Clinical trial results:
A Phase I/II Study Of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumor

Summary

EudraCT number	2011-002008-33
Trial protocol	HU ES Outside EU/EEA CZ PT IT GB PL AT DE FR SK
Global end of trial date	21 August 2017

Results information

Result version number	v1
This version publication date	25 February 2018
First version publication date	25 February 2018

Trial information

Trial identification

Sponsor protocol code	A6181196

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01396148
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 110017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000342-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the plasma pharmacokinetic (PK) profile of Sunitinib and its active metabolite SU012662 in children and young adults with advanced, unresectable Gastrointestinal Stromal Tumor (GIST).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and

in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP)

Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	6
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	6
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 4 centres in 3 countries between 12 June 2012 and 21 August 2017.

Pre-assignment

Screening details:

This was a single arm, multi-center, multi-national study where a total of 6 subjects were dosed based on the body surface area. The starting dose of Sunitinib was 15 milligram/ meter square (mg/m^2) per day administered orally, from Day 1 to 28 in each treatment cycle of 42 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Sunitinib

Arm description:

Subjects received Sunitinib capsules orally at a dose based on body surface area (BSA) (minimum dose of 15 milligram/ meter square [mg/m^2] up to a maximum dose of 30 mg/m^2) once daily, from Day 1 to 28 in each treatment cycle of 42 days (up to a maximum of 18 cycles) until completion of study treatment, disease progression, unacceptable toxicity, required a treatment rest (greater than [>4] weeks), withdrawal of subject consent, or if other withdrawal criteria were met.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	SU011248
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sunitinib capsules orally at a dose based on body surface area (BSA) (minimum dose of 15 milligram/ meter square [mg/m^2] up to a maximum dose of 30 mg/m^2) once daily, from Day 1 to 28 in each treatment cycle of 42 days (up to a maximum of 18 cycles).

Number of subjects in period 1	Sunitinib
Started	6
Completed	5
Not completed	1
Subject Decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Sunitinib

Reporting group description:

Subjects received Sunitinib capsules orally at a dose based on body surface area (BSA) (minimum dose of 15 milligram/ meter square [mg/m^2] up to a maximum dose of 30 mg/m^2) once daily, from Day 1 to 28 in each treatment cycle of 42 days (up to a maximum of 18 cycles) until completion of study treatment, disease progression, unacceptable toxicity, required a treatment rest (greater than [>4] weeks), withdrawal of subject consent, or if other withdrawal criteria were met.

Reporting group values	Sunitinib	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
Adolescents (12-17 years)	6	6	
Age Continuous Units: years			
arithmetic mean	14.3		
standard deviation	± 1.4	-	
Sex: Female, Male Units: Subjects			
Female	5	5	
Male	1	1	
Race/Ethnicity, Customized Units: Subjects			
White|	5	5	
Asian|	1	1	

End points

End points reporting groups

Reporting group title	Sunitinib

Reporting group description:

Subjects received Sunitinib capsules orally at a dose based on body surface area (BSA) (minimum dose of 15 milligram/ meter square [mg/m^2] up to a maximum dose of 30 mg/m^2) once daily, from Day 1 to 28 in each treatment cycle of 42 days (up to a maximum of 18 cycles) until completion of study treatment, disease progression, unacceptable toxicity, required a treatment rest (greater than [>4] weeks), withdrawal of subject consent, or if other withdrawal criteria were met.

Subject analysis set title	Sunitinib: Lower Exposure
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects who received Sunitinib capsules orally at a dose based on BSA (minimum dose of 15 mg/m^2 up to a maximum dose of 30 mg/m^2 once daily, from Day 1 to 28 in each treatment cycle of 42 days (up to a maximum of 18 cycles) and had total drug (sunitinib + SU012662) trough plasma concentration (Ctrough) < the median Ctrough value

Subject analysis set title	Sunitinib: Higher Exposure
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects who received Sunitinib capsules orally at a dose based on BSA (minimum dose of 15 mg/m^2 up to a maximum dose of 30 mg/m^2 once daily, from Day 1 to 28 in each treatment cycle of 42 days (up to a maximum of 18 cycles) and had total drug (sunitinib + SU012662) trough plasma concentration (Ctrough) >= the median Ctrough value

Primary: Maximum Observed Plasma Concentration (Cmax) of Sunitinib and its Metabolite

End point title	Maximum Observed Plasma Concentration (Cmax) of Sunitinib and its Metabolite[1]

End point description:

SU012662 is the metabolite of Sunitinib. The pharmacokinetic (PK) population included all treated subjects with at least 1 PK observation.

End point type	Primary

End point timeframe:

Cycle 1 Day 1: pre-dose, 2, 4, 6, and 8 hours post-dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive data analysis was planned for this endpoint.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Sunitinib| SU012662|	17.58 (± 32) 2.342 (± 18)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Plasma Concentration (Tmax) for Sunitinib and its Metabolite

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) for Sunitinib and its Metabolite[2]

End point description:

SU012662 is the metabolite of Sunitinib. The PK population included all treated subjects with at least 1 PK observation.

End point type	Primary

End point timeframe:

Cycle 1 Day 1: pre-dose, 2, 4, 6, and 8 hours post-dose

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive data analysis was planned for this endpoint.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hours				
median (full range (min-max))				
Sunitinib|	8 (4 to 8)			
SU012662|	8 (4 to 8)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve From Time Zero to 8 hours Post Dose AUC(0-8) for Sunitinib and its Metabolite

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to 8 hours Post Dose AUC(0-8) for Sunitinib and its Metabolite[3]

End point description:

AUC(0-8) was defined as area under the plasma concentration time-curve from time zero to 8 hours post dose. SU012662 is the metabolite of Sunitinib. The PK population included all treated subjects with at least 1 PK observation.

End point type	Primary

End point timeframe:

Cycle 1 Day 1: pre-dose, 2, 4, 6, and 8 hours post-dose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive data analysis was planned for this endpoint.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: nanograms*hour per milliliter (ng*hr)/mL				
geometric mean (geometric coefficient of variation)				
Sunitinib|	77.49 (± 42)			
SU012662|	10.11 (± 37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged insubject hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to end of study (up to Cycle 18) that were absent before treatment or that worsened relative to pretreatment state. AEs included both non-serious adverse events (AEs) and SAEs. The as-treated population included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to Cycle 18, each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
AEs|	6			
SAEs|	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) Greater Than or Equal to (>=) Grade 3, Based on National Cancer Institute (NCI) Common Terminology Criteria (CTC) for AEs (CTCAE), Version 4.0

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) Greater Than or Equal to (>=) Grade 3, Based on

	National Cancer Institute (NCI) Common Terminology Criteria (CTC) for AEs (CTCAE), Version 4.0

End point description:

An AE is any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. As per NCI CTCAE, Grade 3 events =medically significant but not immediately life-threatening, unacceptable or intolerable events, significantly interrupting usual daily activity, require systemic drug therapy/other treatment, Grade 4 events+subject to be in imminent danger of death. Grade 5 events =death. Treatment-emergent events are events between first dose of study drug and up to end of study (up to Cycle 18) that were absent before treatment or that worsened relative to pretreatment state. Number of subjects with AEs of any of the Grade 3 or above (Grade 4, 5) were reported. The as-treated population included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to Cycle 18, each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged insubject hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both non-serious adverse events (AEs) and SAEs. The as-treated population included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to Cycle 18, each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
AEs|	6			
SAEs|	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects with Clinically Significant Laboratory Abnormalities

End point description:

Criteria for clinically significant laboratory abnormalities: Hemoglobin (Hb), hematocrit: less than (<) 0.8*lower limit of normal (LLN), platelet: <75 or greater than (>) 700*10^3/millimeter (mm)^3*upper limit of normal (ULN), leukocyte: <2.5 or >17.5*10^3/mm^3*ULN; total bilirubin 1.5*ULN, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase: >3.0*ULN, total protein, albumin: <0.8*LLN or >1.2*ULN ;blood urea nitrogen, creatinine: >1.3*ULN, uric acid >1.2*ULN; sodium <0.95*LLN or >1.05*ULN, potassium, calcium: <0.9*LLN or >1.1*ULN, albumin, total protein <0.8*LLN or >1.2*ULN; glucose <0.6*LLN or >1.5*ULN, creatine kinase >2.0*ULN; urine (red blood cell, white blood cell >6/high power field). The as-treated population included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to Cycle 18, each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Objective Response

End point title	Number of Subjects With Objective Response

End point description:

Objective response in subjects was defined as the number of subjects with confirmed complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Confirmed response were those that persisted on repeat imaging study for at least 4 weeks after initial documentation of response. CR was defined as disappearance of all lesions (target and non-target). PR was defined as at least 30 percentage (%) decrease in the sum of the longest dimensions of target lesions taking as a reference the baseline sum longest dimensions, with non-target lesions not increased or absent. The full analysis set included all enrolled subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Baseline until death or discontinuation from the study whichever occurred first (maximum duration: up

to Cycle 18; each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
Complete response|	0			
Partial response|	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response: Time (in months) from the first documentation of objective tumor response (confirmed CR or PR) to the first documentation of disease progression or death due to any cause. Confirmed response were those that persisted on repeat imaging study for at least 4 weeks after initial documentation of response. CR: Disappearance of all lesions (target and non-target). PR: At least 30% decrease in the sum of the longest dimensions of target lesions taking as a reference the baseline sum longest dimensions, with non-target lesions not increased or absent. Progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (includes the baseline sum if that is the smallest on study). Analysis was performed on a subset of FAS which included subjects who had confirmed CR or PR. Since, none of the subjects had confirmed CR or PR, hence duration of response was not analyzed.

End point type	Secondary

End point timeframe:

Baseline until death or discontinuation from the study whichever occurred first (maximum duration: up to Cycle 18; each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[4] - None of the subjects were confirmed response,the analysis of duration of response was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression free survival was defined as time (in months) from date of enrollment to the first documentation of disease progression or to death (due to any cause), whichever occurred first. Progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). The full analysis set included all enrolled subjects regardless of what treatment, if any, was received. The upper limit of 95% CI was not reached and has been denoted as 99999.

End point type	Secondary

End point timeframe:

Baseline until death or discontinuation from the study whichever occurred first (maximum duration: up to Cycle 18; each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: months				
median (confidence interval 95%)	5.8 (2.3 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as time (in months) from enrollment to the date of death due to any cause. Analysis was performed using Kaplan-Meier method. The full analysis set included all enrolled subjects regardless of what treatment, if any, was received. Data was not analyzed and has been denoted as 99999, since none of the subjects died.

End point type	Secondary

End point timeframe:

Baseline until death or discontinuation from the study whichever occurred first (maximum duration: up to Cycle 18; each cycle was of 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6[5]			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[5] - Data not analyzed, since none of the subjects died.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) for Pharmacokinetic (PK) Subgroups

End point title	Number of Subjects With Adverse Events Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) for Pharmacokinetic (PK) Subgroups

End point description:

AE: any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. As per NCI CTCAE version 4.0, Grade1= asymptomatic or mild symptoms, Grade 2= Moderate; local or noninvasive intervention indicated; Grade 3 events=medically significant but not immediately life-threatening, require systemic drug therapy/other treatment, Grade 4 events =subject to be in imminent danger of death. Grade 5 events=death. Subjects with any of the Grade 1 to Grade 5 AEs were reported. The PK evaluable subjects were divided into 2 PK subgroups on Day 28 of Cycle 1: those with total drug (sunitinib + SU012662) trough plasma concentration (Ctrough) value less than (<) the median Ctrough value(lower exposure) and those with total drug (sunitinib + SU012662) Ctrough values greater than or equal to (>=) the median Ctrough value(higher exposure). The PK subgroup analysis set included all treated subjects with at least 1 PK observation.

End point type	Secondary

End point timeframe:

Cycle 1 Day 28 up to Cycle 3 (each cycle 42 days)

End point values	Sunitinib: Lower Exposure	Sunitinib: Higher Exposure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects				
Nausea|	0	2		
Vomiting|	0	1		
Diarrhoea|	0	2		
Fatigue|	0	1		
Palmar-Plantar Erythrodysaesthesia Syndrome|	1	0		
Neutropenia|	2	1		
Thrombocytopenia|	1	1		
Lymphopenia|	0	0		
Hypertension|	0	0		
Anaemia|	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pearson Correlation Coefficient Between Percent Change From Baseline in Laboratory Parameters With Total Drug (Sunitinib + SU012662) Concentration

End point title	Pearson Correlation Coefficient Between Percent Change From Baseline in Laboratory Parameters With Total Drug (Sunitinib + SU012662) Concentration

End point description:

Pearson correlation coefficient between percent change from baseline in laboratory parameters with total drug (Sunitinib + SU012662) concentration were calculated on Day 28 of Cycles 1, 2, and 3. Laboratory parameters included absolute neutrophil count, platelet count, lymphocyte count and hemoglobin. The PK population included all treated subjects with at least one PK observation.

End point type	Secondary

End point timeframe:

Baseline, Cycle 1 Day 28 up to Cycle 3 (each cycle 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: correlation coefficient				
number (not applicable)				
Absolute Neutrophil Count: Cycle 1 Day 28|	-0.1870			
Absolute Neutrophil Count: Cycle 2 Day 28|	-0.5914			
Absolute Neutrophil Count: Cycle 3 Day 28|	-0.5536			
Platelet Count: Cycle 1 Day 28|	0.0329			
Platelet Count: Cycle 2 Day 28|	-0.6424			
Platelet Count: Cycle 3 Day 28|	-0.6604			
Lymphocyte Count: Cycle 1 Day 28|	0.1509			
Lymphocyte Count: Cycle 2 Day 28|	-0.4815			
Lymphocyte Count: Cycle 3 Day 28|	-0.2931			
Hemoglobin: Cycle 1 Day 28|	0.9107			
Hemoglobin: Cycle 2 Day 28|	0.4368			
Hemoglobin: Cycle 3 Day 28|	0.2095			

Statistical analyses

No statistical analyses for this end point

Secondary: Pearson Correlation Coefficient Between Percent Change From Baseline in Vital Sign Results with Total Drug (Sunitinib + SU012662) Concentration

End point title	Pearson Correlation Coefficient Between Percent Change From Baseline in Vital Sign Results with Total Drug (Sunitinib + SU012662) Concentration

End point description:

Pearson correlation coefficient between percent change from baseline in vital sign results with total drug (Sunitinib + SU012662) concentration were calculated on Day 28 of Cycles 1, 2, and 3. Vital signs included systolic blood pressure and diastolic blood pressure. The PK population included all treated subjects with at least one PK observation.

End point type	Secondary

End point timeframe:

Baseline, Cycle 1 Day 28 up to Cycle 3 (each cycle 42 days)

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: correlation coefficient				
number (not applicable)				
Systolic Blood Pressure: Cycle 1 Day 28|	-0.3730			
Systolic Blood Pressure: Cycle 2 Day 28|	-0.8146			
Systolic Blood Pressure: Cycle 3 Day 28|	0.2768			
Diastolic Blood Pressure: Cycle 1 Day 28|	0.6854			
Diastolic Blood Pressure: Cycle 2 Day 28|	-0.3638			
Diastolic Blood Pressure: Cycle 3 Day 28|	0.2634			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Stable Disease (SD), Partial Response (PR), Complete Response (CR) and Progressive Disease (PD) for PK Sub-groups

End point title	Number of Subjects With Stable Disease (SD), Partial Response (PR), Complete Response (CR) and Progressive Disease (PD) for PK Sub-groups

End point description:

SD:when there is no sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PR:as at least 30% decrease in the sum of the longest dimensions of target lesions taking as a reference the baseline sum longest dimensions, with non-target lesions not increased or absent. CR:disappearance of all lesions (target and non-target). PD:at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. Subjects with SD, PR, CR and PD responses were assessed according to 2 PK subgroups created on Day 28 of Cycle 1: those with total drug (sunitinib + SU012662) trough plasma concentration (Ctrough) value < the median Ctrough value(lower exposure) and those with total drug (sunitinib + SU012662) Ctrough values >= the median Ctrough value(higher exposure). The PK subgroup analysis set included all treated subjects with at least 1 PK observation.

End point type	Secondary

End point timeframe:

Baseline until disease progression or discontinuation from the study, or death, whichever occurred first(maximum duration: up to Cycle 18; each cycle was of 42 days)

End point values	Sunitinib: Lower Exposure	Sunitinib: Higher Exposure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects				
Stable Disease|	1	2		
Partial Response|	0	0		
Complete Response|	0	0		
Progressive Disease|	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival for PK Sub-groups

End point title	Progression Free Survival for PK Sub-groups

End point description:

Progression free survival was defined as time (in months) from date of enrollment to the first documentation of disease progression or to death (due to any cause), whichever occurred first. Progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). The PK evaluable subjects were assessed according to 2 PK subgroups created on Day 28 of Cycle 1: those with total drug (sunitinib + SU012662) trough plasma concentration (Ctrough) value less than (<) the median Ctrough value(lower exposure) and those with total drug (sunitinib + SU012662) Ctrough values greater than or equal to (>=) the median Ctrough value(higher exposure). The PK population included all treated subjects with at least one PK observation.

End point type	Secondary

End point timeframe:

Baseline until disease progression or discontinuation from the study, or death, whichever occurred first (maximum duration: up to Cycle 18; each cycle was of 42 days)

End point values	Sunitinib: Lower Exposure	Sunitinib: Higher Exposure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: months				
median (confidence interval 95%)	2.6 (2.4 to 99999)	9.0 (2.3 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pearson Correlation Coefficient Between Progression Free Survival With Total Drug (Sunitinib + SU012662) Concentration

End point title	Pearson Correlation Coefficient Between Progression Free

	Survival With Total Drug (Sunitinib + SU012662) Concentration

End point description:

Pearson correlation coefficient between Progression Free Survival (PFS) with total drug (Sunitinib + SU012662) concentration at Day 28 of Cycle 1 was calculated. PFS was defined as time (in months) from date of enrollment to the first documentation of disease progression or to death (due to any cause), whichever occurred first. Progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). The PK population included all treated subjects with at least one PK observation.

End point type	Secondary

End point timeframe:

Baseline until disease progression or discontinuation from the study, or death, whichever occurred first (maximum duration: up to Cycle 18; each cycle was of 42 days

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: correlation coefficient				
number (not applicable)	0.5904			

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Sunitinib Plasma Concentration at Which 50% of the Maximum Effect (EC50) for each Selected Efficacy Parameter (e.g., Sum of Largest Diameters for Target Tumors) was Observed

End point title	Estimated Sunitinib Plasma Concentration at Which 50% of the Maximum Effect (EC50) for each Selected Efficacy Parameter (e.g., Sum of Largest Diameters for Target Tumors) was Observed

End point description:

Due to low number of enrolled subjects (n=6), there was insufficient data to perform any type of pharmacokinetic/ pharmacodynamic modeling to obtain EC50 values, hence data is not reported.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 2, 4, 6, and 8 hours post-dose

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[6] - Data for this endpoint was not collected and summarized due to change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Sunitinib Plasma Concentration at Which 50% of the Maximum Effect (EC50) for Each Selected Safety Endpoint (e.g., Absolute Neutrophil Count) was Observed

End point title	Estimated Sunitinib Plasma Concentration at Which 50% of the Maximum Effect (EC50) for Each Selected Safety Endpoint (e.g., Absolute Neutrophil Count) was Observed

End point description:

Due to low number of enrolled subjects (n=6), there was insufficient data to perform any type of pharmacokinetic/ pharmacodynamic modeling to obtain EC50 values, hence data is not reported.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 2, 4, 6, and 8 hours post-dose

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[7] - Data for this endpoint was not collected and summarized due to change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (up to Cycle 18, each cycle was of 42 days)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Sunitinib

Reporting group description:

Subjects were dosed based on the body surface area. The starting dose of Sunitinib was 15 milligram/ meter square (mg/m^2) per day administered orally, from Day 1 to 28 in each treatment cycle of 42 days until completion of study treatment, disease progression, unacceptable toxicity, required a treatment rest (greater than [>4] weeks), withdrawal of subject consent, or if other withdrawal criteria were met.

Serious adverse events	Sunitinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Sunitinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Fatigue			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Amylase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood alkaline phosphatase			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood phosphorus increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eosinophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		

Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 12		
Weight decreased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
White blood cell count decreased subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 14		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 10		
Migraine subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 7		
Leukopenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Neutropenia subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 23		
Thrombocytopenia			

subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	5		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Impaired gastric emptying			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Lip discolouration			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	5		
Sensitivity of teeth			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vomiting			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Hepatobiliary disorders Hepatic haematoma subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Hair colour changes subjects affected / exposed occurrences (all) Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 2 1 / 6 (16.67%) 1 1 / 6 (16.67%) 2 1 / 6 (16.67%) 5 1 / 6 (16.67%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2		

Muscle spasms subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 6			
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 4			
Myalgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Neck pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2			
Infections and infestations Ear infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Folliculitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Herpes simplex subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Otitis media subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Sinusitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Tooth infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1			
Upper respiratory tract infection				

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Hypermagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2012	The purpose was to revise The Schedule of Activities and associated protocol sections to include growth and pubertal maturation assessments for paediatric subjects, 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 subjects with GIST.
31 July 2017	The purpose was to reduce the numbers of subjects enrolled in the study (in the range of age from 6 to < 18) from 15 to 6 evaluable subjects. The centralized review of imaging (ie, MRI, CT scans etc) aimed to confirm the efficacy endpoint was no longer required. As this study is part of a PIP, both these changes had been agreed with EMA's Pediatric Committee (PDCO) and are aligned with the PIP binding elements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data for three primary PK end points (Estimated steady-state Cmax, AUC24 and CL/F) will be estimated and reported separately as part of the Non-linear Mixed Effects Modeling analysis, and will be provided once available.

Notes: