Clinical trial results:
Trial SAKK 56/07 Dasatinib first-line treatment in gastrointestinal stromal tumors. A multicenter phase II trial.

Summary

EudraCT number	2007-002047-24
Trial protocol	FR DE
Global end of trial date	16 May 2018

Results information

Result version number	v1 (current)
This version publication date	28 September 2022
First version publication date	28 September 2022

Trial information

Trial identification

Sponsor protocol code	SAKK56/07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00568750
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakkcc@sakk.ch

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	01 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2018
Global end of trial reached?	Yes
Global end of trial date	16 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Efficacy of dasatinib treatment as assessed by fusion PET/CT-scan

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continous assessment of laboratory values and vital signs.

Background therapy:

none

Evidence for comparator:

not applicable. This was a single arm study.

Actual start date of recruitment	17 January 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	45
EEA total number of subjects	27

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)	26
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

47 of planned 52 patients at ten sites in France (3 sites, 21 patients), Germany (1 site, 1 patient), Poland (1 site, 7 patients) and Switzerland (8 sites, 18 patients) have been enrolled from January 2008 to November 2011.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fullfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Pre-assignment period milestones

Number of subjects started	47[1]
Number of subjects completed	45

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No baseline CT (violation eligibility criteria): 1
Reason: Number of subjects	PET negative (violation eligibility criteria): 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 47 patients were screened for eligibility. Of these patients, five were deemed ineligible. However, for three of these patients failure of eligibility was noticed as late as after receipt of first study treatment. Thus, these three patients were included in the safety analysis set but rejected from the efficacy analysis set.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dasatinib treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	Sprycel®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

70 mg twice daily

Number of subjects in period 1	Dasatinib treatment
Started	45
Completed	45

Period 2	
Period 2 title	Treatment/FU Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dasatinib treatment

Arm description:

Dasatinib 70 mg BID per os for two years (26 cycles) or until progression or unacceptable toxicity. Elective surgery was allowed after at least six completed cycles in responding and stabilized patients. At time of progression, the patient was transferred to the follow-up phase and was proposed the standard treatment for GIST (i.e. imatinib 400 mg /day per os). Patients were followed up for up to five years after study treatment discontinuation or completing study treatment, respectively.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	Sprycel®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

70 mg twice daily

Number of subjects in period 2	Dasatinib treatment
Started	45
Completed	5
Not completed	40
Physician decision	3
Death	2
Degradation of clinical status	1
Disease progression (confirmed by PET)	14
Late screening failure (PET negative)	1
Unacceptable toxicity	7
Surgery	8

Late screening failure (No GIST)	2
Progressive disease by CT	2

Baseline characteristics

Reporting groups	
Reporting group title	Dasatinib treatment

Reporting group description: -

Reporting group values	Dasatinib treatment	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Adults (18-64 years)	26	26	
From 65-84 years	19	19	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	20	20	
Male	25	25	

End points

End points reporting groups

Reporting group title	Dasatinib treatment
Reporting group description: -	
Reporting group title	Dasatinib treatment
Reporting group description:	
Dasatinib 70 mg BID per os for two years (26 cycles) or until progression or unacceptable toxicity. Elective surgery was allowed after at least six completed cycles in responding and stabilized patients. At time of progression, the patient was transferred to the follow-up phase and was proposed the standard treatment for GIST (i.e. imatinib 400 mg /day per os). Patients were followed up for up to five years after study treatment discontinuation or completing study treatment, respectively.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Analysis set including all eligible patients receiving at least one dose of the study drug.	
Subject analysis set title	KIT - Exon 11
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients with mutational status of KIT = Exon 11.	
Subject analysis set title	KIT - WT
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients with mutational status of KIT = Wildtype.	
Subject analysis set title	KIT - NA / Exon 9
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients with mutational status of KIT = Exon 9 or N/A.	

Primary: Primary Endpoint | PET response at 4 weeks

End point title	Primary Endpoint | PET response at 4 weeks[1]
End point description:	
Efficacy of dasatinib treatment as assessed by fusion PET/CT-scan. EORTC PET Study Group criteria were assessed by a central review board. [mCR: metabolic complete response, mPR: metabolic partial response, mSD: metabolic stable disease, mPD: metabolic progressive disease). Response defined as mCR+ mPR. Response rate presented with the corresponding 95% Clopper Pearson confidence interval. [mCR: 33%, mPR: 40%, mSD: 14%, mPD: 7%; n/a: 5%]	
End point type	Primary
End point timeframe:	
4 weeks	

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: This was a single arm study. No comparative statistical analyses were performed. However, with an exact two stage binomial test with N1=17, R1=9 and N= 42 a decision limit R=26 was calculated to decide if treatment was promising.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Response rate (%)				
number (confidence interval 95%)	74 (58 to 86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Best response according to RECIST as measured on CT scan/MRI

End point title	Secondary Endpoint | Best response according to RECIST as measured on CT scan/MRI

End point description:

Best response according to RECIST. Best response defined as CR+ PR. Response rate presented with the corresponding 95% Clopper Pearson confidence interval.

[CR: 5%, PR: 38%, SD: 31%, PD: 19%; n/a: 7%]

End point type	Secondary

End point timeframe:

From registration until end of treatment.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Best response (%)				
number (confidence interval 95%)	43 (28 to 59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Clinical benefit

End point title	Secondary Endpoint | Clinical benefit

End point description:

Clinical benefit was defined as CR, PR, or as SD lasting at least 12 weeks, determined according to RECIST. PET evaluation was not used for clinical benefit analysis as no comparative data exist. Rate presented with the corresponding 95% Clopper Pearson confidence interval.

[CR:2 patients, PR: 16 patients, SD: 9 patients]

End point type	Secondary

End point timeframe:

From registration until end of treatment.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Patients with clinical benefit (%)				
number (confidence interval 95%)	64 (48 to 78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Best response as measured by fusion PET/CT

End point title	Secondary Endpoint | Best response as measured by fusion PET/CT

End point description:

The best response (mCR+mPR) rate as measur measured by fusion PET/CT scan. The centralized review board had to confirm the mCR.

[mCR/mPR: 76%, mSD: 12%, mPD: 7%; n/a: 5%]

End point type	Secondary

End point timeframe:

From registration until end of treatment

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Best response (%)				
number (confidence interval 95%)	76 (61 to 88)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Response Duration

End point title	Secondary Endpoint | Response Duration

End point description:

Response duration for 32 patients with mPR/mCR.

End point type	Secondary

End point timeframe:

From registration until end of treatment.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	32[2]			
Units: Response duration (months)				
median (confidence interval 95%)	13.2 (10.2 to 17.5)			

Notes:

[2] - 32 patients with mPR/mCR

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Time to progression

End point title	Secondary Endpoint | Time to progression

End point description:

Time to progression was calculated from registration until progression or death due to tumor.

Kaplan Meier analysis. At the time of the analysis 22 patients had experienced disease progression. A mong the others one patient died due to GIST.

There were 23 events for the time to progression analysis.

End point type	Secondary

End point timeframe:

From registration until progression or death due to tumor.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Time to progression (months)				
median (confidence interval 95%)	14.1 (9.4 to 35.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Progression free survival (PFS)

End point title	Secondary Endpoint | Progression free survival (PFS)

End point description:

Time to progression was calculated from registration until progression or death.

Kaplan-Meier Analysis. At the time of the analysis 22 patients had experienced disease progression. A

mong the others one patient died due to GIST.

There were 24 events for the progression free survival analysis.

End point type	Secondary

End point timeframe:

From registration until progression or death.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: PFS (months)				
median (confidence interval 95%)	14.1 (9.4 to 35.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Time to treatment failure

End point title	Secondary Endpoint | Time to treatment failure

End point description:

Time to treatment failure will be calculated from registration until premature trial treatment termination due to any reason. After treatment completion, it is defined as time to progression, time to death if no progression, or change of anti-tumor treatment in absence of progression.

Kaplan-Meier Analysis. At the time of the analysis 41 patients had treatment failure: 37 patients stopped before 26 cycles, and four patients completed 26 cycles and had disease progression later on. One patient completed 26 cycles and had no progression so far.

End point type	Secondary

End point timeframe:

From registration until end of treatment.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Time to treatment failure (months)				
median (confidence interval 95%)	8.5 (5.3 to 11.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Overall survival

End point title	Secondary Endpoint | Overall survival

End point description:

Overall survival will be calculated from registration until death or last follow-up, up to 5 years.

Kaplan-Meier Analysis. Seventeen patients had died at the time of the analysis. Two deaths occurred during treatment. Fifteen deaths occurred in the follow up phase. The median follow up time based on the reverse Kaplan Meier method was 6.2 years the range in surviving patients 3.4 to 7.6 years.

NOTE: UPPER LIMIT OF 95% CI NOT REACHED. DUMMY DATA ("999") ENTERED DUE TO DATABASE RESTRICTIONS.

End point type	Secondary

End point timeframe:

From registration until death or last follow-up, up to 5 years.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Overall Survival (months)				
median (confidence interval 95%)	6.5 (5.6 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Best response of 2nd-line treatment with another TK-inhibitor

End point title	Secondary Endpoint | Best response of 2nd-line treatment with another TK-inhibitor

End point description:

37 patients had started a 2nd-line treatment but 15 of them had elective surgery or started 2nd-line treatment before progression under 1st-line treatment. Thus for the analysis of 2nd-line treatment 22 patients were remaining.

Best response according to RECIST.

End point type	Secondary

End point timeframe:

From second-line treatment with another TK-inhibitor until end of study.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	22[3]			
Units: Number of patients				
CR	2			
PR	9			
SD	8			
PD	3			

Notes:

[3] - See description for endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Time to progression (TTP) of 2nd-line treatment with another TK-inhibitor

End point title	Secondary Endpoint | Time to progression (TTP) of 2nd-line treatment with another TK-inhibitor

End point description:

Time to progression (TTP) of 2nd-line treatment with another TK-inhibitor.

37 patients had started a 2nd-line treatment but 15 of them had elective surgery or started 2nd-line treatment before progression under 1st-line treatment. 17 of the 22 patients had a progression under 2nd-line treatment.

Note: This TTP analysis is descriptive only and for the moment non informative as some of these patient had been disease free after surgery.

End point type	Secondary

End point timeframe:

From start of 2nd-line treatment until progression or death.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	22[4]			
Units: TTP (months)				
median (confidence interval 95%)	13.6 (5.7 to 21.7)			

Notes:

[4] - See endpoint desciption.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | PET response by mutational status of KIT

End point title	Secondary Endpoint | PET response by mutational status of KIT

End point description:

PET response at 4 weeks by mutational status of KIT.

The mutational status of the most common KIT mutations (exons 9, 11, 13 and 17 of KIT) was assessed using standard PCR techniques and/or DHPLC.

Mutational status of PDGFR was not available.

End point type	Secondary

End point timeframe:

At 4 weeks

End point values	KIT - Exon 11	KIT - WT	KIT - NA / Exon 9	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	7	15	
Units: Number of patients				
mCR	6	3	5	
mPR	10	1	6	
mSD	2	2	2	
mPD	0	1	2	
N/A	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Time to progression (KIT Exon 11)

End point title	Secondary Endpoint | Time to progression (KIT Exon 11)

End point description:

Time to progression (TTP) was calculated from registration until progression or death due to tumor.

Kaplan Meier analysis of TTP for subgroup of patients with KIT = Exon 11.

End point type	Secondary

End point timeframe:

From registration until progression or death due to tumor.

End point values	KIT - Exon 11			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Time to progression (months)				
median (confidence interval 95%)	17.3 (11.1 to 26.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint | Time to progression (KIT WT)

End point title	Secondary Endpoint | Time to progression (KIT WT)

End point description:

Time to progression (TTP) was calculated from registration until progression or death due to tumor.

Kaplan Meier analysis of TTP for subgroup of patients with KIT = WT.

End point type	Secondary

End point timeframe:

From registration until progression or death due to tumor.

End point values	KIT - WT			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Time to progression (months)				
median (confidence interval 95%)	11.1 (2.4 to 56.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From registration up to 30 days after last dose of trial treatment.

Adverse event reporting additional description:

SAEs were recorded from registration up to 30 days after last dose of trial treatment. After this period the following events were recorded: (i) fatalities and severe events possibly, probably or definitely related to late effects of therapy, (ii) disabling events, (iii) second primary cancer, (iv) congenital anomaly

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Safety Analysis Set

Reporting group description:

The Safety Analysis Set (n=45) includes 42 patients of the FAS and three additional patients initiating study treatment but who were deemed screening failures later on.

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 45 (60.00%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Gastrointestinal anastomotic leak	Additional description: Duodenal leak grade 1 post duodenectomy		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal anastomosis complication	Additional description: Pleural effusion grade 3, anastomosis insufficiency, Staphylococcus infection grade 3		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Including one event: Abdominal pain NOS G3, nausea G2, vomiting G2		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: Including one event: Anorexia grade 1, nausea grade 2, diarrhea grade 2, repeated dark stools		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage	Additional description: Acute intratumoral hemorrhage (liver metastases), acute gastrointestinal bleeding		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Ileus			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction	Additional description: Including one event (1): Functional intestinal obstruction grade 3 with vomiting caused by stromal tumor mass (without tumor progression); and one event (2): Intestinal obstruction grade 4 due to gastrointestinal stromal tumor with stable disease		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage	Additional description: Hemorrhage grade2 of lower gastrointestinal (NOS), hemorrhage grade 1 GU (bladder), INR grade 2, PTT grade 1 due to diverticulosis, probably acquired auto-antibodies against factor II and possible vitamine K deficit		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haematoma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction	Additional description: Paralytic ileus and small intestine occlusion		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: Decompensated digestive problems related to gastrointestinal stromal tumor, vomiting and diarrhea grade 3		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia requiring surgical excision		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst	Additional description: Ovarian cyst requiring laparotomic excision		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis	Additional description: Abdominal pain grade 3 due to cholecystitis grade 3 requiring cholecystectomy		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: Including one event (1): Dyspnea grade 1 in context of pleural effusion grade 3; and one event (2): Dyspnea grade 2 due to pleural effusion		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Pulmonary edema	Additional description: Dyspnea grade 4 due to pulmonary capillary leak grade 3		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism	Additional description: Including one event (1): Pulmonary embolism grade 4, headache grade 3, dyspnea grade 2, heart failure grade 2; and one event (2): Irreversible cardiac arrest due to massive pulmonary embolism		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis	Additional description: Degenerative arthrosis grade 3 (hip) requiring total hip replacement		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis	Additional description: Diarrhea grade 3, fever grade 2 due to suspected gastroenteritis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection	Additional description: Pulmonary infection, pulmonary edema		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration	Additional description: Nausea, vomiting, diarrhea, dehydration grade 3, fever grade 1		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia	Additional description: Hypocalcemia grade 2, diarrhea grade 1		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Investigations			
Haemoglobin			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Aspartate aminotransferase			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Nervous system disorders			
Taste disorder			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	8		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	21 / 45 (46.67%)		
occurrences (all)	32		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 45 (77.78%)		
occurrences (all)	59		
Pyrexia			
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	10		
Chills			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		

Localised oedema	Additional description: Edema: head and neck		
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	12		
Diarrhoea			
subjects affected / exposed	29 / 45 (64.44%)		
occurrences (all)	60		
Nausea			
subjects affected / exposed	19 / 45 (42.22%)		
occurrences (all)	31		
Vomiting			
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	16		
Abdominal pain			
subjects affected / exposed	19 / 45 (42.22%)		
occurrences (all)	25		
Respiratory, thoracic and mediastinal disorders			
Laryngeal pain	Additional description: Throat/pharynx/larynx pain		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	16		
Dyspnoea			
subjects affected / exposed	22 / 45 (48.89%)		
occurrences (all)	37		
Pleural effusion			

subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all)	21 / 45 (46.67%) 44 3 / 45 (6.67%) 4		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 5 / 45 (11.11%) 6 4 / 45 (8.89%) 4 6 / 45 (13.33%) 8 3 / 45 (6.67%) 3 15 / 45 (33.33%) 19		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 4 / 45 (8.89%) 4		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 4		
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 3 6 / 45 (13.33%) 7		

Myalgia subjects affected / exposed occurrences (all)	11 / 45 (24.44%) 16		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	14 / 45 (31.11%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

This study was terminated by the sponsor due to low accrual after about 90% of patients had been enrolled.

Notes: