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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sutent

sunitinib

Procedure no: EMEA/H/C/000687/P46/053

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 12/02/2018, the MAH submitted a completed paediatric study for SUTENT (A6181196), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the single-arm, multi-center, multi-national, Phase I/II clinical trial A6181196 evaluating the pharmacokinetic (PK), safety, and preliminary anti-tumour efficacy of sunitinib in children and young adults diagnosed with advanced unresectable gastrointestinal stromal tumour (GIST) is currently included in the approved sunitinib Paediatric Investigational Plan (PIP).

Considering that the PIP for sunitinib is still ongoing, the MAH does not consider that a change in the Sutent Product Information is warranted at this stage.

2.2. Information on the pharmaceutical formulation used in the study

In the Study A6181196 sunitinib malate study medication was supplied to the clinic pharmacy as hard gelatin capsules in HDPE bottles containing 28 or 30 capsules for oral administration. Sunitinib malate capsules contained 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

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final Clinical Study Report for Study A6181196: A Phase I/II Study of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumour.

2.3.2. Clinical study

"A Phase I/II Study of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumour" (Study A6181196)

Methods

Objective(s)

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 maximum tolerated dose (MTD) were 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 pharmacokinetic (PK)–pharmacodynamic (PD) relationships with respect to safety and efficacy in children and young adults with GIST.

Study design

This was a single arm, multi-center, multi-national, Phase 1/2 clinical trial evaluating the PK, safety, and preliminary anti-tumor efficacy of sunitinib in children and young adults diagnosed with advanced, unresectable GIST.

Study population /Sample size

Protocol Amendment 2 (see Section 9.8.2) was implemented to reduce the sample size to 6 patients from the originally planned 15 patients because of the rarity of the disease and the difficulties in identifying pediatric patients suitable for participation in the study. The revised sample size was expected to still allow characterization of the PK profile, ie, analysis of the primary endpoint.
The originally planned sample size calculations were as follows. Assuming the coefficient of variation of sunitinib clearance among pediatric patients is approximately 35%, a total of 15 patients would allow detection of a 35% margin of error in sunitinib CL/F with 95% confidence and 80% power. Furthermore, assuming the coefficient of variation of sunitinib clearance among young adult patients is also ~35%, a total of 30 patients would allow detection of a 25% margin of error with 95% confidence and 80% power.

Pediatric patients with GIST aged 6 to 18 years who met the selection criteria were to be enrolled in the study. A total of 8 patients were screened, of which 6 patients were enrolled in the study and were included in the analysis of PK, safety, and efficacy (see table below). Of the 6 enrolled patients, 4 patients discontinued the treatment due to objective disease progression or relapse, 1 patient discontinued treatment due to an AE, and 1 patient completed the treatment phase with 18 cycles and the follow-up phase. Of the 5 patients who discontinued treatment, 4 patients were followed up for survival and completed the study phase. One (1) patient discontinued treatment and chose to not participate in the follow-up phase.

Table 6 Patient Disposition

Patients	Sunitinib, (N=6)
Screening and randomization	
Screened (n)	8
Assigned to treatment (Enrolled), n (%)	6 (100)
Study Completion, n (%)	
Completed Study	5 (83.3)
Discontinued from Study	1 (16.7)
Treatment phase completion, n (%)	
Treated	6 (100)
Completed Treatment	1 (16.7)
Discontinued Treatment	5 (83.3)
due to an AE	1 (16.7)
due to objective disease progression or relapse	4 (66.7)
Analysis Sets, n (%)	
Intent-to-Treat [a]	6 (100)
As-treated [b]	6 (100)
PK set [c]	6 (100)

Sources: Tables 14.1.1.1, 14.1.1.3, and 14.1.1.4.
[a] All enrolled patients; analysis set for efficacy assessment.
[b] All enrolled patients who received at least 1 dose of study treatment; analysis set for safety assessment.
[c] All treated patients with at least 1 PK observation; analysis set for PK assessment.
Abbreviations: AE=adverse event; N=number of patients analyzed; n=number of patients with an assessment result; PK=pharmacokinetics.

Full Analysis Population

The full analysis (or intent-to-treat) population included all enrolled patients regardless of what treatment, if any, was received. The efficacy analysis was based on the full analysis population. Note that if all patients received at least 1 dose of study treatment, this population would be equivalent to the as -treated population.

As-Treated Population

The as-treated population included all enrolled patients who received at least 1 dose of study drug. The safety analysis was based on the as-treated population.

Pharmacokinetic Population

The PK population included all treated patients with at least 1 PK observation. The PK analysis was based on PK population.

Treatments

Eligible patients were dosed based on the body surface area (BSA). The starting dose of sunitinib was 15 mg/m2 per day administered orally per Schedule 4/2, (ie, 4 weeks on study treatment followed by 2 weeks off treatment).

Intra-patient dose escalation of sunitinib was allowed after completion of Cycle 1, based on dose modification guidelines. Patients were monitored for toxicity, and the sunitinib dose was adjusted according to individual patient tolerance at the discretion of the Investigator. For patients <18 years, intra–patient dose escalation of sunitinib was allowed after completion of Cycle 1 and/or later cycles, and in the absence of toxicity greater than Grade 1 in the prior cycle.

Dose escalation was in increments of 7.5 mg/m2 up to a maximum dose of 30 mg/m2 (not to exceed 50 mg/day).

The dose could be reduced in response to toxicities based on Investigator discretion. Dose reductions in patients <18 years was in decrements of 7.5 mg/m2.

A treatment cycle was 42 days, and patients could receive up to 18 cycles of sunitinib therapy for up to 24 months. Patients were to be followed for overall survival (OS) until either 2 years from the first dose of the study drug or completion of 18 cycles of study treatment.

Doses higher than the previously defined MTD (15 mg/m2 per day) were generally well tolerated in this limited population (increase to 22.5 mg/m2 per day in 5 of the 6 patients, and a further increase to 30 mg/m2 per day in 2 patients).

Outcomes/endpoints

Primary Study Endpoints:

- PK parameters of sunitinib and its main active metabolite (SU012662) including total plasma exposure (AUC24) and oral clearance (CL/F).

Secondary Study 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 (AEs) and laboratory abnormalities;
- Objective response rate (ORR), duration of response (DOR), progression-free survival (PFS) and OS at 2 years after study enrollment;
- PK-PD relationships with respect to safety and efficacy in paediatric GIST, if data allowed.

Clinical Pharmacology-Methodology

The primary objective of the study was characterization of PK profile.
Pharmacokinetic endpoints were: PK parameters of sunitinib and its main active metabolite, SU012662, including total plasma exposure (AUC from 0 to 24 hours [AUC24]) and CL/F.
The post dose PK profile samples for sunitinib and its active metabolite (SU012662) were obtained at 2, 4, 6, and 8 hours post dose on Day 1 of Cycle 1 (see Table below). Trough/pre-dose samples were collected on Days 1, 15, and 28 of Cycle 1 and on Days 1 and 28 of Cycles 2−3. Trough PK sample collection on Days 7 and 21 of Cycle 1 was optional. In addition, trough PK sample collection on Day 15 of Cycles 2-3 was required only if the patient underwent dose escalation during that cycle.

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-D42	Day 1 (D-2 to D2)		
Pharmacokinetic Sampling [11]		Cycle 1: Pre-dose and 2,4,6, and 8 hours post first dose Cycles 2 and 3: Pre-dose	Pre-dose	Pre-dose				

Pharmacokinetic evaluation. Standard plasma PK parameters including trough plasma concentration (Ctrough), Cmax, time to first occurrence of maximum observed plasma concentration (Tmax), and area under the curve for concentration versus time profile from time 0 to 8 hours post dose (AUC8) for sunitinib and SU012662 were estimated following non-compartmental analysis methods, using eNCA. Nominal sample collection times were used for non-compartmental analyses of sunitinib and SU012662.
Descriptive statistics for observed and dose-corrected (where appropriate) PK data was 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 were reported where appropriate.
In addition to the non-compartmental analyses, NONMEM approaches were to be used to estimate PK parameters absorption rate constant (Ka), CL/F, inter-compartmental clearance (Q/F), volume of distribution for the central compartment (Vc/F) and peripheral compartment (Vp/F). Other parameters such as half-life for the distribution phase (t1/2α) and elimination phase (t1/2β), Cmax, and AUC24 were to be estimated based on individual patient parameter estimates.

Pharmacokinetic Analytical Methods. Human plasma samples were analyzed for sunitinib (also referred to as SU-011248 or SUTENT) and its active metabolite SU012662 (also referred to as SU-012662) concentrations at Bioanalytical Systems, Inc (BASi, Inc, West Lafayette, Indiana) using a validated analytical assay in compliance with Pfizer standard operating procedures. Sunitinib and SU012662 samples were assayed using a validated, sensitive, and specific high performance liquid chromatographic tandem mass spectrometric (HPLC/MS/MS) method.

Pharmacokinetic-Pharmacodynamic. In addition to the analyses of the PK data listed above, **PK-PD analyses** were carried out with respect to selected safety and efficacy parameters. The PK-evaluable patients on Day 28 of Cycle 1 were divided into 2 PK subgroups: those with Total Drug Ctrough values less than the median Ctrough value (Lower Exposure) and those with Total Drug Ctrough values greater than or equal to the median Ctrough value (Higher Exposure).
Subsequently, the summary statistics (n, %) of incidence of adverse events (AEs) Nausea, Vomiting, Diarrhea, Fatigue, Hand-foot syndrome, Neutropenia, Thrombocytopenia, Lymphopenia, Anemia, and Hypertension by maximum CTCAE Grade and for all Grades combined during Cycles 1 to 3 for both PK subgroups were generated.
The Pearson correlation coefficients (R) between the percent change in the laboratory values for absolute neutrophil count (ANC), thrombocyte count, lymphocyte count, systolic blood pressure (SBP), diastolic blood pressure (DBP), and hemoglobin (Hgb) with Total Drug Ctrough values were calculated with respect to PK visits Day 28 of Cycles 1, 2, and 3. The laboratory value nearest to the time of PK sample collection was used for correlation purposes. The overall assessment was based on an overall trend observed based on the 3 individual correlation values and is included in the Sponsor's Clinical Pharmacology Contribution (CPC) report.
Furthermore, the summary statistics (n, %, or median) for the rate of SD, ORR (PR+CR), and progressive disease based on Response Evaluation Criteria in Solid Tumours (RECIST), as well as for PFS were provided in both PK subgroups, based on Total Drug Ctrough values on Day 28 of Cycle 1. Finally, the R values between the PFS with Total Drug Ctrough values on Day 28 of Cycle 1 were calculated.

Statistical Methods

Analysis of Primary Endpoint (PK)
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 paediatric patients will be compared to adult patients with GIST based on historical data. The formal comparison will be carried out as part of the NONMEM portion using the historical PK data in adult GIST patients.

Analysis of Efficacy Endpoints

Efficacy endpoints were objective response rate (ORR), duration of response (DR), progression-free survival (PFS), and OS.

All baseline tumour imaging assessments were performed within 28 days prior to the first dose of medication and then within 14 days prior to the end of each even-numbered cycle (ie, Cycles 2, 4, etc.). Magnetic resonance imaging (MRI) or computed tomography (CT) scans with contrast agents (unless contraindicated), and positron emission tomography (PET) scans were used for tumor measurements. The determination of anti-tumor efficacy was based on Investigator's objective tumor assessments. Assessments of confirmed complete response (CR) or partial response (PR) were according to RECIST version 1.1. Designation of best response of stable disease (SD) required the criteria to be met at least once after the first dose of medication, at a minimum interval of 8 weeks. For effusions or ascites, only cases having cytologic proof of malignancy were recorded as tumour lesions on the case report form (CRF). Effusions that were not evaluated using cytology or were found to be non-malignant were not recorded on the 'non-target and new lesion' CRF. Measurable lesions that were previously irradiated were not considered target lesions unless increase in size was observed following completion of radiation therapy.

ORR was defined as the proportion of patients with a confirmed CR or PR according to RECIST version 1.1. The number and percent of patients who achieved objective response (CR or PR) was summarized along with the corresponding exact 2-sided 95% confidence interval (CI) calculated using a method based on the F distribution.

DOR was defined as the time from the first objective documentation of complete or partial response (according to RECIST version 1.1) that was subsequently confirmed to the first documentation of disease progression or to death due to any cause, whichever occurred first. DOR was calculated for the subgroup of patients who had objective disease response and was summarized using Kaplan-Meier methods and displayed graphically where appropriate.

PFS was defined as the time from the date of the first dose of the study drug to the date of the first documentation of objective tumour progression or death due to any cause, whichever occurred first. PFS data were censored on the day following the date of the last tumour assessment documenting absence of progressive disease for patients who 1) were given antitumour treatment other than the study treatment prior to observing objective tumour progression; 2) were removed from the study prior to documentation of objective tumour progression; or 3) were ongoing at the time of the analysis. Patients who did not have any post-baseline tumour assessments had their PFS endpoint censored on the date of enrollment. Death or disease progression that occurred after more than 1 missed visit was censored on the day following the date of the last tumour assessment as well. PFS was summarized using Kaplan-Meier methods and displayed graphically where appropriate. Median PFS and its corresponding 2-sided 95% CI for the median were summarized.

Overall survival was defined as the time from the date of the first dose to the date of death due to any cause. For patients still alive at the time of analysis, the OS time was censored on the last date the patients were known to be alive.

Analysis of safety parameters

Frequencies of patients experiencing at least 1 AE were displayed by System Organ Class(SOC) and Preferred Term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. Detailed information collected for each AE include a description of the event, duration, severity, seriousness, study drug relatedness, action taken, and clinical outcome. The severity of the AEs was graded according to the NCI CTCAE version 4.0. The analyses were performed on AEs classified as

treatment-emergent. Summary tables presented the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consisted of the patients enrolled since all of them received at least 1 dose of study medication. Within each table, the AEs were categorized by MedDRA system organ class and preferred term. Additional subcategories were based on event intensity and relationship to study drug. Hematology and blood chemistry data were graded according to NCI CTCAE version 4.0. The frequencies of the worst severity grade observed were displayed for each parameter for the study and by cycle.

Results

Recruitment / Number analysed

A total of 8 patients were screened, of which 6 patients were enrolled in the study and were included in the analysis of PK, safety, and efficacy.

Baseline data

The full analysis population was used for the analysis of baseline characteristics.
Demographic and baseline characteristics of the intent-to-treat population are presented in the following table:

Table 8 Summary of Demographic and Baseline Characteristics at Screening: Intent–to–Treat

Characteristic	Sunitinib, (N=6)
Gender [a]	**n (%)**
Male	1 (16.7)
Female	5 (83.3)
Age, years	
Median	14.0
Mean (Standard deviation)	14.3 (1.4)
Range, minimum-maximum	13-16
Race	**n (%)**
White	5 (83.3)
Asian	1 (16.7)
Weight, kg	
Median	45.3
Mean (Standard deviation)	47.3 (9.9)
Range, minimum-maximum	39.2-66.8
Height, cm	
Median	155.4
Mean (Standard deviation)	155.6 (6.3)
Range, minimum-maximum	147.2-163.0
ECOG Performance Status	**n (%)**
0	6 (100)

Sources: Tables 14.1.2.1 and 14.1.1.7.
[a] Percentages were calculated based on the number of patients enrolled.
Abbreviations: ECOG=Eastern Cooperative Oncology Group; N=number of patients enrolled; n=number of patients with an assessment result.

Baseline disease characteristics are presented here below:

Table 9 Other Baseline Characteristics: Intent–to–Treat

Characteristic	Sunitinib, (N=6)
Measurable Disease Present [a]	**n (%)**
Yes	6 (100)
Adequate Baseline Assessment [b]	**n (%)**
Yes	6 (100)
Number of Involved Disease Sites [c]	**n (%)**
1	2 (33.3)
2	1 (16.7)
3	3 (50.0)
4	0
>4	0
Not reported	0
Involved Disease Sites [d]	**n (%)**
Liver	4 (66.7)
Lung	1 (16.7)
Peritoneum	3 (50.0)
Stomach	3 (50.0)
Other	2 (33.3)

Source: Table 14.1.1.8.
[a] At least 1 target lesion as assessed according to RECIST version 1.1.
[b] Patients with target lesions=patients with all target lesions that have measurement(s) within the baseline window and are measurable.
[c] Each disease site is counted as a separate disease site.
[d] Involved sites include both target and non-target sites. Sites with multiple lesions are counted once.
Abbreviations: N=number of patients analyzed; n=number of patients with an assessment result.

Pharmacokinetics results

The summary of PK parameters is provided in the table reported below. At an oral dose of 15 mg/m2 in pediatric patients with GIST, the median Tmax values were 8.0 h and 8.0 h for sunitinib and SU012662, respectively. The mean Cmax values were 18.4 and 2.37 ng/mL for sunitinib and SU012662, respectively. The AUC8 was 82.7 and 10.7 ng.h/mL for sunitinib and SU012662, respectively. The respective inter-patient variability (CV%) in Cmax and AUC8 were 34% and 39% for sunitinib, and 17% and 35% for SU012662. The respective mean observed Ctrough values on Day 15 of Cycle 1, and on Day 28 of Cycles 1, 2, 3 were 24.4, 29.1, 44.7, 31.3 ng/mL for sunitinib; 11.7, 13.0, 20.9, and 20.5 ng/mL for SU012662; and 36.0, 42.1, 65.6, and 51.8 ng/mL for Total Drug.
Furthermore, the respective mean dose–corrected Ctrough values on Day 15 of Cycle 1, and on Day 28 of Cycles 1, 2, 3 were 24.4, 29.1, 32.5, 19.9 ng/mL for sunitinib; 11.7, 13.0, 15.2, and 13.1 ng/mL for SU012662; and 36.0, 42.1, 47.7, and 32.9 ng/mL for Total Drug. The CV% in steady state observed or dose-corrected Ctrough on Day 28 of Cycle 1 was 46%, 36%, and 42% for sunitinib, SU012622, and Total Drug, respectively.

Table 12 Summary of Sunitinib, SU012662 and Total Drug Single-Dose Pharmacokinetic Parameters and Multiple-Dose Trough Concentrations Following Sunitinib Oral Doses (Starting Dose of 15 mg/m^2) in Pediatric Patients with GIST

PK Parameter	Sunitinib Mean (CV%) [Median]	SU012662 Mean (CV%) [Median]	Total Drug Mean (CV%) [Median]
Observed (n=6)			
T_{max} (h)	8.0 (4.0–8.0)[a]	8.0 (4.0–8.0)[a]	NC
C_{max} (ng/mL)	18.4 (34) [16.1]	2.37 (17) [2.44]	NC
AUC_8 (ng·h/mL)	82.7 (39) [80.0]	10.7 (35) [9.82]	NC
C_{trough} C1D15 (ng/mL)	24.4 (42) [20.8]	11.7 (15) [11.7]	36.0 (31) [32.4]
C_{trough} C1D28 (ng/mL)	29.1 (46) [29.3]	13.0 (36) [12.8]	42.1 (42) [42.1]
C_{trough} C2D28 (ng/mL)	44.7 (90) [30.9]	20.9 (63) [15.9]	65.6 (80) [48.7]
C_{trough} C3D28 (ng/mL)	31.3 (49) [27.8]	20.5 (46) [19.5]	51.8 (46) [43.5]
Dose-Corrected (n=6)			
C_{trough} C1D15 (ng/mL)	24.4 (42) [20.8]	11.7 (15) [11.7]	36.0 (31) [32.4]
C_{trough} C1D28 (ng/mL)	29.1 (46) [29.3]	13.0 (36) [12.8]	42.1 (42) [42.1]
C_{trough} C2D28 (ng/mL)	32.5 (69) [24.9]	15.2 (45) [14.8]	47.7 (61) [38.9]
C_{trough} C3D28 (ng/mL)	19.9 (36) [18.6]	13.1 (31) [13.8]	32.9 (31) [29.8]

Sources: Tables 14.4.3.1, 14.4.3.2, 14.4.3.3, 14.4.3.4, 14.4.3.5, 14.4.3.6, and Table 16.2.5.3.2.
[a] Median (minimum-maximum).
Abbreviations: AUC_8=area under plasma concentration-time curve from time 0 to 8 hours post dose; C=Cycle; C_{max}=maximum observed plasma concentration; C_{trough}=trough concentration; CV=coefficient of variation; D=Day; Dose-corrected=dose-corrected to the starting dose by multiplying observed concentration by correction factor starting dose/current dose; NC=not calculated; T_{max}=time to first occurrence of maximum observed plasma concentration; Total Drug=sunitinib+SU012662.

Pharmacokinetic-pharmacodynamic

The PK-evaluable patients on Day 28 of Cycle 1 were divided into 2 PK subgroups: those with Total Drug Ctrough values less than the median Ctrough value (Lower Exposure) and those with Total Drug Ctrough values greater than or equal to the median Ctrough value (Higher Exposure).

Relationship between Incidence of Selected Adverse Events And Plasma Drug Exposures

The summary of incidence of AEs in Cycles 1-3 for PK subgroups below and above median trough Total Drug (sunitinib+SU012662) concentration on Day 28 of Cycle 1 is given in the following table:

Table 14.4.3.9.1 Page 1 of 2
SU-011248 Protocol A6181196 (Date of Data Snapshot: 13Sep2017)
Summary of Incidence of Special Adverse Events by Maximum Grade and for All Grades Combined in Cycles 1-3 for PK Subgroups Below and Above Average Cycle 1 Day 28 Median Total Drug Conc. - PK population
Treatment Group: Sunitinib

AE Preferred Term	All Evaluable Subjects Grade 1 n(%)	Grade 2 n(%)	Grade 3 n(%)	Grade 4 n(%)	Grade 5 n(%)	Total n(%)
Nausea	2 (33.3)	0	0	0	0	2 (33.3)
<Median Total Drug (N=3)	0	0	0	0	0	0
>= Median Total Drug (N=3)	2 (66.7)	0	0	0	0	2 (66.7)
Vomiting	1 (16.7)	0	0	0	0	1 (16.7)
<Median Total Drug (N=3)	0	0	0	0	0	0
>= Median Total Drug (N=3)	1 (33.3)	0	0	0	0	1 (33.3)
Diarrhoea	1 (16.7)	1 (16.7)	0	0	0	2 (33.3)
<Median Total Drug (N=3)	0	0	0	0	0	0
>= Median Total Drug (N=3)	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Fatigue	0	1 (16.7)	0	0	0	1 (16.7)
<Median Total Drug (N=3)	0	0	0	0	0	0
>= Median Total Drug (N=3)	0	1 (33.3)	0	0	0	1 (33.3)
Palmar-Plantar Erythrodysaesthesia Syndrome	1 (16.7)	0	0	0	0	1 (16.7)
<Median Total Drug (N=3)	1 (33.3)	0	0	0	0	1 (33.3)
>= Median Total Drug (N=3)	0	0	0	0	0	0
Neutropenia	0	1 (16.7)	1 (16.7)	1 (16.7)	0	3 (50.0)
<Median Total Drug (N=3)	0	1 (33.3)	0	1 (33.3)	0	2 (66.7)
>= Median Total Drug (N=3)	0	0	1 (33.3)	0	0	1 (33.3)
Thrombocytopenia	1 (16.7)	1 (16.7)	0	0	0	2 (33.3)
<Median Total Drug (N=3)	1 (33.3)	0	0	0	0	1 (33.3)
>= Median Total Drug (N=3)	0	1 (33.3)	0	0	0	1 (33.3)
Lymphopenia	0	0	0	0	0	0
<Median Total Drug (N=3)	0	0	0	0	0	0
>= Median Total Drug (N=3)	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0
<Median Total Drug (N=3)	0	0	0	0	0	0
>= Median Total Drug (N=3)	0	0	0	0	0	0
Anaemia	1 (16.7)	0	0	0	0	1 (16.7)
<Median Total Drug (N=3)	1 (33.3)	0	0	0	0	1 (33.3)
>= Median Total Drug (N=3)	0	0	0	0	0	0

% =(n/N)*100
AEs = Adverse Events, Conc. = Concentration
Special AEs: Nausea, Vomiting, Diarrhea, Fatigue, Palmar-plantar erythrodysaesthesia syndrome, Neutropenia, Thrombocytopenia, Lymphopenia, Hypertension and Anaemia.
Total Drug Concentration (ng/mL) = SU011248+SU012662 Drug Concentration (ng/mL)
MedDRA (v20.0) coding dictionary applied, CTCAE v3.0 was used.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 17SEP2017 Date of Table Generation: 03NOV2017 (09:14)

Relationship between Efficacy Parameters and Plasma Drug Exposures

The relationship between efficacy parameters and plasma drug exposures for PK subgroups Lower Exposure (<median total drug) and Higher Exposure (>= total median drug) is summarized below:

Table 14.4.3.9.4 Page 1 of 1
SU-011248 Protocol A6181196 (Date of Data Snapshot: 13Sep2017)
Summary of Incidence of Stable Disease, Partial Response, Complete Response, and Progressive Disease for PK Subgroups Below and Above Average Cycle 1 Day 28 Median Total Drug Conc. - PK population
Study Treatment: Sunitinib

PK Subgroups	All Patients with Data at Cycle 1 Day 28 (SU011248 + SU012662) Stable Disease n(%)	Partial Response n(%)	Complete Response n(%)	Progressive Disease n(%)
<Median Total Drug (N=3)	1 (33.3)	0	0	2 (66.7)
>= Median Total Drug (N=3)	2 (66.7)	0	0	1 (33.3)

% =(n/N)*100 Conc. = Concentration
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 17SEP2017 Date of Table Generation: 30OCT2017 (06:56)

The rate of RECIST-defined SD and objective response (CR or PR) were 33.3% and 0% in the PK subgroup with less than median Ctrough value (Lower Exposure) and 66.7% and 0% in the PK subgroup with greater than or equal to median Ctrough value (Higher Exposure) on Day 28 of Cycle 1, respectively.

Table 14.4.3.9.5 Page 1 of 1
SU-011248 Protocol A6181196 (Date of Data Snapshot: 13Sep2017)
Summary of Progression Free Survival for PK Subgroups Below and Above Cycle 1 Day 28 Median Total Drug Concentration - PK population
Study Treatment: Sunitinib

	< Median Total Drug Conc. (N=3)		>= Median Total Drug Conc. (N=3)	
	n	(%)	n	(%)
Number with event	2	(66.7)	2	(66.7)
Type of event				
Objective progression	2	(66.7)	2	(66.7)
Death without objective Progression	0		0	
Number censored	1	(33.3)	1	(33.3)
Reason for censorship				
No adequate baseline assessments	0		0	
No on-study disease assessments	0		0	
Given new anti-cancer treatment prior to tumor progression	0		0	
Off treatment prior to progression	1	(33.3)	0	
Withdrew consent for follow-up	0		0	
Lost to follow-up	0		0	
Unacceptable gap (>16 weeks) between PD or Death to the most recent prior adequate assessment	0		0	
In follow-up for progression	0		1	(33.3)
Kaplan-Meier estimates of Time to Event (Month) [1]				
50%	2.6[2.4, .]		9.0[2.3, .]	

[1] Based on the Brookmeyer and Crowley Method
Conc. = Concentration
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The median PFS was 2.6 months for the PK subgroup with Lower Exposure and 9.0 months in the PK subgroup with Higher Exposure on Day 28 of Cycle 1 (Study A6181196 CSR Table 14.4.3.9.5). The R value for the relationship between PFS and trough Total Drug plasma concentration on Day 28 of Cycle 1 was 0.59, indicating a moderate positive correlation (0.5≤R< 0.7)

Efficacy results

Best overall response, PFS, and OS were measured as secondary efficacy endpoints in the intent-to-treat population and are summarized in the table below. Since none of the study patients experienced CR or PR, an analysis of DOR was not performed. The best overall response was SD (reported in 3 patients [50.0%]) and objective progression (observed in 3 patients [50.0%]). PFS events were reported in 4 (66.7%) patients. Two (2) patients (33.3%) were censored from the PFS analysis because they did not have disease progression. The median PFS was estimated to be 5.8 months (95% CI: 2.3, not reached [NR])

There were no deaths in the study population. Consequently, all patients were censored and OS was not summarized using the Kaplan-Meier method. The time from the first study dose to the last available survival follow-up ranged from 0.9 years to 2.4 years for the 6 patients.

Best Overall Response to Treatment (Investigator-Reported) and Progression-Free Survival - Intent-to-Treat Population

Response	Sunitinib (N=6)
Best Overall Response, n (%)	
Complete response	0
Partial response	0
Stable/No response	3 (50.0)
Objective progression	3 (50.0)
Symptomatic deterioration	0
Early death	0
Indeterminate	0
Progression-Free Survival Event Status, n (%)	
Objective progression	4 (66.7)
Censored	2 (33.3)
Off treatment prior to progression	1 (16.7)
In follow-up for progression	1 (16.7)
Progression-Free Survival, median (95% CI)	
Kaplan-Meier estimates (months)	5.8 (2.3, NR)

Sources: Study A6181196 CSR Table 14.2.1 and Table 14.2.2.
Abbreviations: CI=confidence interval; CT=computed tomography; N=number of patients analyzed; n=number of patients with an event; PET=positron emission tomography; NR=not reached.
For patient 10521002, best response was determined based on the CT PET scans at baseline

Safety results

Extent of Exposure to Sunitinib

Extent of exposure to the study treatment was assessed in terms of number of treatment days, treatment cycles, and dose levels. Treatment duration ranged from 110 to 742 days with a median duration of 219 days (Table 3). Of the 6 patients in the as-treated population, all received at least 3 cycles of the study treatment and 1 patient received all 18 of the planned cycles. The mean cumulative dose was 4866.67 mg, with a mean relative intensity of 97.62%, and the mean daily dose was 27.12 mg or 19.07 mg/m2.

Summary of Adverse Events (All Causalities)

A total of 82 AEs were reported as TEAEs in the as-treated population. In all 6 patients, at least 1 TEAE was reported. AEs of Grade 3 or 4 severity were reported in 5 (83.3%) patients. There were no patients with SAEs or Grade 5 AEs.

One (1) patient had a dose reduction due to an AE, 4 patients temporarily discontinued study treatment, and 1 patient permanently discontinued study treatment due to an AE.

Summary of Adverse Events (All Causalities) – As-Treated Population

Treatment-Emergent Adverse Events	Sunitinib (N=6) n (%)
Number of AEs	82
TEAEs	6 (100)
SAEs	0
TEAEs severity Grade 3 or 4	5 (83.3)
TEAEs severity Grade 5	0
Dose reduction due to AEs	1 (16.7)
Temporary discontinuation due to AEs	4 (66.7)
Permanent discontinuation due to AEs	1 (16.7)

Source: Study A6181196 CSR Table 14.3.1.2.1.
Abbreviations: AE=adverse event; N=number of patients analyzed; n=number of patients with an event; SAE=serious adverse event, TEAE=treatment-emergent adverse event.
All AEs were considered as treatment-emergent AEs, unless present at baseline with the same severity grade.
Includes data up to 28 days after last dose of study drug.
Patients are counted only once per treatment in each row.
SAEs - according to the Investigator's assessment.
Severity counts are based on the maximum severity or grade of events.

Treatment-Emergent Adverse Events (All Causalities)

The overall incidence of TEAEs of any grade was 100% (6 patients) (Table 5). The majority of the reported AEs were Grade 1 or 2 in severity. Three (3) patients had 1 Grade 3 AE each, and 2 patients had 1 Grade 4 AE each. There were no reports of Grade 5 TEAEs.

Overall, Headache (Grades 1 or 2) was reported in 4 (66.7%) patients and Diarrhoea (Grades 1 or 2), Nausea (Grade 1), Neutropenia (Grades 2 to 4), or white blood cell (WBC) count decreased (Grade 2) were reported in 3 patients each, respectively.

Hepatic hematoma and Intra-abdominal hemorrhage TEAEs (Grade 4) were reported in 1 patient. Both of these events were determined by the Investigator to be related to disease progression. This conclusion was supported by laparotomy showing multiple lesions localized at stomach wall, liver, lymph node at falx hepatis, and massive peritoneal dissemination, with hemorrhagic ascites.

The other Grade 4 TEAE was Neutropenia that was reported in 1 patient and led to dose reduction. Grade 3 TEAEs reported were Hypoglycaemia, Hypophosphataemia, Neutropenia, and Thrombocytopenia.

Treatment-Related Adverse Events

A total of 59 treatment-related TEAEs were reported in the study.

Treatment-Related Adverse Events	Sunitinib (N=6) n (%)
Number of Treatment-Related AEs	59
Patients with, n (%)	
At least 1 treatment-related AEs	6 (100)
At least 1 treatment-related SAEs	0
Treatment-related AEs Grade 3 or 4	4 (66.7)
Treatment-related AEs Grade 5	0
Dose reduction due to treatment-related AEs	1 (16.7)
Temporary discontinuation due to treatment-related AEs	4 (66.7)
Permanent discontinuation due to treatment-related AEs	1 (16.7)

Source: Study A6181196 CSR Table 14.3.1.3.1.
Abbreviations: AE=adverse event, N=number of patients analyzed; n=number of patients with an event; SAE=serious adverse event.
Includes data up to 28 days after last dose of study drug.
Patients are counted only once per treatment in each row.
SAEs were according to the Investigator's assessment.
Severity counts are based on the maximum severity or grade of events.

Adverse Events Leading to Treatment Delay, Dose Reduction, or Permanent Discontinuation

One (1) patient (16.7%) was permanently discontinued from the study treatment due to a treatment-related AE of Anaemia (Grade 2) that was eventually resolved. One (1) patient (16.7%) had a dose reduction due to Grade 4 Neutropenia TEAE.
Four (4) patients (66.7%) had temporary discontinuations due to treatment-related TEAEs that were Neutropenia, Hypoglycaemia, and Thrombocytopenia (all Grade 3), and Neutropenia (Grade 2), in 1 patient (16.7%) each respectively.
All events that led to treatment delay, dose reduction, or permanent discontinuation had resolved.

Deaths and Other Serious Adverse Events

There were no deaths or SAEs reported in Study A6181196.

Clinical Laboratory Evaluation

Most of the results for laboratory chemistry were within normal range (shown as Grade 0) or severity Grade 1. Hypoglycaemia and hypophosphataemia findings (Grade 3) were reported in 1 patient each, respectively. Creatinine, hyperglycaemia, and hypoglycaemia findings (Grade 2) were reported in 1 patient each, respectively.
Grade 3 hypoglycemia and hypophosphataemia were also reported as TEAEs.

With regard to the laboratory hematology tests,the only Grade 4 abnormality reported was neutrophils (absolute) decreased in 1(16.7%) patient. The other abnormalities included Grades 3 neutropenia, platelets decreased and anaemia in 1 (16.7%) patient each. Grade 2 abnormalities were a decrease in WBC in all 6 (100%) patients, decrease in neutrophils (absolute) in 4 (66.7%) patients, and anaemia in 1 (16.7%) patient. Grade 1 abnormalities were lymphopenia in all 6 (100.0%) patients, decrease in platelets in 3 (50.0%) patients, anaemia in 2 (33.3%) patients, and hemoglobin increased in 1 (16.7%) patient.
Grade 4 decrease in neutrophils (absolute) and Grade 3 anaemia, decrease in neutrophils (absolute), and decrease in platelets were also reported as TEAE.

Vital Signs and Other Measurements

Vital signs of body weight, body temperature, blood pressure (BP), heart rate, and respiratory rate were measured at screening and at every study visit.
None of the patients had abnormal pulse rate (>120 bpm or <50 bpm) or a high body temperature (>38.3°C) at any visit. No patients had abnormal BP (SBP >150 mmHg/DBP >100 mmHg or SBP >200 mmHg/DBP >110 mmHg). A change from baseline in SBP of ⩾20 mm Hg was reported in 1 (16.7%) patient. A change from baseline in DBP of ⩾10 mm Hg was reported in 5 (83.3%) patients and of ⩾20 mm Hg in 3 (50.0%) patients.
The number and percentage of patients who had shifts in QTcF interval from within normal range (Grade 0) at baseline to Grade ⩾3 post-baseline (Grade 3: QTc ⩾501 ms on at least 2 separate electrocardiograms (ECGs) Grade 4: QTc ⩾501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia).

Parameter Name: QTCF INTERVAL (FRIDERICIA'S CORRECTION) (msec)

			Maximum On-Study CTC Grade									
			OTR*		Grade 1		Grade 2		Grade 3/4		Total	
Treatment	N	Baseline Grade	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sunitinib	6	OTR*	2	(33.3)	0		0		2	(33.3)	4	(66.7)
		Grade 1	0		1	(16.7)	0		0		1	(16.7)
		Grade 2	1	(16.7)	0		0		0		1	(16.7)
		Grade 3/4	0		0		0		0		0	
		Total	3	(50.0)	1	(16.7)	0		2	(33.3)	6	(100.0)

*OTR-Outside Toxicity Range: Non-missing standardized result that falls outside grading range for corresponding QTc parameter.
PFIZER CONFIDENTIAL Source Data: Table 16.2.8.3.1 Date of Reporting Dataset Creation: 17SEP2017 Date of Table Generation: 04OCT2017

2.3.3. Discussion on clinical aspects

The MAH submitted a *Phase (I/II Study A6181196) of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumour*. Study A6181196 was a single-arm, multi-center, multi-national, Phase I/II clinical trial evaluating the pharmacokinetic (PK), safety, and preliminary anti-tumour efficacy of sunitinib in children and young adults diagnosed with advanced unresectable gastrointestinal stromal tumour (GIST).

The primary objective of the study was characterization of PK profile.

A total of 8 patients were screened, of which 6 patients (age: 14.3 years (1.4 SD) were enrolled in the study and were included in the analysis of PK, safety, and efficacy.

Eligible patients were dosed based on the body surface area (BSA). The starting dose of sunitinib was 15 mg/m2 per day administered orally per Schedule 4/2, (ie, 4 weeks on study treatment followed by 2 weeks off treatment). Intra-patient dose escalation of sunitinib was allowed after completion of Cycle 1, based on dose modification guidelines. Dose escalation was in increments of 7.5 mg/m2 up to a maximum dose of 30 mg/m2 (not to exceed 50 mg/day). The dose could be reduced in response to toxicities based on Investigator discretion.

A treatment cycle was 42 days, and patients could receive up to 18 cycles of sunitinib therapy for up to 24 months. Patients were to be followed for overall survival (OS) until either 2 years from the first dose of the study drug or completion of 18 cycles of study treatment.

Doses higher than the previously defined MTD (15 mg/m2 per day) were generally well tolerated in this limited population (increase to 22.5 mg/m2 per day in 5 of the 6 patients, and a further increase to 30 mg/m2 per day in 2 patients).

At an oral dose of 15 mg/m2 in pediatric patients with GIST, the median T_{max} values were 8.0 h and 8.0 h for sunitinib and SU012662, respectively. The mean C_{max} values were 18.4 and 2.37 ng/mL for sunitinib and SU012662, respectively. The AUC_8 was 82.7 and 10.7 ng.h/mL for sunitinib and SU012662, respectively. The respective inter-patient variability (CV%) in C_{max} and AUC_8 were 34% and 39% for sunitinib, and 17% and 35% for SU012662. The respective mean observed C_{trough} values on Day 15 of Cycle 1, and on Day 28 of Cycles 1, 2, 3 were 24.4, 29.1, 44.7, 31.3 ng/mL for sunitinib; 11.7, 13.0, 20.9, and 20.5 ng/mL for SU012662; and 36.0, 42.1, 65.6, and 51.8 ng/mL for Total Drug. Furthermore, the respective mean dose–corrected C_{trough} values (the dose-corrected trough concentrations were calculated by multiplying the observed concentration by the correction factor: starting dose/actual dose) on Day 15 of Cycle 1, and on Day 28 of Cycles 1, 2, 3 were 24.4, 29.1, 32.5, 19.9 ng/mL for sunitinib; 11.7, 13.0, 15.2, and 13.1 ng/mL for SU012662; and 36.0, 42.1, 47.7, and 32.9 ng/mL for Total Drug. The CV% in steady state observed or dose-corrected C_{trough} on Day 28 of Cycle 1 was 46%, 36%, and 42% for sunitinib, SU012622, and Total Drug, respectively.

The PK-evaluable patients on Day 28 of Cycle 1 were divided into 2 PK subgroups: those with Total Drug C_{trough} values less than the median C_{trough} value (Lower Exposure) and those with Total Drug C_{trough} values greater than or equal to the median Ctrough value (Higher Exposure).
Regarding the relationship between safety and plasma drug exposures, it was observed that a higher incidence of all grade AEs (gastrointestinal-related and fatigue) and a higher degree of decrease in some of the haematology findings (a greater percent decrease from baseline in absolute neutrophil count and platelet count was observed) with higher Total Drug plasma concentrations.
Furthermore, regarding the relationship between efficacy and plasma drug exposures a higher rate of SD and a longer PFS time in patients with higher total drug plasma concentrations have been observed, indicating sunitinib's anti-tumour activity at higher plasma drug concentrations in paediatric patients with GIST.

No confirmed objective responses were reported in the 6 patients enrolled and treated, with SD reported in 50% of the evaluable population as best overall response.

A total of 82 TEAEs (59 considered treatment-related by the investigator), mostly Grade 1-2 in severity were reported in the as-treated population. No SAEs or Grade 5 TEAEs were reported. Only one patient permanently discontinued treatment due a treatment-related AE (anaemia Grade 2). No new safety signals were identified, and the safety profile appeared to be in line with the known safety profile in adults.

In conclusion, the number of patients enrolled in study A6181196 do not allow to draw any sound conclusion about pharmacokinetic (PK), safety, and efficacy of sunitinib in children and young adults diagnosed with advanced unresectable gastrointestinal stromal tumour (GIST).

3. Rapporteur CHMP overall conclusion and recommendation

At present, based on the limited available data on the paediatric population it is agreed that modification to the SmPC is not required at this stage. An update of the Product Information to include the final results of all the measures included in the PIP will be submitted by July 2018

☒ **Fulfilled**:

No regulatory action required.

4. Additional clarification requested

Not Applicable

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Extrapolation, modelling and simulation studies

Product Name: Sutent Active substance: sunitinib malate

Study title	Study number	Date of completion	Date of submission of final study report
Measure to extrapolate efficacy to the paediatric population	PMAREQDDA618w-Other-366	9 MAY 2014	Submitted to the EMA with variation EMEA/H/C/000687/II/0060/G on November 2015
Modelling and simulation study to develop a population PK model and predict the PK profile and confidence interval of sunitinib in paediatric patients with gastro-intestinal stromal tumour.	N/A	Ongoing	

Other measure

Product Name: Sutent Active substance: sunitinib malate

Study title	Study number	Date of completion	Date of submission of final study report
Retrospective analysis of medical records of paediatric patients (and young adults) with gastrointestinal stromal tumour included in three publications to provide information on sunitinib activity.	N/A	Ongoing	
A Phase I Study of Sunitinib	ADVL0612	Last Subject Last Visit: - For the MTD portion	Submitted to the EMA on June 2013 under Article 46

(SU11248), an Oral Multi-Targeted Tyrosine Kinase Inhibitor, in Children With Refractory Solid Tumors		of the study: 07 December 2009 - For the dose formulation portion of the study: 12 July 2012	(EMA procedure #: EMA/H/C/687/P46-048)
Open label, single-arm, multi-centre trial to evaluate pharmacokinetics, safety and activity of sunitinib in children from 18 months to less than 18 years of age (and in adults) with high-grade glioma or ependymoma.	ACNS1021	31 December 2013 (Data Cut-Off Date for Final Analysis) The study was closed by COG at the time of the planned interim analysis	
A Phase I/II study of sunitinib in young patients with advanced gastrointestinal stromal tumor.	A6181196	Last Patient Last Visit 21 August 2017	February 2018 (Article 46)