Clinical trial results:
An open-label, pharmacokinetic, pharmacodynamic, and tolerability study of AVE5026 administered at weight-adjusted doses to patients under 18 years of age with a Central Venous Line (CVL)

Summary

EudraCT number	2011-005155-14
Trial protocol	HU ES SK Outside EU/EEA
Global end of trial date	10 July 2012

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	05 November 2014

Trial information

Trial identification

Sponsor protocol code	PKM11204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01567904
WHO universal trial number (UTN)	U1111-1115-8281

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis Recherche & Developpement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000562-PIP01-09
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	18 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of Semuloparin (AVE5026) (assessed from the anti-Xa activity of of the compound) in children in order to determine the dose to be assessed in the subsequent clinical efficacy/safety study

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric patients. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesic may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 May 2012
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	Hungary: 2
Worldwide total number of subjects	2
EEA total number of subjects	2

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)	2
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was early terminated per Sponsor decision after two subjects were enrolled in the first age group. The decision has been taken in keeping with the Company's decision to withdraw, on a worldwide basis, the marketing authorization applications [MAA] for semuloparin in adult indication.

Pre-assignment

Screening details:

Enrollment was to stagger by age group starting with the older children (≥12 years). Enrollment in a younger age group was planned to initiate only following a review by the Data Monitoring Committee of the clinical safety data and available PK and PD data from the first 3 out of 7 children from the previous older age group.

Period 1

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

Arms

Arm title	Semuloparin - 12 to <18 years (group 1)

Arm description:

Semuloparin sodium for 6-30 days to children aged from 12 to <18 years

Arm type	Experimental
Investigational medicinal product name	Semuloparin sodium
Investigational medicinal product code	AVE5026
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Weight-adjusted dose, 0.3 milligram per kilogram (mg/kg), once daily

Number of subjects in period 1	Semuloparin - 12 to <18 years (group 1)
Started	2
Treated	2
Completed	2

Baseline characteristics

Reporting groups	
Reporting group title	Semuloparin - 12 to <18 years (group 1)
Reporting group description:	
Semuloparin sodium for 6-30 days to children aged from 12 to <18 years	

Reporting group values	Semuloparin - 12 to <18 years (group 1)	Total	
Number of subjects	2	2	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15		
full range (min-max)	13 to 17	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	1	1	

End points

End points reporting groups

Reporting group title	Semuloparin - 12 to <18 years (group 1)

Reporting group description:

Semuloparin sodium for 6-30 days to children aged from 12 to <18 years

Primary: Pharmacokinetic (PK): Plasma concentration

End point title	Pharmacokinetic (PK): Plasma concentration[1]

End point description:

A validated anti-Xa chromogenic enzyme assay, with addition of Antithrombin(AT)-III in excess, was to be used to assess plasma concentrations of Semuloparin.

End point type	Primary

End point timeframe:

Up to a maximum of 6 samples between Day 4, Day 5 and Day 6.
The number of samples and the timing was adjusted according to the age of the child.

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: Due to early termination of the study, no PK parameters were determined.

End point values	Semuloparin - 12 to <18 years (group 1)			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: µgEq/mL				
arithmetic mean (standard deviation)	()			

Notes:

[2] - Due to early termination of the study, no PK parameters were determined.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacodynamic (PD): Factor Xa inhibition

End point title	Pharmacodynamic (PD): Factor Xa inhibition[3]

End point description:

A validated anti-Xa chromogenic enzyme assay, without addition of AT-III in excess, was to be used to assess pharmacodynamic activity (factor Xa inhibition) of semuloparin.

End point type	Primary

End point timeframe:

Up to a maximum of 6 samples between Day 4, Day 5 and Day 6.
The number of samples and the timing was adjusted according to the age of the child.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to early termination of the study, no PD parameters were determined.

End point values	Semuloparin - 12 to <18 years (group 1)			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: percentage of the maximum inhibition				
arithmetic mean (standard deviation)	()			

Notes:

[4] - Due to early termination of the study, no PD parameters were determined.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of subjects with bleeding events

End point title	Safety: Number of subjects with bleeding events

End point description:

End point type	Secondary

End point timeframe:

up to 30 +/- 2 days post treatment

End point values	Semuloparin - 12 to <18 years (group 1)			
Subject group type	Reporting group			
Number of subjects analysed	2[5]			
Units: subjects	0			

Notes:

[5] - Safety population: All subjects enrolled and exposed to the compound.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of subjects requiring blood transfusion

End point title	Safety: Number of subjects requiring blood transfusion

End point description:

End point type	Secondary

End point timeframe:

up to 30 +/- 2 days post treatment

End point values	Semuloparin - 12 to <18 years (group 1)			
Subject group type	Reporting group			
Number of subjects analysed	2[6]			
Units: Subjects	1			

Notes:

[6] - Safety population: All subjects enrolled and exposed to the compound

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (30 +/- 2 days after end of treatment) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events i.e. AEs that developed/worsened during the 'on treatment period' (from the first dose up to 3 days after the last dose of study drug).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Semuloparin - 12 to <18 years (group 1)

Reporting group description:

Semuloparin sodium for 6-30 days to children aged from 12 to <18 years

Serious adverse events	Semuloparin - 12 to <18 years (group 1)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Semuloparin - 12 to <18 years (group 1)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			

Generalised oedema subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 2 (50.00%) 1 1 / 2 (50.00%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 1 / 2 (50.00%) 1		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 2 (50.00%) 1		

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

None reported