Clinical trial results:
A Multi-Centre, Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Investigate Efficacy and Safety of Sevuparin Infusion for the Management of Acute Vaso-Occlusive Crisis (VOC) in Subjects with Sickle-Cell Disease (SCD)

Summary

EudraCT number	2014-004416-11
Trial protocol	NL BE
Global end of trial date	10 February 2019

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	TVOC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02515838
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Modus Therapeutics AB
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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	10 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the time to painful VOC resolution, measured from first dose given to achievement of crises resolution, as compared to placebo.

This was a multicentre, randomised, double-blind, placebo-controlled study. Eligible patients (adults and adolescents), who were hospitalised with VOC for parenteral opioid analgesia, were randomised to receive sevuparin (3 mg/kg loading dose followed by 18 mg/kg/day continuous infusion) or matching placebo. Study drug was administered within 24 hours of the hospitalisation and continued for a minimum of 48 hours. The infusion was stopped when the VOC resolved, otherwise treatment continued for a maximum of 7 days. Patients also received site-specific standard of care treatment for their VOC.

Key secondary endpoints were:
Mean change in pain intensity from baseline,
Duration of severest pain, and
Accumulated dose of parenteral opiods from baseline until VOC resulotion/readiness for discharge

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in accordance with ICH GCP.

An independent Data and Safety Monitoring Board (DSMB) performed interim safety data reviews that were independent of both the Sponsor and the CRO. The DSMB reviewed data of the first adult 12 patients who received the investigational product. Any dose adjustments based on this review were to occur before adolescents were randomised into the study.

Background therapy:

No pre-defined background therapy was given but the subject were given site-specific standard of care treatment for their VOC.

Evidence for comparator:

This was a placebo-controlled trial vs investigational drug.
No other comparators were used.

Abbreviations used:
CPID: Cumulative pain intensity difference
IP: Investigational product
PK: Pharmacokinetics
IV: Intravenous
SCD: Sickle cell disease
VOC: Vaso-occlusive crisis

Actual start date of recruitment	07 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bahrain: 13
Country: Number of subjects enrolled	Jamaica: 15
Country: Number of subjects enrolled	Lebanon: 28
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Oman: 26
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Turkey: 43
Worldwide total number of subjects	144
EEA total number of subjects	17

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)	33
Adults (18-64 years)	111
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was performed in 16 hospitals in the Netherlands, Lebanon, Turkey, Bahrain, Oman, Saudi Arabia, and Jamaica. Patients aged 12–50 years with a diagnosis of sickle cell disease (types HbSS, HbSC, HbSβ-thalassaemia, or HbSβ+-thalassaemia) were recruited between Oct 2015 and February 2019.

Pre-assignment

Screening details:

Adult and adolescent patients with SCD were screened for eligibility when presenting at the hospital for acute VOC. Patients with more than 5 hospitalisations for VOC during the last 6 months were excluded (to exclude patients with exacerbations of chronic pain rather than true VOC) as were patients with acute SCD complications other than VOC.

Period 1

Period 1 title	Overall Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor

Blinding implementation details:

The appearance of the test product was the same as the NaCl solution which was used as placebo. Test product and placebo were provided in identical vials with identical labelling.
Central laboratories analysed biomarkers; no data from these analyses were available to investigator sites to avoid inadvertent unblinding.
An Independent Statistician was unblinded and was responsible for the generation of the randomisation list and to provide support to the DSMB meetings with unblinded analyses.

Arms

Are arms mutually exclusive?	No
Arm title	Sevuparin

Arm description:

Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours. The IP and morphine (morphine hydrochloride or morphine sulphate) in the concentration 1 mg/mL were compatible and could be administered via the same infusion line.

Arm type	Experimental
Investigational medicinal product name	Sevuparin 150 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to treatment with sevuparin received a loading dose of 3 mg/kg in 15 minutes followed by a continuous infusion of 18 mg/kg/day (0.75 mg/kg/h) for 2-7 days.

Arm title	Placebo

Arm description:

Patients with SCD, hospitalised with acute VOC, received placebo as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours. The placebo solution and morphine (morphine hydrochloride or morphine sulphate) in the concentration 1 mg/mL were compatible and could be administered via the same infusion line.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to treatment with placebo received a short infusion of placebo at the same dose volume as patients randomised to receive sevuparin, followed by continuous infusion of placebo solution at the same infusion rate in mL/h for 2-7 days.

Arm title	PK - Sevuparin, Adult Male

Arm description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Arm type	Experimental
Investigational medicinal product name	Sevuparin 150 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to treatment with sevuparin received a loading dose of 3 mg/kg in 15 minutes followed by a continuous infusion of 18 mg/kg/day (0.75 mg/kg/h) for 2-7 days.

Arm title	PK - Sevuparin, Adult Female

Arm description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Arm type	Experimental
Investigational medicinal product name	Sevuparin 150 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to treatment with sevuparin received a loading dose of 3 mg/kg in 15 minutes followed by a continuous infusion of 18 mg/kg/day (0.75 mg/kg/h) for 2-7 days.

Arm title	PK - Sevuparin, Adolescent Male

Arm description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Arm type	Experimental
Investigational medicinal product name	Sevuparin 150 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to treatment with sevuparin received a loading dose of 3 mg/kg in 15 minutes followed by a continuous infusion of 18 mg/kg/day (0.75 mg/kg/h) for 2-7 days.

Arm title	PK - Sevuparin, Adolescent Female

Arm description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received

sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Arm type	Experimental
Investigational medicinal product name	Sevuparin 150 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to treatment with sevuparin received a loading dose of 3 mg/kg in 15 minutes followed by a continuous infusion of 18 mg/kg/day (0.75 mg/kg/h) for 2-7 days.

Number of subjects in period 1	Sevuparin	Placebo	PK - Sevuparin, Adult Male
Started	69	75	8
Completed	58	69	8
Not completed	11	6	0
Consent withdrawn by subject	3	-	-
Physician decision	1	-	-
Adverse event, non-fatal	1	2	-
Lost to follow-up	6	4	-

Number of subjects in period 1	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Started	2	2	2
Completed	2	2	2
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Sevuparin
Reporting group description:	
Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours. The IP and morphine (morphine hydrochloride or morphine sulphate) in the concentration 1 mg/mL were compatible and could be administered via the same infusion line.	
Reporting group title	Placebo
Reporting group description:	
Patients with SCD, hospitalised with acute VOC, received placebo as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours. The placebo solution and morphine (morphine hydrochloride or morphine sulphate) in the concentration 1 mg/mL were compatible and could be administered via the same infusion line.	
Reporting group title	PK - Sevuparin, Adult Male
Reporting group description:	
Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.	
Reporting group title	PK - Sevuparin, Adult Female
Reporting group description:	
Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.	
Reporting group title	PK - Sevuparin, Adolescent Male
Reporting group description:	
Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.	
Reporting group title	PK - Sevuparin, Adolescent Female
Reporting group description:	
Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.	

Reporting group values	Sevuparin	Placebo	PK - Sevuparin, Adult Male
Number of subjects	69	75	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	15	18	0
Adults (18-64 years)	54	57	8
From 65-84 years	0	0	0
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	27	27	0
Male	42	48	8

Reporting group values	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Number of subjects	2	2	2
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	2	2
Adults (18-64 years)	2	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	0	2
Male	0	2	0

Reporting group values	Total		
Number of subjects	144		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	33		
Adults (18-64 years)	111		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	54		
Male	90		

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients in the ITT population consisted of all patients who met all inclusion and exclusion criteria.

Reporting group values	ITT		
Number of subjects	144		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	33		
Adults (18-64 years)	111		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	54		
Male	90		

End points

End points reporting groups

Reporting group title	Sevuparin

Reporting group description:

Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours. The IP and morphine (morphine hydrochloride or morphine sulphate) in the concentration 1 mg/mL were compatible and could be administered via the same infusion line.

Reporting group title	Placebo

Reporting group description:

Patients with SCD, hospitalised with acute VOC, received placebo as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours. The placebo solution and morphine (morphine hydrochloride or morphine sulphate) in the concentration 1 mg/mL were compatible and could be administered via the same infusion line.

Reporting group title	PK - Sevuparin, Adult Male

Reporting group description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Reporting group title	PK - Sevuparin, Adult Female

Reporting group description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Reporting group title	PK - Sevuparin, Adolescent Male

Reporting group description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Reporting group title	PK - Sevuparin, Adolescent Female

Reporting group description:

Sevuparin subgroup for pharmakokinetics. Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days until resolution of VOC, whichever was sooner, but not for less than 48 hours.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients in the ITT population consisted of all patients who met all inclusion and exclusion criteria.

Primary: Time from IP administration start until VOC resolution

End point title	Time from IP administration start until VOC resolution[1]

End point description:

Time to vaso-occlusive crisis resolution defined as the time from the start of IP infusion until resolution of the crisis/episode which required freedom from parenteral opioid use in the preceding 8 ± 2 hours and the readiness for discharge as judged by the patient or physician, whichever occurred first.

End point type	Primary

End point timeframe:

The primary endpoint was assessed from start of IP infusion and up to a maximum of 7 days.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[2]	75[3]		
Units: hours				
median (confidence interval 95%)	100.4 (85.50 to 116.82)	86.4 (70.62 to 95.05)		

Notes:

[2] - 69 subjects were randomised to sevuparin but only 68 subjects actually received sevuparin.

[3] - 75 subjects were randomised to placebo but 76 subjects received placebo.

Statistical analyses

Statistical analysis title	Cox proportional hazards model

Statistical analysis description:

The treatment difference was estimated with hazard ratios and associated confidence intervals.

Comparison groups	Sevuparin v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5536
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.3

Secondary: Mean change in pain intensity from baseline

End point title	Mean change in pain intensity from baseline[4]

End point description:

Pain intensity assessed using a VAS (0–100 mm, with 0 mm equalling no pain and 100 mm equalling the worst possible pain). Pain was assessed 30 minutes prior to start of infusion and then every 4 hours (while awake) until VOC resolution.

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	75		
Units: mm VAS				
arithmetic mean (standard deviation)	-35.3 (± 19.76)	-34.1 (± 18.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median duration of severest pain

End point title	Median duration of severest pain[5]

End point description:

The median duration of severest pain was defined as time to a 30% reduction in pain intensity (VAS) compared to baseline and maintained during at least 8 hours.

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	75		
Units: hours				
median (confidence interval 95%)	24.10 (16.00 to 39.92)	20.08 (16.00 to 24.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cumulative dose of parenteral opioids

End point title	Mean cumulative dose of parenteral opioids[6]

End point description:

The use of parenteral opioids (accumulated parenteral opioid consumption until readiness for discharge).

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK

arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	73		
Units: mg				
arithmetic mean (standard deviation)	150.2 (± 138.37)	137.0 (± 124.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to discharge

End point title	Median time to discharge[7]

End point description:

Number of hours between the first study drug dose given and discharge.

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	75		
Units: hours				
median (confidence interval 95%)	121.5 (99.00 to 141.00)	94.5 (79.42 to 118.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to readiness for discharge

End point title	Median time to readiness for discharge[8]

End point description:

Time to readyness for discharge, as judged by the the subject or investigator (number of hours between the first study drug dose given and timepoint at which the subject feels readiness or the investigator judges readiness for discharge from the hospital) which ever comes first. The assessment was done every 4 hours during awake time, starting from the time when the subject had been without parenteral opioids for 8 hours.

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	75		
Units: hours				
median (confidence interval 95%)	99.0 (74.33 to 114.50)	85.3 (70.50 to 94.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to IV opioid discontinuation

End point title	Median time to IV opioid discontinuation[9]

End point description:

Time to discontinuation of IV opioids, defines as number of hours between the first study drug dose given and discontinuation of parenteral opioids.

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	75		
Units: hours				
median (confidence interval 95%)	84.0 (63.33 to 93.17)	67.8 (60.43 to 78.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative frequency of VOC resolution

End point title	Cumulative frequency of VOC resolution[10]

End point description:

Time from start of infusion to 25%, 50% and 75% of subjects achieving VOC resolution.

End point type	Secondary

End point timeframe:

Assessments were performed from start of IP infusion and up to a maximum of 7 days.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	75		
Units: Cumulative frequency (%)				
Within 24 hours	1	0		
Within 48 hours	12	16		
Within 72 hours	29	44		
Within 96 hours	46	63		
Within 120 hours	65	71		
Within 144 hours	74	80		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Clinical Global Impression of Change

End point title	Mean Clinical Global Impression of Change[11]

End point description:

The CGIC is an instrument that measures change in a patient overall status on a 7-point scale ranging from 1 (Very much improved) to 7 (Very much worse), rated by the physician.

N differed for the different time points.
Clarification for Notes below:
First digit = Visit No.
DI = During infusion
EoI = End of infusion
Value = N

End point type	Secondary

End point timeframe:

The Clinician Global Impression of Change (CGIC) was measured once daily, starting on Day 3 until end of treatment.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[12]	75[13]		
Units: Score				
arithmetic mean (standard deviation)				
Visit 3, During infusion	4.3 (± 1.57)	4.6 (± 1.64)		
Visit 3, End of infusion	6.3 (± 0.98)	5.8 (± 1.53)		
Visit 4, During infusion	5.1 (± 1.43)	4.8 (± 1.78)		
Visit 4, End of infusion	6.2 (± 1.70)	6.1 (± 1.24)		
Visit 5, During infusion	5.3 (± 1.65)	5.0 (± 1.86)		
Visit 5, End of infusion	6.3 (± 0.65)	6.3 (± 1.29)		
Visit 6, During infusion	5.1 (± 1.39)	5.2 (± 1.76)		
Visit 6, End of infusion	6.3 (± 0.82)	5.6 (± 2.00)		
Visit 7, During infusion	5.4 (± 1.68)	5.2 (± 1.64)		
Visit 7, End of infusion	6.4 (± 1.01)	5.0 (± 2.83)		
Visit 8, End of infusion	4.0 (± 1.83)	4.8 (± 1.47)		

Notes:

[12] - 3 DI:60
3 EoI:12
4 DI:47
4 EoI:12
5 DI:32
5 EoI:11
6 DI:18
6 EoI:6
7 DI:12
7 EoI:9
8 EoI:4

[13] - 3 DI:70
3 EoI:12
4 DI:51
4 EoI:19
5 DI:31
5 EoI:16
6 DI:18
6 EoI:8
7 DI:9
7 EoI:4
8 EoI:6

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Patient Global Impression of Change

End point title	Mean Patient Global Impression of Change[14]

End point description:

The PGIC is an instrument that measures change in a patient overall status on a 7-point scale ranging from 1 (Very much improved) to 7 (Very much worse), rated by the patient.

N differed for the different time points.
Clarification for Notes below:
First digit = Visit No.
DI = During infusion
EoI = End of infusion
Value = N

End point type	Secondary

End point timeframe:

The Patient Global Impression of Change (PGIC) was measured once daily, starting on Day 3 until end of treatment.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[15]	75[16]		
Units: Score				
arithmetic mean (standard deviation)				
Visit 3, During infusion	4.4 (± 1.48)	4.4 (± 1.79)		
Visit 3, End of infusion	6.2 (± 0.75)	6.3 (± 1.28)		
Visit 4, During infusion	5.0 (± 1.60)	4.7 (± 1.89)		
Visit 4, End of infusion	6.3 (± 1.72)	5.9 (± 1.39)		
Visit 5, During infusion	5.2 (± 1.50)	4.9 (± 1.81)		
Visit 5, End of infusion	6.1 (± 0.70)	6.1 (± 1.31)		
Visit 6, During infusion	5.0 (± 1.64)	5.1 (± 1.55)		
Visit 6, End of infusion	6.0 (± 1.10)	5.6 (± 2.00)		
Visit 7, During infusion	4.9 (± 2.02)	4.6 (± 1.81)		
Visit 7, End of infusion	6.0 (± 1.50)	5.0 (± 2.71)		
Visit 8, End of infusion	4.5 (± 1.91)	4.0 (± 1.55)		

Notes:

[15] - 3 DI:60
3 EoI:11
4 DI:46
4 EoI:12
5 DI:32
5 EoI:11
6 DI:18
6 EoI:6
7 DI:12
7 EoI:9
8 EoI:4

[16] - 3 DI:69
3 EoI:15
4 DI:51
4 EoI:19
5 DI:31
5 EoI:16
6 DI:18
6 EoI:8
7 DI:9
7 EoI:4
8 EoI:6

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cumulative pain intensity

End point title	Mean cumulative pain intensity[17]

End point description:

Pain intensity was assessed on VAS every 4 hours during awake time, until VOC resolution.
The mean accumulated change in pain intensity (CPID), defined as the difference between VAS at each of the time points assessed compared to baseline, for each visit and timepoint was evaluated.

End point type	Secondary

End point timeframe:

From 30 min before infusion treatment and up to a maximum of 7 days.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	74		
Units: CPID				
arithmetic mean (standard deviation)	-2985.746 (± 2218.7055)	-2827.853 (± 2152.4352)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean daily dose of opioid consumption

End point title	Mean daily dose of opioid consumption[18]

End point description:

Amount of parenteral opioids (accumulated opioid consumption as average per 24 hours after start of IP administration and until VOC resolution.

End point type	Secondary

End point timeframe:

From start of IP administration and up to a maximum of 7 days.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	73		
Units: mg				
arithmetic mean (standard deviation)	45.227 (± 40.4522)	37.779 (± 20.6040)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients re-hospitalised for VOC

End point title	Proportion of patients re-hospitalised for VOC[19]

End point description:

Re-occurrence of VOC within 3 or 28 days from last dose of study medication.

End point type	Secondary

End point timeframe:

From resolution of VOC and up to 28 days thereafter.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	Sevuparin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	62		
Units: percent (%)				
Re-occurrence of VOC within 3 days: Yes	2	5		
Re-occurrence of VOC within 3 days: No	98	95		
Re-occurrence of VOC within 28 days: Yes	14	13		
Re-occurrence of VOC within 28 days: No	86	87		

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Cmax

End point title	PK: Cmax[20]

End point description:

In adult subjects, blood samples for PK measurements were drawn at the following time points: predose, 1, 2, 24 hours, during treatment (one per day) and at the end of infusion.
In adolescents, blood samplings were performed at predose, 1, 2, 24 hours and at the end of sevuparin infusion.

End point type	Secondary

End point timeframe:

Predose and until end of infusion.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	PK - Sevuparin, Adult Male	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	2	2	2
Units: µg/mL				
arithmetic mean (standard deviation)	15.0 (± 5.41)	16.8 (± 1.48)	11.5 (± 1.06)	13.4 (± 3.04)

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Cmin

End point title	PK: Cmin[21]

End point description:

In adult subjects, blood samples for PK measurements were drawn at the following time points: predose, 1, 2, 24 hours, during treatment (one per day) and at the end of infusion.
In adolescents, blood samplings were performed at predose, 1, 2, 24 hours and at the end of sevuparin infusion.

End point type	Secondary

End point timeframe:

Predose and until end of infusion.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	PK - Sevuparin, Adult Male	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	2	2	2
Units: µg/mL				
arithmetic mean (standard deviation)	7.93 (± 2.22)	8.2 (± 4.50)	5.6 (± 3.27)	4.9 (± 5.02)

Statistical analyses

No statistical analyses for this end point

Secondary: PK: AUClast

End point title	PK: AUClast[22]

End point description:

In adult subjects, blood samples for PK measurements were drawn at the following time points: predose, 1, 2, 24 hours, during treatment (one per day) and at the end of infusion.
In adolescents, blood samplings were performed at predose, 1, 2, 24 hours and at the end of sevuparin infusion.

End point type	Secondary

End point timeframe:

Predose and until end of infusion.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	PK - Sevuparin, Adult Male	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	2	2	2
Units: µg*hr/mL				
arithmetic mean (standard deviation)	684 (± 579)	1300 (± 75.7)	911 (± 616)	769 (± 472)

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Css,av

End point title	PK: Css,av[23]

End point description:

In adult subjects, blood samples for PK measurements were drawn at the following time points: predose, 1, 2, 24 hours, during treatment (one per day) and at the end of infusion.
In adolescents, blood samplings were performed at predose, 1, 2, 24 hours and at the end of sevuparin infusion.

End point type	Secondary

End point timeframe:

Predose and until end of infusion.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	PK - Sevuparin, Adult Male	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	2	2	2
Units: µg/mL				
arithmetic mean (standard deviation)	10.2 (± 2.55)	12.4 (± 1.87)	7.2 (± 3.13)	9.5 (± 0.27)

Statistical analyses

No statistical analyses for this end point

Secondary: PK: CL

End point title	PK: CL[24]

End point description:

In adult subjects, blood samples for PK measurements were drawn at the following time points: predose, 1, 2, 24 hours, during treatment (one per day) and at the end of infusion.
In adolescents, blood samplings were performed at predose, 1, 2, 24 hours and at the end of sevuparin infusion.

End point type	Secondary

End point timeframe:

Predose and until end of infusion.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	PK - Sevuparin, Adult Male	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	2	2	2
Units: L/h				
arithmetic mean (standard deviation)	5.5 (± 1.48)	3.5 (± 0.36)	4.6 (± 2.90)	4.4 (± 0.77)

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Total dose

End point title	PK: Total dose[25]

End point description:

In adult subjects, blood samples for PK measurements were drawn at the following time points: predose, 1, 2, 24 hours, during treatment (one per day) and at the end of infusion.
In adolescents, blood samplings were performed at predose, 1, 2, 24 hours and at the end of sevuparin infusion.

End point type	Secondary

End point timeframe:

From start of IP administration and until end of infusion.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The subjects in the arms PK - Sevuparin Adult Male and Female, and PK - Adolescent Male and Female are all included in the Sevuparin arm and efficay is reported in the Sevuparin arm. The PK arms were created only for reporting of PK parameters.

End point values	PK - Sevuparin, Adult Male	PK - Sevuparin, Adult Female	PK - Sevuparin, Adolescent Male	PK - Sevuparin, Adolescent Female
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	2	2	2
Units: mg				
arithmetic mean (standard deviation)	4441.3 (± 2361.4)	4946 (± 480.1)	3417.4 (± 166)	3608.4 (± 1106.5)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the start of study treatment, or as required by local regions, until the last FU visit or 30 days after the last dose of study drug whichever lasted longer.

Adverse event reporting additional description:

Clinically relevant changes in vital signs, physical examination, ECG, and laboratory safety analyses were reported as advese events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Sevuparin

Reporting group description:

Patients with SCD, hospitalised with acute VOC, received sevuparin as an IV infusion for 2-7 days.

Reporting group title	Placebo

Reporting group description:

Patients with SCD, hospitalised with acute VOC, received placebo solution as an IV infusion for 2-7 days.

Serious adverse events	Sevuparin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 68 (22.06%)	17 / 76 (22.37%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus tachycardia			

subjects affected / exposed	1 / 68 (1.47%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypersplenism			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	6 / 68 (8.82%)	4 / 76 (5.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	2 / 68 (2.94%)	6 / 76 (7.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteomyelitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 68 (4.41%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sevuparin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 68 (66.18%)	50 / 76 (65.79%)	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	8 / 68 (11.76%)	0 / 76 (0.00%)	
occurrences (all)	8	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 68 (5.88%)	2 / 76 (2.63%)	
occurrences (all)	4	2	
Bilirubin conjugated increased			

subjects affected / exposed	4 / 68 (5.88%)	4 / 76 (5.26%)	
occurrences (all)	4	4	
Blood bilirubin increased			
subjects affected / exposed	5 / 68 (7.35%)	4 / 76 (5.26%)	
occurrences (all)	5	4	
Blood calcium decreased			
subjects affected / exposed	4 / 68 (5.88%)	3 / 76 (3.95%)	
occurrences (all)	4	3	
C-reactive protein increased			
subjects affected / exposed	11 / 68 (16.18%)	12 / 76 (15.79%)	
occurrences (all)	11	12	
Haemoglobin decreased			
subjects affected / exposed	18 / 68 (26.47%)	8 / 76 (10.53%)	
occurrences (all)	20	8	
Oxygen saturation decreased			
subjects affected / exposed	5 / 68 (7.35%)	1 / 76 (1.32%)	
occurrences (all)	5	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 68 (2.94%)	5 / 76 (6.58%)	
occurrences (all)	2	5	
Sickle cell anaemia with crisis			
subjects affected / exposed	3 / 68 (4.41%)	6 / 76 (7.89%)	
occurrences (all)	6	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 68 (7.35%)	2 / 76 (2.63%)	
occurrences (all)	5	2	
Chest pain			
subjects affected / exposed	6 / 68 (8.82%)	3 / 76 (3.95%)	
occurrences (all)	6	6	
Pyrexia			
subjects affected / exposed	17 / 68 (25.00%)	17 / 76 (22.37%)	
occurrences (all)	20	17	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	4 / 68 (5.88%)	1 / 76 (1.32%)	
occurrences (all)	4	1	
Constipation			
subjects affected / exposed	12 / 68 (17.65%)	17 / 76 (22.37%)	
occurrences (all)	13	17	
Diarrhoea			
subjects affected / exposed	5 / 68 (7.35%)	2 / 76 (2.63%)	
occurrences (all)	5	2	
Nausea			
subjects affected / exposed	8 / 68 (11.76%)	13 / 76 (17.11%)	
occurrences (all)	10	15	
Vomiting			
subjects affected / exposed	6 / 68 (8.82%)	10 / 76 (13.16%)	
occurrences (all)	7	10	
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	5 / 68 (7.35%)	0 / 76 (0.00%)	
occurrences (all)	5	0	
Cough			
subjects affected / exposed	4 / 68 (5.88%)	2 / 76 (2.63%)	
occurrences (all)	4	2	
Dyspnoea			
subjects affected / exposed	4 / 68 (5.88%)	1 / 76 (1.32%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	5 / 68 (7.35%)	0 / 76 (0.00%)	
occurrences (all)	6	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 68 (7.35%)	4 / 76 (5.26%)	
occurrences (all)	5	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 68 (2.94%)	4 / 76 (5.26%)	
occurrences (all)	2	4	

Pain in extremity subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5	3 / 76 (3.95%) 3	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	4 / 76 (5.26%) 4	
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 3	3 / 76 (3.95%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2015	Modification of the pharmacokinetic evaluations sections in compliance with the main text (section 12.6) Definition of DSMB (section V) Description of DSMB roles, responsibilities and decision criteria (section 12.6) Clarification that, for ethical reasons, biomarkers samples were not to be taken in adolescents who provided PK samples. The reason was to reduce blood volumes to be drawn in adolescents.
14 December 2015	The number of sites was increased. The study period was extended. The timeframes for study procedures were altered. ULN for hepatic and coagulation factors were altered. Inclusion and exclusion criteria were modified. Dose adjustment was permitted earlier to increase patient safety.
16 January 2017	Inclusion and exclusion criteria were adjusted. Methodology, statistical methods, and administrative structure were clarified. The sample size was increased. Secondary objectives were added. Safety analyses and methodology for concomitant medication usage were further specified. The treatment and dose justification were clarified. The informed consent for adolescents was altered. The number of Investigator sites were increased. The study enrollment period was extended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported