Clinical trial results:
Pazopanib in advanced gastrointestinal stromal tumors refractory to imatinib and sunitinib . A non-comparative phase II multicenter study by the Scandinavian Sarcoma Group

Summary

EudraCT number	2011-004404-37
Trial protocol	SE FI DE DK IS
Global end of trial date	07 January 2015

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	SSGXXI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01524848
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Scandinavian Sarcoma Group
Sponsor organisation address	Barngatan 2B, Lund, Sweden, SE-22185
Public contact	SSG secretariat, Scandinavian Sarcoma Group, 46 46275 21 82, ssg@med.lu.se
Scientific contact	SSG secretariat, Scandinavian Sarcoma Group, 46 46275 21 82, mikael.eriksson@med.lu.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2015
Global end of trial reached?	Yes
Global end of trial date	07 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Calculate the disease control rate (DCR)=complete remission (CR)+partial remission (PR) + stable disease (SD) at 12 weeks

Protection of trial subjects:

Adverse drug reactions, adverse events and laboratory tests was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
Adverse events was monitored continuosly during the treatment phase and for 30 days after the last intake of study drug.
Haematology and blood chemistry was performed before treatment start, at week 4,8,12 and every 8 weeks thereafter.
Proteinuria (dipstick urinanalysis) was peformed before start of treament, at week 4,8,12 and every 8 weeks thereafter.
Left Ventricular Ejection Fraction was performed before treatment start, at week 12 and every 16 weeks thereafter.
For women with childbearing potential a pregnancy test was performed before start of treament and those women had to accept the use of adequate contraception throughout the study period.
The trial was performed according to ICH-GCP guidelines, as well as the Declaration of Hesinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 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	Norway: 10
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	0
Adults (18-64 years)	35
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 72 patients was enrolled in the study as per plan if the interim analysis after 22 patients showed that at least six patients achieved disease control rate (DCR=CR+PR+SD) at 12 weeks according to RECIST version 1.1

Pre-assignment

Screening details:

Patients with metastatic and/or locally advanced GIST and with a history of progressive disease after both imatinib and sunitinib treatment, and also nilotinib if this drug has been given was screened for eligibility.

Period 1

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

Arms

Arm title	Pazopanib

Arm description:

This is a single arm study with Pazopanib. Pazopanib is a tyrosin kinase receptor inhibitor given as tablets of 400 mg with the standard dose being two tablets given at one occasion at the same time each day without food at least one hour before or two hours after a meal.

Arm type	Single
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	Votrient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg (two tablets á 400 mg) taken once daily orally without food for at least one hour before or two hours after a meal.

Number of subjects in period 1	Pazopanib
Started	72
Completed	72

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Treatment with 800 mg Pazopanib orally once a day.

Reporting group values	Overall trial	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	35	35	
From 65-84 years	37	37	
85 years and over	0	0	
Age continuous Units: years			
median	64.2		
full range (min-max)	32 to 83	-	
Gender categorical Units: Subjects			
Female	25	25	
Male	47	47	

Subject analysis sets

Subject analysis set title	Pazopanib
Subject analysis set type	Full analysis

Subject analysis set description:

Pazopanib is a tyrosin kinase inhibitor given as tablets of 400 mg with the standard dose being two tablets given at one occasion at the same time each day without food at least one hour before or two hours after a meal. This is a single arm study.

Reporting group values	Pazopanib		
Number of subjects	72		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months)			

Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	35		
From 65-84 years	37		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Pazopanib

Reporting group description:

This is a single arm study with Pazopanib. Pazopanib is a tyrosin kinase receptor inhibitor given as tablets of 400 mg with the standard dose being two tablets given at one occasion at the same time each day without food at least one hour before or two hours after a meal.

Subject analysis set title	Pazopanib
Subject analysis set type	Full analysis

Subject analysis set description:

Pazopanib is a tyrosin kinase inhibitor given as tablets of 400 mg with the standard dose being two tablets given at one occasion at the same time each day without food at least one hour before or two hours after a meal. This is a single arm study.

Primary: Disease control rate (DCR=CR+PR+SD) at 12 weeks according to RECIST 1.1

End point title	Disease control rate (DCR=CR+PR+SD) at 12 weeks according to RECIST 1.1

End point description:

End point type	Primary

End point timeframe:

Disease control rate (DCR=CR+PR+SD) evaluated at 12 weeks and every 8 weeks as long as treatment continues by CT abdomen/pelvic region.

End point values	Pazopanib	Pazopanib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	72	72[1]		
Units: Procentage	72	72		

Notes:

[1] - Note that this is a single arm study with a total of 72 patients.

Statistical analyses

Statistical analysis title	Non-comparative statistical analysis of pazopanib

Statistical analysis description:

Demographic and prognostic variables were presented by means of descriptive statistics.
Whenever appropriate, results are illustrated with a graph. The primary endpoint was Disease control rate (DCR=CR+PR+SD) at 12 weeks from start of pazopanib treatment according to RECIST version 1.1. The primary endpoint was analysed using Simon's two stage analysis will be used. Since sample size calculation is an integral part of Simon’s method, no separate section on sample size was made.

Comparison groups	Pazopanib v Pazopanib
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority[2]
Method	Simon`s two stage method
Parameter estimate	Proportion with clinical benefit
Point estimate	44.4

Confidence interval	
level	90 %
sides	2-sided
lower limit	34
upper limit	60

Notes:

[2] - Superiority to a fixed value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment, and 30 days after end of treatment.

Adverse event reporting additional description:

All AEs was documented on the case report forms (CRF) where a lot of AEs was listed including the most common described in relation with pazopanib treatment. For AEs not specifically listed, space for "other" was created.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 72 (43.06%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Vascular disorders			
Trombosis left leg			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Amputation right foot			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hospitalisation due to insert of stent			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart failure			

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Circulatory collapse				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Decreased activity				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
Pain in extremity				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Amotio retinae				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Nausea and vomiting				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Diarrhea				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Perforation of colon				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric bleeding				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ulcer				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural effusion				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Bladder perforation				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
General infection			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wound infection bacterial			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 72 (100.00%)		
General disorders and administration site conditions			
Headache			
subjects affected / exposed	16 / 72 (22.22%)		
occurrences (all)	32		
Hypertension			
subjects affected / exposed	54 / 72 (75.00%)		
occurrences (all)	228		
Epistaxis			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	27		
Hoarseness			
subjects affected / exposed	21 / 72 (29.17%)		
occurrences (all)	48		
Stomatitis			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	37		

Hair color change subjects affected / exposed occurrences (all)	35 / 72 (48.61%) 145		
Fatigue subjects affected / exposed occurrences (all)	54 / 72 (75.00%) 117		
Sweating subjects affected / exposed occurrences (all)	11 / 72 (15.28%) 23		
Change of voice subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 5		
Fever subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 4		
Dry mouth subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 4		
Respiratory, thoracic and mediastinal disorders			
Insomnia subjects affected / exposed occurrences (all)	7 / 72 (9.72%) 12		
Dyspnoea subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 7		
Investigations			
Increased ALT subjects affected / exposed occurrences (all)	17 / 72 (23.61%) 53		
Increased AST subjects affected / exposed occurrences (all)	23 / 72 (31.94%) 52		
Increased ALP subjects affected / exposed occurrences (all)	26 / 72 (36.11%) 65		
Cardiac disorders			

Left ventricular dysfunction subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	15 / 72 (20.83%) 39		
Blood and lymphatic system disorders Trombocytopeni subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Anemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Lymphoblast count increased subjects affected / exposed occurrences (all) Embolism subjects affected / exposed occurrences (all) Thrombosis subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 26 11 / 72 (15.28%) 20 5 / 72 (6.94%) 14 1 / 72 (1.39%) 3 3 / 72 (4.17%) 4 1 / 72 (1.39%) 1 1 / 72 (1.39%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 4		
Eye disorders Blurred vision subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 6		

Cataract			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	42 / 72 (58.33%)		
occurrences (all)	106		
Nausea			
subjects affected / exposed	31 / 72 (43.06%)		
occurrences (all)	91		
Vomiting			
subjects affected / exposed	18 / 72 (25.00%)		
occurrences (all)	24		
Dyspepsia			
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	31		
Diarrhoea			
subjects affected / exposed	45 / 72 (62.50%)		
occurrences (all)	212		
Flatulence			
subjects affected / exposed	19 / 72 (26.39%)		
occurrences (all)	46		
Abdominal distension			
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	62		
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Ileus			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	6		
Hepatobiliary disorders			

Hyperbilirubinaemia			
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	32		
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	17		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	21		
Skin hypopigmentation			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	44		
Rash maculo-papular			
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	13		
Hand and foot syndrome			
subjects affected / exposed	17 / 72 (23.61%)		
occurrences (all)	43		
Erythema			
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	13		
Edema face			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	12		
Edema limbs			
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	32		
Edema trunk			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	6		
Dry skin			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	9		
Sensitive skin			

subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	10		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	20 / 72 (27.78%)		
occurrences (all)	59		
Creatinine increased			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	6		
Haematuria			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
Nocturia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	24 / 72 (33.33%)		
occurrences (all)	72		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	30 / 72 (41.67%)		
occurrences (all)	93		
Pain			
subjects affected / exposed	16 / 72 (22.22%)		
occurrences (all)	27		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Common cold			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Unknown infection			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	37 / 72 (51.39%)		
occurrences (all)	93		
Dysgeusia			
subjects affected / exposed	16 / 72 (22.22%)		
occurrences (all)	52		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2013	The main reasons for this amendment were the following: a) An extra blood sampling for liver tests three weeks after start of the study drug was introduced after a safety warning from the company producing the drug. b) It was made clearer that the trial would encompass in total 72 evaluable patients, whereby two categories of patients could be substituted after registration if they had either not received any dose of the study drug, or were shown not to be eligible. Furthermore, some eligibility criteria were slightly adjusted as a consequence of claims from German authorities when this country joined the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported