Clinical trial results:
An Open-label, Randomized, Active Comparator-Controlled, Adaptive Parallel-group Phase 2 Study to Assess the Safety and Efficacy of Multiple Doses of ISIS 416858 Administered Subcutaneously to Patients Undergoing Total Knee Arthroplasty

Summary

EudraCT number	2012-001836-72
Trial protocol	LV BG
Global end of trial date	14 August 2014

Results information

Result version number	v1 (current)
This version publication date	27 July 2019
First version publication date	27 July 2019

Trial information

Trial identification

Sponsor protocol code	ISIS416858-CS3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01713361
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, CA 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com

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	14 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To assess the safety and efficacy profile of ISIS 416858, including incidence of bleeding and Venous thromboembolism (VTE), in subjects undergoing total knee arthroplasty
• To compare the efficacy and safety profile of ISIS 416858 in subjects who achieve </= 0.2 units per millilitre (U/mL) factor XI (FXI) activity levels to that of enoxaparin

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Latvia: 36
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Russian Federation: 109
Country: Number of subjects enrolled	Ukraine: 111
Worldwide total number of subjects	314
EEA total number of subjects	58

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)	178
From 65 to 84 years	136
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were randomised to 19 study centres in 5 countries (Bulgaria, Canada, Latvia, Russian Federation and Ukraine).

Pre-assignment

Screening details:

14 subjects were randomised under the original protocol in the treatment arms ISIS 416858 100 mg (n=3), ISIS 416858 200 mg (n=4), ISIS 416858 300 mg (n=4), and enoxaparin 40 mg (n=3). Of these 14 subjects, 12 received study treatment. After amendment, 300 subjects were randomised in the ISIS 416858 200mg, 300mg and enoxaparin 40 mg arm groups.

Pre-assignment period milestones

Number of subjects started	314
Number of subjects completed	293

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subject not analysed per protocol amendment: 14
Reason: Number of subjects	Did not receive study treatment: 7

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Enoxaparin 40 mg

Arm description:

Enoxaparin 40 mg was administered subcutaneously (SC) the evening prior to surgery (optional), 6 to 8 hours after surgery followed by daily injections for at least 8 additional days post surgery.

Arm type	Active comparator
Investigational medicinal product name	Enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg Enoxaparin was administered SC evening prior to surgery (optional), 6 to 8 hours after surgery followed by daily injections for at least 8 additional days post surgery.

Arm title	ISIS 416858 200 mg

Arm description:

Subjects received SC doses of ISIS 416858 200 mg 7 times prior to total knee arthroplasty (TKA), and 2 times after surgery (6 hours and 3 days after surgery).

Arm type	Experimental

Investigational medicinal product name	ISIS 416858
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 416858 200 mg SC was administered 7 times prior to TKA, and 2 times after surgery (6 hours and 3 days after surgery).

Arm title	ISIS 416858 300 mg

Arm description:

Subjects received SC doses of ISIS 416858 300 mg 7 times prior to TKA, and 2 times after surgery (6 hours and 3 days after surgery).

Arm type	Experimental
Investigational medicinal product name	ISIS 416858
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 416858 300 mg SC was administered 7 times prior to TKA, and 2 times after surgery (6 hours and 3 days after surgery).

Number of subjects in period 1[1]	Enoxaparin 40 mg	ISIS 416858 200 mg	ISIS 416858 300 mg
Started	72	144	77
Completed	71	141	73
Not completed	1	3	4
Adverse Event or SAE	1	1	-
Voluntary withdrawal	-	2	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period is for the safety population of the amended protocol. The subjects in the trial information are the total subjects enrolled worldwide.

Baseline characteristics

Reporting groups	
Reporting group title	Enoxaparin 40 mg
Reporting group description:	
Enoxaparin 40 mg was administered subcutaneously (SC) the evening prior to surgery (optional), 6 to 8 hours after surgery followed by daily injections for at least 8 additional days post surgery.	
Reporting group title	ISIS 416858 200 mg
Reporting group description:	
Subjects received SC doses of ISIS 416858 200 mg 7 times prior to total knee arthroplasty (TKA), and 2 times after surgery (6 hours and 3 days after surgery).	
Reporting group title	ISIS 416858 300 mg
Reporting group description:	
Subjects received SC doses of ISIS 416858 300 mg 7 times prior to TKA, and 2 times after surgery (6 hours and 3 days after surgery).	

Reporting group values	Enoxaparin 40 mg	ISIS 416858 200 mg	ISIS 416858 300 mg
Number of subjects	72	144	77
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64	63	63
standard deviation	± 9	± 9	± 8
Gender categorical Units: Subjects			
Female	60	118	60
Male	12	26	17

Reporting group values	Total		
Number of subjects	293		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	238		
Male	55		

End points

End points reporting groups

Reporting group title	Enoxaparin 40 mg
Reporting group description:	
Enoxaparin 40 mg was administered subcutaneously (SC) the evening prior to surgery (optional), 6 to 8 hours after surgery followed by daily injections for at least 8 additional days post surgery.	
Reporting group title	ISIS 416858 200 mg
Reporting group description:	
Subjects received SC doses of ISIS 416858 200 mg 7 times prior to total knee arthroplasty (TKA), and 2 times after surgery (6 hours and 3 days after surgery).	
Reporting group title	ISIS 416858 300 mg
Reporting group description:	
Subjects received SC doses of ISIS 416858 300 mg 7 times prior to TKA, and 2 times after surgery (6 hours and 3 days after surgery).	

Primary: Percentage of Subjects with Venous Thromboembolism (VTE)

End point title	Percentage of Subjects with Venous Thromboembolism (VTE)
End point description:	
Total VTE includes asymptomatic DVT, adjudicated symptomatic VTE (includes symptomatic DVT and symptomatic pulmonary embolism [PE]), and adjudicated fatal PE or unexplained death for which PE cannot be ruled out. The Per-Protocol Set (PPS) consists of amendment protocol subjects as a subset of the Safety Set who had the scheduled surgery and were evaluable for efficacy. Subjects in the enoxaparin group who did not follow the enoxaparin dose regimen for at least 5 consecutive days after surgery were not included in the PPS.	
End point type	Primary
End point timeframe:	
Up to 10 days post surgery (46 days)	

End point values	Enoxaparin 40 mg	ISIS 416858 200 mg	ISIS 416858 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	134	71	
Units: percentage of subjects				
number (confidence interval 95%)	30 (20 to 43)	27 (20 to 35)	4 (1 to 12)	

Statistical analyses

Statistical analysis title	VTE: Enoxaparin 40 mg v ISIS 416858 200 mg
Statistical analysis description:	
A superiority test was evaluated using the chi-square test to assess the difference between subjects in the ISIS 416858 group and enoxaparin group.	
Comparison groups	Enoxaparin 40 mg v ISIS 416858 200 mg

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-4
Confidence interval	
level	95 %
sides	1-sided
upper limit	8

Statistical analysis title	VTE: Enoxaparin 40 mg v ISIS 416858 300 mg

Statistical analysis description:

A superiority test was evaluated using the chi-square test to assess the difference between subjects in the ISIS 416858 group and enoxaparin group.

Comparison groups	ISIS 416858 300 mg v Enoxaparin 40 mg
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-26
Confidence interval	
level	95 %
sides	1-sided
upper limit	-16

Secondary: Percentage of Subjects with all Proximal Deep Vein Thrombosis (DVTs), all Distal-Only DVTs and non-Fatal and Fatal Pulmonary Embolism (PEs)

End point title	Percentage of Subjects with all Proximal Deep Vein Thrombosis (DVTs), all Distal-Only DVTs and non-Fatal and Fatal Pulmonary Embolism (PEs)

End point description:

PPS consists of amendment protocol subjects as a subset of the Safety Set who had the scheduled surgery and were evaluable for efficacy. Subjects in the enoxaparin group who did not follow the enoxaparin dose regimen for at least 5 consecutive days after surgery were not included in the PPS.

End point type	Secondary

End point timeframe:

From first study drug administration up to 4 weeks after mandatory bilateral venography (up to 74 days)

End point values	Enoxaparin 40 mg	ISIS 416858 200 mg	ISIS 416858 300 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	134	71	
Units: percentage of subjects				
number (confidence interval 95%)				
Proximal DVTs	5.8 (1.602 to 14.183)	5.2 (2.126 to 10.467)	1.4 (0.036 to 7.599)	
Distal-Only DVTs	24.6 (15.055 to 36.490)	21.6 (14.998 to 29.580)	2.8 (0.343 to 9.808)	
Non-Fatal PE	0.0 (0.000 to 5.206)	0.0 (0.000 to 2.715)	0.0 (0.000 to 5.063)	
Fatal PE	0.0 (0.000 to 5.206)	0.0 (0.000 to 2.715)	0.0 (0.000 to 5.063)	

Statistical analyses

Statistical analysis title	Proximal DVT for ISIS 416858 200 mg
Comparison groups	Enoxaparin 40 mg v ISIS 416858 200 mg
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	1-sided
upper limit	5

Statistical analysis title	Proximal DVT for ISIS 416858 300 mg
Comparison groups	Enoxaparin 40 mg v ISIS 416858 300 mg
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.205
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.8

Statistical analysis title	Distal-Only DVTs for ISIS 416858 200 mg

Comparison groups	Enoxaparin 40 mg v ISIS 416858 200 mg
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.629
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-3
Confidence interval	
level	95 %
sides	1-sided
upper limit	7.4

Statistical analysis title	Distal-Only DVTs for ISIS 416858 300 mg
Comparison groups	Enoxaparin 40 mg v ISIS 416858 300 mg
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-21.8
Confidence interval	
level	95 %
sides	1-sided
upper limit	-12.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 22 months

Adverse event reporting additional description:

The safety set population included all subjects who were enrolled under the protocol amendment and received at least 1 dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Enoxaparin 40 mg

Reporting group description:

Enoxaparin 40 mg was administered subcutaneously (SC) the evening prior to surgery (optional), 6 to 8 hours after surgery followed by daily injections for at least 8 additional days post surgery.

Reporting group title	ISIS 416858 200 mg

Reporting group description:

Subjects received SC doses of ISIS 416858 200 milligrams (mg) 7 times prior to total knee arthroplasty (TKA), and 2 times after surgery (6 hours and 3 days after surgery).

Reporting group title	ISIS 416858 300 mg

Reporting group description:

Subjects received SC doses of ISIS 416858 300 mg 7 times prior to TKA, and 2 times after surgery (6 hours and 3 days after surgery).

Serious adverse events	Enoxaparin 40 mg	ISIS 416858 200 mg	ISIS 416858 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 72 (0.00%)	3 / 144 (2.08%)	1 / 77 (1.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural fistula			
subjects affected / exposed	0 / 72 (0.00%)	2 / 144 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 72 (0.00%)	1 / 144 (0.69%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Device related infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 144 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Enoxaparin 40 mg	ISIS 416858 200 mg	ISIS 416858 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 72 (65.28%)	114 / 144 (79.17%)	62 / 77 (80.52%)
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	19 / 72 (26.39%)	46 / 144 (31.94%)	18 / 77 (23.38%)
occurrences (all)	19	46	18
Anaemia postoperative			
subjects affected / exposed	9 / 72 (12.50%)	16 / 144 (11.11%)	13 / 77 (16.88%)
occurrences (all)	9	16	13
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	18 / 72 (25.00%)	30 / 144 (20.83%)	3 / 77 (3.90%)
occurrences (all)	18	31	3
Haematoma			
subjects affected / exposed	4 / 72 (5.56%)	3 / 144 (2.08%)	2 / 77 (2.60%)
occurrences (all)	4	3	4
Hypertension			
subjects affected / exposed	1 / 72 (1.39%)	2 / 144 (1.39%)	5 / 77 (6.49%)
occurrences (all)	1	2	5
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	4 / 72 (5.56%)	5 / 144 (3.47%)	6 / 77 (7.79%)
occurrences (all)	6	5	6
Injection site erythema			
subjects affected / exposed	0 / 72 (0.00%)	26 / 144 (18.06%)	23 / 77 (29.87%)
occurrences (all)	0	61	73
Injection site haematoma			

subjects affected / exposed	2 / 72 (2.78%)	7 / 144 (4.86%)	9 / 77 (11.69%)
occurrences (all)	10	9	21
Injection site pain			
subjects affected / exposed	0 / 72 (0.00%)	3 / 144 (2.08%)	7 / 77 (9.09%)
occurrences (all)	0	10	9
Injection site pruritus			
subjects affected / exposed	0 / 72 (0.00%)	2 / 144 (1.39%)	8 / 77 (10.39%)
occurrences (all)	0	2	26
Injection site swelling			
subjects affected / exposed	0 / 72 (0.00%)	1 / 144 (0.69%)	6 / 77 (7.79%)
occurrences (all)	0	5	29
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 72 (5.56%)	7 / 144 (4.86%)	6 / 77 (7.79%)
occurrences (all)	4	7	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 144 (0.69%)	4 / 77 (5.19%)
occurrences (all)	0	1	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2013	• Extended the ISIS 416858 treatment period in order to achieve reduction in Factor XI (FXI) activity to levels ≤0.2 U/mL. • Extended the duration of treatment with ISIS 416858 to include two additional doses prior to surgery and one additional dose after surgery compared with the original protocol dosing regimen. • Eliminated the lowest dose cohort (100 mg). • Modified the primary and secondary objectives/endpoints to better reflect the importance of assessing antithrombotic efficacy of ISIS 416858 as a function of FXI activity reduction, especially in subjects who achieve the targeted level of FXI activity (≤0.2 U/mL). • Modified the timing of TKA surgery and venography with respect to Study Day 1, and extended the screening period in order to make it easier to get all test results back prior to treatment assignment. • Modified the reporting of serious adverse events (SAEs) to better discriminate between SAEs associated with the study drug and those associated with the surgical procedure. • Clarified the exclusion criteria; Added more lab tests to the schedule of procedures; and included additional follow-up for subjects with FXI activity ≤0.3 U/mL at the end of the follow-up period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported