIATELY TO BASi FOR BIO-ANALYSIS.

All subsequent PK samples will be batched and sent to BASi for bio-analysis after completion of Cycle 3.

- Optional pre-dose (trough) samples:

  Cycle 1: Day 7 (between Days 4 – 10), and/or Day 21 (between Days 18 – 24);

  At the time of sample collection, recording of the exact actual time of draw and last dose taken prior to sampling is crucial;

  NOTE: These pre-dose samples should be collected synchronous with other clinically relevant blood draws for patient comfort and convenience. Additional unplanned PK samples may be collected per investigator discretion.

- Assessment of compliance/accountability of study drugs;
- Assessment of adverse events;
- Assessment of concomitant medications and treatments.

After Cycle 1, Day 1, visits for assessments in subsequent cycles may commence from two days prior until one day after the scheduled visit.

Day 15 visits:

Day 15 of Cycle 1 is a mandatory visit. Day 15 visits of subsequent cycles are required if a dose escalation occurs during that cycle.

- Physical examination; follow baseline BP measurement guidelines provided in Section 5.2.8; Height and weight for pediatric patients at day 1 of each cycle (see Appendix 3 for reference; local standards may vary);
- Hematology and blood chemistry labs: Same as Screening;

6.3. Follow-up Procedures

6.3.1. Day 28 Visit

Patients should continue to be evaluated for 28 calendar days after the last dose of study drug. During the post-treatment follow-up visit, the following procedures should be performed:

- Assessment of adverse events;
- Physical examination, height, weight, vital signs, (see Appendix 3 for reference; local standards may vary);
- Tanner Stage if not performed within the prior 6 months;
- Bone age if not performed within the past year;
- Laboratory assessments or other tests necessary to follow unresolved or evaluate new adverse events;
- Assessment of concomitant medications and treatments.

In the event a patient is unable to return to the clinic for the follow-up visit, telephone contact with the patient to assess adverse events and concomitant medications and treatments is expected. If a physical examination and/or laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the patient is acceptable. If laboratory analyses are performed at a local laboratory, the laboratory's relevant normal ranges must be submitted to the Sponsor. The outcome of adverse events with a date of onset during the study period should be reevaluated, and any new adverse events should be recorded. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after patient withdrawal from study. These adverse events should be followed until resolution or until the investigator assesses them to be "chronic" or "stable".

6.3.2. Long Term Follow-Up

Follow-up survival information will be collected by telephone contact every 3 months (± 7 days) until death, or either 2 years from the patient's first dose of study treatment or completion of 18 cycles. Any new anti-cancer therapy given to the patient during this time should also be recorded on the relevant CRF by telephone contact or clinic visit. After completion of follow-up procedures, any developmental or growth delays that are possibly related to treatment should be reported through on the Adverse Event Monitoring Form as are routinely done for treatment-related SAEs that occur following completion of any trial.

6.4. Patient Withdrawal / End of Treatment

End of study occurs when the patient has completed 18 cycles of therapy, has completed follow-up survival, was lost to follow-up, or in the event of the patient's unplanned death.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the subject. In the case of a patient lost to follow-up the appropriate box should be checked off in the Patient Summary-End of Treatment CRF page. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product, request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

In addition, patients may be withdrawn from treatment in the case of:

- Disease progression, unless there is reasonable evidence of clinical benefit to justify continuation on protocol (the latter must be discussed with the Sponsor);
- Unacceptable toxicity;
- Need for treatment rest >4 weeks (if investigator considers there is potential for sustained clinical benefit, this may be discussed with the Sponsor);
- Need for anticancer therapy not specified in the protocol;
- Patient noncompliance;
- Patient lost to follow-up;
- Patient choice to withdraw from treatment (follow-up permitted by patient);
- Withdrawal of patient consent (cessation of follow-up);
- Completion of study therapy (18 cycles of study treatment; or maximum 24 months).

6.4.1. End of Treatment Procedures

At the end of the treatment or at withdrawal, the following procedures should be performed if they were not performed during the last week on treatment (exceptions: during the last 8 weeks for tumor assessments; during the last 6 months for Tanner staging, and during the last year for bone age assessment):

- Physical examination including major body systems, height, weight, and vital signs, Height and weight for pediatric (see Appendix 3 for reference; local standards may vary);
- Tanner Staging if meeting all of the following: performed at screen, < Tanner Stage 5 at last assessment, and > 6 months from last assessment;
- Bone age if at least 1 year from last assessment and growth plates open at last assessment;
- Hematology and blood chemistry labs as described in Section 7.2.2, including urinalysis for urine protein (dipstick);
- TSH, as clinically indicated;
- Urinalysis (If the results of the dipstick test indicate a ≥2+ proteinuria, then follow-up should be performed with a quantitative urine protein analysis according to local standard practices);
- Pregnancy test (urine) if applicable (refer to Section 7.2.3);
- PT or INR, as clinically indicated (The same test should be used throughout the study);
- Three 12-lead ECGs approximately 2 minutes apart in the morning (preferred), preferably time matched (±1 hour) with Screening;
- MUGA scan or ECHO, if clinically indicated;
- MRI (or CT) scan of abdomen and pelvis, in addition to any other applicable sites of disease, if not performed within the last 8 weeks prior to withdrawal;
- Chest radiograph, if clinically indicated;
- Assessment of adverse events;
- Assessment of concomitant medications and treatments;
- Assessment of compliance/accountability of study drugs.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the patient. When a protocol required test cannot be performed, the

investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Assessments

Blood to be used for pre-dose and post-dose pharmacokinetic (PK) plasma samples will be collected according to Table 7 for determination of plasma concentrations of sunitinib and its active metabolite SU012662 in 6 children aged between 6-17 years and up to 15 patients aged 18-<21 years in 1.2 mL K_3EDTA tubes. The blood draw methods for PK sampling should adhere to standard practice at the local institution. The post-dose samples obtained on Day 1 are all mandatory; however, some of the pre-dose samples are mandatory, whereas others are optional (Table 7). In situations where the mandatory PK samples cannot be obtained, the patient will be scheduled to provide the missed PK sample time point(s) on the same time and day of another cycle.

During Cycle 1, the mandatory (M) PK samples are the pre-dose, 2, 4, 6, and 8 hour post dose samples for Day 1 Visit, and the pre-dose sample for Days 15 and 28 Visits (Table 7). The optional (O) PK samples are pre-dose samples for Days 7 and 21 Visits (Table 7).

During Cycles 2 and 3, the mandatory PK samples are the pre-dose sample for Days 1, 15 [Day 15 collection is applicable only if a visit is required due to dose escalation], and 28 Visits (Table 7).

For each nominal Visit Day referred to above, the actual visit day can fall within a pre-specified interval to provide more flexibility for each individual patient (Table 7). All pre-dose samples can be collected at the same time as other chemistry lab tests. Additional PK samples may also be collected at the discretion of the investigator.

In Cycle 1, after collection of the pre-dose sample for Day 28 Visit, all PK samples collected should be batched together and shipped immediately to BASi for bio-analysis (Table 7). In addition, after collection of the last PK sample all the PK samples should be batched together and shipped to BASi for bio-analysis (Table 7).

Detailed instructions for collection, processing and storage of blood and tissue samples will be provided in the Central Lab manual. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the study report.

For all samples collected, 1) the actual date and time of sample collection, and 2) the actual date and time of the last dose prior to the PK sample collection should be properly recorded on the appropriate Case Report Form (Table 7).

Table 7. Table of Pharmacokinetic Sampling Time Points

Parameters	**Visit; Cycle (C) & Day (D)**										
	Cycle 1					Cycle 2			Cycle 3		
	Day 1	D7	D15	D21	D28	D1	D15	D28	D1	D15	D28
Actual Visit Day/Period (Inclusive)	D1	D4-D10	D12-D18	D18-D24	D25-D29	D1	D12-D18	D25-D29	D1	D12-D18	D25-D29
Sampling Time	**Pre-dose, 2, 4, 6, and 8 hr Post dose**	Pre-dose	**Pre-dose**	Pre-dose	**Pre-dose**	**Pre-dose**	*Pre-dose*	**Pre-dose**	**Pre-dose**	*Pre-dose*	**Pre-dose**
Mandatory (M) versus Optional (O)	**M**	O	**M**	O	**M**	**M**	*M*[a]	**M**	**M**	*M*[a]	**M**
Sample Shipments	**After collection of C1 D28 visit PK sample, batch all collected PK samples and ship to BASi immediately**					**After Collection of the last PK sample, batch all the remaining PK samples and ship to BASi**					
Dosing and Sampling Time & Date	**For all samples collected, record on the appropriate CRF: 1) the actual date and time for sample collection, 2) the actual date and time for the last dose prior to sample collection, and 3) actual date of any missed/held dose(s).**										

[a] only obtained if a visit is required due dose escalations within that cycle.

Non-Compartmental Analyses (NCA) will be carried out to estimate pharmacokinetic parameters maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration versus time curve from time zero to 8 hr post dose (AUC_8).

In addition to the NCA, Non-linear Mixed Effects Modeling (NONMEM) approaches will be used to estimate PK parameters absorption rate constant (K_a), oral clearance (CL/F), intercompartmental clearance (Q/F), volume of distribution for the central compartment (V_c/F) and peripheral compartment (V_p/F). Other parameters such as half life for the distribution phase ($t_{1/2\alpha}$) and elimination phase ($t_{1/2\beta}$), maximum plasma concentration (C_{max}), and area under the curve from time zero to 24 hr post dose (AUC_{24}) will be estimated based on individual patient parameter estimates.

Subsequently, sequential PK-pharmacodynamic modeling techniques using NONMEM will be applied to explore the relationships between safety and efficacy with plasma drug concentrations, if data allows.

Preliminary Analysis: Following the preliminary quantification of sunitinib and its active metabolite in plasma samples from Cycle 1 in each patient, and the PK analysis using NONMEM or other approaches, the steady state maximum and total plasma exposures will be estimated for that individual patient and compared to typical C_{max} and AUC_{24} observed in adults GIST patients from historical data. The PK analysis results, in addition to the comparative analysis, will be provided to the investigator as soon as possible, preferably prior to starting Cycle 2 therapy.

Definition of Evaluable: A patient will be declared evaluable for the primary endpoint if oral clearance of sunitinib and its active metabolite can be calculated, using a population PK approach (NONMEM).

7.2. Safety Assessments

7.2.1. Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the NCI CTCAE v4.0), timing, seriousness, and relatedness; and laboratory abnormalities.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.2.2. Laboratory Safety Assessments

Local laboratory studies will include:

- Hematology, coagulation and blood chemistry labs will be drawn as described in the Schedule of Activities (Table 1).
- Complete blood count (CBC); WBC with differential, hemoglobin, and platelets;
- Coagulation: Prothrombin time (PT) and/or INR;

- TSH;
- Blood chemistry: Sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphorous, uric acid, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total protein, albumin, amylase and lipase;
- Additional blood tests may be performed for the purpose of planning treatment administration, dose modification or following adverse events. At any time after initiation of dosing if liver function tests are abnormal refer to Section 8.5.2 for guidelines. *Electrolyte levels, particularly potassium and magnesium, should be monitored throughout the study, addressing any abnormalities that are observed;*
- Urinalysis (dipstick) will be performed locally for protein. Patients who develop ≥2+ proteinuria will undergo testing of 24-hour urine protein. In case of urine protein on two assessments, 24-hour urine protein should be re-assessed at least every other cycle;
- Urine pregnancy test for women. See the following section.
- Laboratory safety assessments may be performed outside of study sites in cases where patient travel to the study site for these tests is not possible. In such cases, accurate reporting of these results remains the responsibility of the study site.
- See Appendix 7 for a full listing of required tests

7.2.3. Pregnancy Testing

For female patients above age 11, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, within 7 days before sunitinib administration. A positive urine pregnancy test can be confirmed by a second urine pregnancy test prior to study exclusion. If the results of the urine pregnancy test are positive, the patient will not be eligible for study participation. Female subjects above age 11 must have a pregnancy test on Day 1 of each cycle of therapy and at the end of treatment. For female patients below the age of 11, if pregnancy testing is not performed, the investigator will document why testing was not necessary based on the level of sexual maturity. During the study period, positive urine pregnancy test can be confirmed by a second urine pregnancy test. A positive urine pregnancy test will require withdrawal from the study. Patients of less than 11 yrs at study start who turn 11 while on-study will then require pregnancy testing per the Schedule of Activities. For contraception guidelines, please refer to Section 4.3. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

7.2.4. Other Safety Assessments

- Height and body weight will be recorded prior to starting each treatment cycle for pediatric patients.

- Physical examination: A physical examination including, but not limited to, general, lungs, heart, abdomen, and extremities will be performed. The physical examination will include examination of known and suspected sites of disease.

- Performance Status: ECOG performance status scale will be used for patients ≥11 years of age or Lansky score for patients <11 years of age. Patients below the age of 11 who turn 11 while on-study will then require ECOG performance evaluations. (Refer to Appendix 5);

- Vital signs: Measurements of temperature, blood pressure, heart rate and respiratory rate after 5 minutes of rest;

    - ECG: Three consecutive 12 lead ECGs (with a 10-second rhythm strip) will be collected approximately 2 minutes apart at screening, on Cycle 2 Day 1 (pre-dose) and at the end of treatment visit to determine the mean QTc interval. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. If the mean QTc interval is prolonged (>500 msec), the ECGs should be overread by a cardiologist at the site for confirmation. Additional ECGs should be performed as clinically indicated, ie, after a new steady state of sunitinib is reached (ie, approximately 2 weeks) following:

- Intrapatient sunitinib dose escalation, or

- Intrapatient sunitinib dose reduction in response to:

    a. QTc interval prolongation,

    b. Significant electrolyte changes, vomiting, diarrhea, or addition of a strong CYP3A4 inhibitor listed in Section 5.5.2 after consultation with the sponsor's medical monitor.

7.3. Growth and Pubertal Maturation Assessments (Patients <18 yr only)

The testing below may be performed by a pediatric endocrinologist if not standard practice within the local oncology clinic.

Growth Assessments: Imaging of growth plate for bone age determination per standard local practice at screening is required for patients less than 18 years of age. Patients with closed growth plates will not be required to have further imaging for bone age determination. For patients with open growth plates, imaging for bone age determination will be conducted at one year intervals from the initiation of treatment until the Day 28 follow-up visit after the last dose of study drug.

Tanner Staging: Tanner staging for patients less than 18 years of age will be conducted, when locally feasible, at Screening. For patients who are Tanner Stage 1-4, Tanner staging should be repeated every 6-9 months until the end of sunitinib treatment, including the 28 day observation period post-treatment, or until the patient reaches Tanner stage 5. An end of

treatment assessment should be repeated if more than 6 months have elapsed since the prior assessment and if the prior staging was Tanner Stage 1-4. Tanner Staging will be captured for the following: pubic hair, breast (females), penis, and testes.

7.4. Efficacy Assessments

All baseline tumor imaging assessments are to be performed within 28 days prior to the first dose of medication, and then within 14 days (closer to Day 28 of the Cycle if possible) prior to the end of each even numbered cycle (ie, Cycles 2, 4, etc.). In the case of tumor response (PR or CR), confirmatory imaging studies should be performed at least 4 weeks after initial documentation of response and may be scheduled at 8 weeks for convenience.

Imaging studies will include MRI (or CT) scan of the abdomen and pelvis, plus other applicable sites of disease.

The determination of anti-tumor efficacy will be based on objective tumor assessments made according to the RECIST criteria v1.1. (See Appendix 4). MRI (or CT) scans should be performed with contrast agents unless contraindicated for medical reasons. In each patient, the same imaging modality should be used throughout the study to measure disease whenever possible. Tumor evaluation by positron emission tomography (PET) scan (baseline and at cycle 1 day 28 only) or by ultrasound may not substitute for MRI (or CT) scans. PET scans will be used for exploratory purposes only and will not be used in the assessment of efficacy.

For effusions or ascites, only cases having cytologic proof of malignancy should be recorded as tumor lesions on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the 'non-target and new lesion' CRF.

Measurable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

7.4.1. Time-To Event Endpoints

For the purposes of endpoint definitions, the term "on-study" includes the period of study medication treatment plus 28 days following the last dose of study medication.

Progression-free survival (PFS) is defined as the time from the date of enrollment to the date of the first documentation of objective tumor progression.

PFS will be censored on the date of the last on-study tumor assessment documenting absence of progressive disease for patients who are alive, on study and progression free at the time of the analysis, are given antitumor treatment other than study treatment or are removed from treatment prior to documentation of disease progression or death on study. For PFS, patients having no tumor assessments after screening will have tumor related endpoints censored on the date of enrollment. Other censoring situations will be described in detail in the statistical analysis plan (SAP), for each endpoint analyzed.

Overall Survival (OS) is defined as the time from the date of enrollment to the date of death due to any cause. For patients still alive at the time of analysis, the OS time will be censored on the last date the patients were known to be alive. Patients lacking data beyond enrollment will have their OS censored at date of enrollment.

The 2-year survival probability is defined as the probability of survival at 2 years after the date of enrollment based on the Kaplan-Meier estimate.

7.4.2. Response Rate Endpoints

Objective response rate (ORR) is defined as the percent of the full analysis population with a confirmed CR or PR according to RECIST Criteria v1.1, relative to all enrolled patients with measurable disease at baseline. Confirmed responses are those that persist on repeat imaging study ≥4 weeks after initial documentation of response. Designation of best response of stable disease (SD) requires the criteria to be met at least once after the first dose of medication, at a minimum interval of 8 weeks.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study (ie, prior to undergoing any study-related procedure and/or receiving investigational product) through and including 28 calendar days after the last administration of the investigational product.

SAEs occurring to a patient after the active collection period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are reported to the sponsor.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through the patient's last visit.

- If a patient begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;

- Clinically significant symptoms and signs;

- Changes in physical examination findings;

- Hypersensitivity;

- Drug abuse;

- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;

- Drug withdrawal;

- Drug misuse;

- Drug interactions;

- Extravasation;

- Exposure during pregnancy;

- Exposure via breastfeeding;

- Medication error.

- Worsening of signs and symptoms of the malignancy under study should be reported as adverse events in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect;

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTC Grade 5 (see Section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above.

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- **Concurrent with**

    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen (paracetamol), recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

Investigators will use the following definitions of Severity in accordance with the appropriate Common Terminology Criteria (CTCAE) term for Adverse Events (Version 4.0, Publish Date: October 1, 2009, (http://ctep.cancer.gov/reporting/ctc.html) to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event (SAE) report.

NOTE: The highlighted text above is not standard template language; please ensure Safety Risk Lead (SRL) has approved language and document on Study Decision Log.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the v 4.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marked products, an exposure during pregnancy (also referred to as exposure in-utero [EIU] occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

Additional information about pregnancy outcomes that are reported as serious adverse events follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the patient was given this letter to provide to his partner.

8.10. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also Section 6.4 Patient Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study patient. In addition, each study patient will be questioned about adverse events.

8.13. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding cases, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations. In this clinical trial, the reference document for determining whether an event is unexpected is the Investigator's Brochure.

9. DATA ANALYSIS/STATISTICAL METHODS

The detailed methodology for summary and statistical analysis of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outline in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

The following patient populations will be used in this study:

Full Analysis population: Full Analysis (or intent-to-treat) population will include all enrolled patients regardless of what treatment, if any, was received.

Per Protocol (PP) population: Per Protocol (or as-treated) population will include all enrolled patients who receive at least one dose of study drug.

The efficacy analysis will be based on the full analysis population. The pharmacokinetic analysis and safety analysis will be based on per protocol population.

9.1. Sample Size Determination

Due to the rarity of the disease and the difficulties in identifying pediatric patient suitable for participation in this study only 6 patients will be included. The statistical power has not been calculated. Descriptive analysis approach will be adopted to report study results.

9.2. Analysis of Primary Endpoint

Descriptive statistics for observed and dose-corrected (where appropriate) PK data will be reported for all patients with at least one PK observation by presenting the population size, arithmetic mean, standard deviation, percent coefficient of variation (CV%), median, minimum, maximum values. In addition, geometric mean and the 95% CI for the geometric mean, will be reported where appropriate. The key PK parameters in pediatric patients will be compared to adult patients with GIST based on historical data if data allows. The formal comparison will be carried out as part of the NONMEM portion using the historical PK data in adult GIST patients if data allows.

9.3. Efficacy Analysis

Efficacy analysis will be performed using full analysis population, which includes all enrolled patients in the study. In addition, efficacy analysis may be performed on the subgroups of patients aged 6 years to less than 18 years, patients aged 18 years to less than 21 years.

9.3.1. Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a confirmed complete (CR) or partial response (PR) relative to the number of patients enrolled in the treatment group. The number and percent of patients achieving objective response (CR or PR) will be summarized along with the corresponding exact 2-sided 95% CI calculated and presented.

9.3.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of enrollment to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first. PFS data will be censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who 1) are given anti-tumor treatment other than the study treatment prior to observing objective tumor progression; 2) are removed from the study prior to documentation of objective tumor progression; 3) are ongoing at the time of the analysis.

Patients who do not have any post-baseline tumor assessments will have their PFS endpoint censored on the date of enrollment. Death or disease progression that occurs after more than one missed visit will be censored on the day following the date of the last tumor assessment as well.

PFS will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. Median PFS and its corresponding 2-sided 95% CI for the median will be provided.

9.3.3. Duration of Response

Duration of response (DR) is defined as the time from the first objective documentation of complete or partial response that is subsequently confirmed to the first documentation of disease progression or to death due to any cause, whichever occurs first. DR will be calculated for the subgroup of patients with objective disease response. DR will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 2-sided 95% CI for the median will be provided if appropriate. The number of patients experiencing CR and PR may be small and thereby limit the use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics or listings will be provided.

9.3.4. Overall Survival

Overall survival (OS) is defined as the time from enrollment to the date of death due to any cause. OS data will be censored on the day following the date of the last contact at which the patient is known to be alive. OS will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median survival time and 2-sided 95% CI for the median will be estimated.

The 2-year survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log(1-year survival probability)] will be calculated using a normal approximation and then back transformed to give a CI for the 2-year survival probability.

9.4. Additional Analyses

9.4.1. Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. Patients not meeting the eligibility criteria and/or deviating from the protocol will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized. The full analysis population will be the analysis population for study conduct and patient disposition.

9.4.2. Baseline Characteristics

Demographic characteristics such as patient age, gender, height, weight, ethnicity, prior therapy, prior medication, medical history, tumor characteristics (including *KIT* genotype, optional *PDGFRA* genotype, and optional SDH expression by IHC), and signs and symptoms will be tabulated. The full analysis population will be the analysis population for baseline characteristics.

9.4.3. Treatment Administration/Compliance

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy. The per protocol population will be the analysis population for treatment administration and compliance.

9.5. Safety Analysis

Safety analysis will be performed using the per protocol population.

9.5.1. Analysis of Adverse Events

Frequencies of patients experiencing at least one AE will be displayed by System Organ Class and Preferred Term according to MedDRA terminology. Detailed information collected for each AE will include a description of the event, duration, severity, seriousness, study drug relatedness, action taken, and clinical outcome. Severity of the AEs will be graded according to the NCI CTCAE v4.0. The analysis will be performed on AEs classified as treatment emergent.

Summary tables will present the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of patients receiving at least 1 dose of study medication. Within each table, the AEs will be categorized by MedDRA system organ class and preferred term. Additional subcategories will be based on event intensity and relationship to study drug.

Individual patient listings will be prepared for all AE data.

9.5.2. Analysis of Clinical Laboratory Data

Hematology and blood chemistry data will be graded according to NCI CTCAE v4.0 severity grade. The frequencies of the worst severity grade observed will be displayed for each parameter for the study and by cycle.

Listing tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment.

Summary tables will be prepared to examine the worst toxicity grade on-study and distribution of laboratory measures over time. Shift tables may be provided to examine the distribution of laboratory toxicities.

9.5.3. Concomitant Medications

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary; patients who received concomitant medications will be listed.

9.6. Interim Analysis

No interim analysis is planned in this study.

9.7. Safety Review

Regular safety review will be performed by designated team members of the Sponsor's primary study team. In the cases of SAEs, a separate oversight function is performed as an ongoing review of all SAEs for trials testing sunitinib. This team is led by representatives

from the Sponsor's Worldwide Safety and Risk Management who are independent of the study team.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be patient to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections from regulatory authorities or audits from Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization (ICH) guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Children and some adolescents are legally unable to provide informed consent to participate in clinical trials. Informed consent must be obtained instead from the legally acceptable representative of the child or adolescent, usually their parent(s) or guardian. However, children and adolescents should be involved in health care decisions affecting them. To that end, ICH guidelines, EMEA Guideline on the Ethics of Clinical Trials in Children (in framework of Directive 2001/20/EC) and FDA regulations require that the assent from the child or adolescent be obtained when this is appropriate and when the potential patient is capable of providing assent. The determination of appropriateness and capacity is made by the investigator and/or the relevant IRB or IEC. Assent is not required if the Investigator and/or the IRB/IEC determine that the capability of the child or adolescent patient is so limited that they cannot provide assent.

If a patient signed assent for a study, a consent must be signed once the patient turns legal age, based on local requirements.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees, investigator outreach through cooperative groups, patient advocacy groups, and posting of the study outline on websites may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application [ie, Clinical Trial Application (CTA) and ethics application in the Member State]. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as collection of the final data point in the study. Because this clinical trial includes a survival endpoint, the last data point is anticipated to be the last survival follow-up (ie, date last known alive or of death) prior to the cutoff date for database lock for the final Clinical Study Report.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of sunitinib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1. Communication of Results by Pfizer

Pfizer fulfils its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- Results will be posted within one year of the primary outcome completion date (PCD).

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, patient to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Concentration versus Time Curve
AUC_{24}	AUC from time zero to 24 hr post dose
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C#	Cycle (1, 2, 3, etc.)
CBC	Complete Blood Count
CI	Confidence Interval
CL/F	Oral clearance
Cmax	Maximum Plasma Concentration
Cmin	Minimum Plasma Concentration
COG	Children's Oncology Group
CR	Complete Response
CRO	Contract Research Organization
CRF	Case Report Form
CT	Computerized Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Percent Coefficient of Variation
CYP3A4	Cytochrome P450 Enzyme, 3A4
D	Day
DR	Duration of Response
DLT	Dose Limiting Toxicity
EKG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EIU	Exposure In Utero (or during pregnancy)
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FDA	US Food and Drug Administration
FDAAA	US Food and Drug Administration Amendments Act of 2007
FDG-PET	Fluorodeoxyglucose-Positive Electron Tomography
GCP	Good Clinical Practice
GIST	Gastrointestinal Stromal Tumor
GGT	Gamma Glutamyl Transpeptidase
HCT	Hematocrit
Hgb	Hemoglobin
IB	Investigator Brochure
HR	Hazard Ratio
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IHC	Immunohistochemistry

INR	International Normalized Ratio
IRB	Institutional Review Board
KIT	Stem Cell Factor Receptor
LLN	Lower Limit of Normal
LSLV	Last Subject, Last Visit
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCA	Non-Compartmental Analyses
NONMEM	Non-linear Mixed Effects Modeling
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDCO	EMA's Pediatric Committee
PDGF(R)	Platelet-derived Growth Factor (Receptor)
pGIST	Pediatric Gastrointestinal Stromal Tumor(s)
PE	Physical Exam
PFS	Progression-Free Survival
PHRMA	Pharmaceutical Research and Manufacturers of America
PWS	PHRMA Website Synopsis
PK	Pharmacokinetic(s)
PP	Per Protocol
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RTK	Receptor Tyrosine Kinases
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDH	Succinate Dehydrogenase
SmPC	Summary of Product Characteristics
t_{max}	time to C_{max}
$t_{1/2\alpha}$	Half Life for the Distribution Phase
$t_{1/2\beta}$	Half Life for the Elimination Phase
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USPI	United States Package Insert
VEGF(R)	Vascular Endothelial Growth Factor (Receptors)
V_c/F	Volume of Distribution for the Central Compartment
V_p/F	Volume of Distribution for the Peripheral Compartment
v4.0	Version 4.0
WBC	White Blood Cells
WT	Wild-type

Appendix 2. ADVL0612 SUMMARY TABLES

ADVL0612 A Phase I Study of Sunitinib (SU011248), an Oral Multi-Targeted Tyrosine Kinase Inhibitor, in Children with Refractory Solid Tumors – **SUMMARY TABLES**

Patient Characteristics	**Overall Study** (n = 23)	**Part A** (n = 12)	**Part B** (n = 11)
Median age, years (range)	13.9 (3.9 – 20.6)	14.5 (10.6 – 20.6)	11.1 (2.9 – 18.2)
Male : Female	11 : 12	8 : 4	3 : 8
Diagnosis			
Brain tumor (Part B only)	8		8
Soft tissue sarcoma	4	3	1
Ewing sarcoma	2	2	
Neuroblastoma	2	2	
Osteosarcoma	2	2	
Other	5*	3	2
Measurable disease by RECIST	17	8	9
Bone marrow involved at study entry (Part A only)	1		
Prior receptor tyrosine kinase inhibitor	5**	3	2
Prior anthracycline (Part A only)	10	10	
Prior radiation therapy	14	7	7
Open tibial growth plate	15	6	9
Median number sunitinib cycles (range)	1 (1 – 9)	1 (1 – 4)	1 (1 – 9)

*Includes 1 patient each with desmoplastic small round cell tumor (Part A); renal cell carcinoma (Part A); spindle epithelial tumor with thymus like differentiation (Part A); gastrointestinal stromal tumor (Part B); and malignant meningioma (Part B).

**Includes 2 patients treated with imatinib (1 each on Parts A and B) and 1 patient each treated with dasatinib (Part A), sorafenib (Part A) and gefitinib (Part B).

Hematologic and Non-Hematologic Toxicities Observed in 21 Evaluable Patients in Cycle 1 and in 23 Subsequent Cycles of Therapy with Sunitinib.*

PART A	Cycle 1				Subsequent Cycles (2-4)			
	G1	G2	G3	G4	G1	G2	G3	G4
	N = 12 cycles				N = 5 cycles			
Hematologic Toxicity								
Leukopenia	33%	17%	25%		40%			
Thrombocytopenia	42%	25%			40%			
Neutropenia	8%	17%	33%	8%	20%		20%	
Lymphopenia	17%		17%	8%	20%			
Anemia	25%	8%			20%			
Non-Hematologic Toxicity								
AST elevation	33%	8%			20%			
ALT elevation	17%	8%	8%		20%			
Anorexia	8%	17%	8%					
Diarrhea	33%							
Fatigue	8%	8%	8%					
Hypoalbuminemia	25%							
Hypocalcemia	25%							
Vomiting	25%							
Amylase elevation	17%							
Hyponatremia	8%		8%					
Hypophosphatemia			17%					
Hypothyroidism	8%	8%				20%		
Left ventricular systolic dysfunction		17%			20%			
Mucositis	17%							
Nausea	8%	8%						
Weight loss		17%						

PART B	Cycle 1				Subsequent Cycles (2-9)			
	G1	G2	G3	G4	G1	G2	G3	G4
	N = 9 cycles**				N = 18 cycles			
Hematologic Toxicity								
Neutropenia	29%	14%	14%		6%		6%	6%
Leukopenia	43%				6%	6%		
Lymphopenia	14%	14%						
Non-Hematologic Toxicity								
AST elevation	44%				6%			
ALT elevation	22%	11%			11%			
Diarrhea	11%	11%						
Fatigue	22%							
Hypermagnesemia	22%							
Hyperuricemia	11%			11%				
Muscle or joint pain	11%	11%				6%		
Rash or hypopigmentation	22%					12%		
Amylase elevation	11%							
Anorexia	11%							
CNS hemorrhage				11%				
Constipation	11%							
Cranial neuropathy				11%				
Decreased serum bicarbonate	11%							
Dehydration	11%							
Epistaxis	11%							
Eye swelling	11%							
Headache	11%							
Hypernatremia	11%				6%			
Hypertension	11%				6%	6%		
Hypoalbuminemia	11%							
Hypomagnesemia	11%							
Hypophosphatemia			11%		11%			
Hypothyroidism	11%				6%			
Lipase elevation	11%							
Mucositis	11%							
Vomiting	11%							

*Data are presented for patients in Parts A and B of the study. Only toxicities possibly, probably or definitely related to sunitinib and which occurred in more than 10% of patients in cycle 1 are displayed. Values represent percent of patient cycles with listed toxicity according to grade.

** Of 9 evaluable patients in Part B, only 7 were evaluable for hematologic toxicity.

Appendix 3. Blood Pressure Levels for Girls and Boys by Age

The following tables were taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Instructions for using these BP Charts:

1. Measure the patient's BP using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column, determine if the BP is within the ULN. The BP tables use height percentile data found on the CDC growth charts (www.cdc.gov/growthcharts). See below.
4. See Section 5.2.11 for suggested guidelines for medical treatment of sunitinib-related hypertension.

Blood pressure (BP) levels for GIRLS aged 6-17 years

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentage of Height							Percentage of Height						
Years	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
6	95th	108	109	110	111	112	113	114	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	129	130	131	82	82	82	83	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Blood pressure (BP) levels for BOYS aged 6-17 years

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentage of Height							Percentage of Height						
Years	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Appendix 4. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Adapted from Eisenhauer et al (2009) Eur 2009 Jan;45(2):228-47.

a. Measurability of Lesions

Measurable disease.

1. Lesions with longest diameter 10 mm or greater in the axial plane (bone lesions not included except for soft tissue expansile masses arising from bone) when assessed by MRI or CT.

2. Lesions with longest diameter at least 20 mm when assessed by X-ray.

3. Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

4. Malignant lymph nodes with the short axis 15 mm or greater when assessed by MRI or CT.

A previously irradiated lesion is not measurable unless it has progressed since completion of RT.

MRI and CT should be performed with cuts of 5 mm or less in slice thickness contiguously. If greater than 5 mm, then minimum lesion size should be twice the slice thickness.

Non-measurable disease.

All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, nodes with short axis ≥10 but <15 mm, disease documented by indirect evidence only (eg, by lab values), or previously radiated lesions that have not progressed.

Target and non-target disease.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Measurements must be provided for target measurable lesions.

Non-target disease: All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease.

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 4 weeks prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate. Note: A tumor is considered evaluable but not measurable if an increase in tumor mass can be assessed even though it does not meet the minimum requirements for measurability as defined by RECIST v1.1. Examples would include ascites, pericardial effusion, or pleural effusion.

Objective Status is to be recorded at each evaluation.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Complete Response (CR): Complete disappearance of all target and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal size (short axis <10 mm). No new lesions. All disease sites must be assessed.

Partial Response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. No unequivocal progression of non-target disease. No new lesions. No reappearance of lesions after a CR. All target lesions must be assessed.

Stable: Does not qualify for CR, PR, Progression. All target lesions must be assessed.

Objective Progression: One or more of the following must occur. 1) 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. 2) Unequivocal progression of non-target disease. Unequivocal progression is assessed with respect to non-target disease as a whole, not to each individual lesion. An explanation must be provided. 3) Appearance of any new lesion/site. 4) Reappearance of lesions after a CR. 5) A modest increase in an evaluable but not measurable tumor is usually not considered sufficient to indicate unequivocal disease progression.

Indeterminate, objective status unknown. Progression has not been documented, and

- One or more target measurable lesions have not been assessed;
- Or assessment methods used were not the same as baseline;

- Or one or more target lesions cannot be measured accurately unless due to being too small to measure;

- Or one or more target lesions were excised or irradiated and have not reappeared or increased.

Objective status notes:

- Non-target disease does not necessarily affect objective status except in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, can at best be classified as PR), and in determination of progression (if new lesions develop or if unequivocal progression occurs). Cases for which target disease is assessed as stable or better but non-target assessments are missing must reviewed carefully. By considering the whole sequence, it may be reasonable to assume missed non-target assessments were not progression;

- For unequivocal progression of non-target disease, generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare. In particular, increase of a single small non-target measurable lesion by 20% would not ordinarily constitute unequivocal increase in non-target disease as a whole;

- An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds;

- For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression;

- Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin. In the case of worsening, the change must be substantial, eg, from trace to large;

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate;

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status;

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used;

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm is used;

- If a new lesion is identified in a location not scanned at baseline, this is considered progression;

- PET results are not used in determination of objective status;

- Disease that is poorly visible on scan such that status or size cannot be adequately determined should be assessed as Indeterminate;

- If a target lesion becomes non-evaluable (for reasons other than too small) this is recorded as indeterminate;

- Measurable lesions that are irradiated or excised on study are no longer measurable and should be assessed as Indeterminate on the Tumor Assessment-Target Lesions CRF. Subsequent increase or reappearance may constitute progression of disease.

Appendix 5. Lansky and ECOG Performance Scales

Lansky Scale to be used for patients aged <11 years. ECOG Scale to be used for patients aged ≥11 years.

Score	Lansky	Score	ECOG
100%	Fully active	0	Normal, no complaints
90%	Minor restriction in physically strenuous play	1	Mild complaints for physical activities, but patient needs no assistance and can do easy work
80%	Restricted in strenuous activities, tires more easily, otherwise active		
70%	Both greater restriction of, and less time spent in active play	2	Ambulatory, patient cares for self, but age-appropriate activity severely impaired
60%	Ambulatory up to 50% of time, limited active play with assistance/supervision		
50%	Frequently nursing in bed during day, considerable assistance required for any active play, fully able to engage in quiet play	3	Confined to bed more than 50% of time, needs nursing care
40%	Frequently confined to bed; able to initiate quiet activities		
30%	Confined to bed, needs assistance for quiet activities	4	Confined to bed or prostrated on chair, needs intensive care
20%	Frequently asleep, limited to very passive activity initiated by others		
10%	Completely disabled, not even passive play		
0%	No reaction		

Adapted from J Clin Onc, 2003. 21(22): p. 4235-4238.

Appendix 6. Sunitinib Total Daily Dose Levels per BSA

Pediatric doses are stated in mg (rounded to a multiple of 6.25 mg), based on individual patient BSA (m^2) at daily dose levels of 15 mg/m^2, 22.5 mg/m^2 or 30 mg/m^2 never exceeding 50 mg/day.

Dose Level (mg/m^2)	**BSA** (m^2)	**Total Dose** (mg)
15	≤0.62	6.25
	0.63-1.03	12.50
	1.04-1.45	18.75
	1.46-1.87	25.00
	1.88-2.28	31.25
	2.29-2.70	37.50
	2.71-3.12	43.75
	3.13-3.53	50.00
22.5	≤0.41	6.25
	0.42-0.68	12.50
	0.69-0.96	18.75
	0.97-1.24	25.00
	1.25-1.52	31.25
	1.53-1.80	37.50
	1.81-2.07	43.75
	≥2.08	50.00
30	≤0.30	6.25
	0.31-0.51	12.50
	0.52-0.72	18.75
	0.73-0.93	25.00
	0.94-1.14	31.25
	1.15-1.34	37.50
	1.35-1.55	43.75
	1.56-1.76	50.00
	≥1.77	50.00

Appendix 7. Required Laboratory Tests

Screen	At Each Visit	Frequency Per Table 1. Schedule Of Activities
White blood count/differential	White blood count/differential	TSH
Hemoglobin	Hemoglobin	Prothrombin time (PT or INR)
Platelets	Platelets	Urinalysis
Sodium	Sodium	Urine pregnancy test
Potassium	Potassium	
Chloride	Chloride	
Blood urea nitrogen (BUN)	Blood urea nitrogen (BUN)	
Serum creatinine	Serum creatinine	
Glucose	Glucose	
Uric acid	Uric acid	
Calcium	Calcium	
Magnesium	Magnesium	
Phosphorous	Phosphorous	
Total bilirubin	Total bilirubin	
Alanine aminotransferase (ALT)	Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	Aspartate aminotransferase (AST)	
Alkaline phosphatase	Alkaline phosphatase	
Total protein	Total protein	
Albumin	Albumin	

Amylase	Amylase	
Lipase	Lipase	
TSH		
Prothrombin time (PT or INR)		
Urinalysis		
Urine pregnancy test		