



Clinical trial results: Recombinant Factor VIIa: Local treatment of severe postpartum hemorrhage

Summary

EudraCT number	2013-005036-20
Trial protocol	DK
Global end of trial date	15 April 2016

Results information

Result version number	v1 (current)
This version publication date	05 December 2021
First version publication date	05 December 2021
Summary attachment (see zip file)	Results (2013-005036-20 Results.pdf)

Trial information

Trial identification

Sponsor protocol code	VEK40624
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Stellaris Pharmaceuticals ApS
Sponsor organisation address	Vaernedamsvej 10,4 tv, Copenhagen, Denmark, 1619
Public contact	Birgit Schjoldager, Stellaris Pharmaceuticals ApS, 45 29852973, birgit.schjoldager@gmail.com
Scientific contact	Birgit Schjoldager, Stellaris Pharmaceuticals ApS, 45 29852973, birgit.schjoldager@gmail.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	15 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2016
Global end of trial reached?	Yes
Global end of trial date	15 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Through a pilot study involving 1-5 patients undergoing cesarean section for Placenta Previa to demonstrate hemostatic effect of recombinant FVIIa placed directly upon the placenta site.

To ensure that rFVIIa was not entering the systemic circulation blood samples were taken from an arm vein for analysis just before the Cesarean Section and 15 minutes after the removal of the placenta. To investigate possible coagulation changes in the systemic circulation due to the Cesarean Section itself blood samples were likewise drawn from a control group of 5 patients undergoing Cesarean Section for other reasons.

Protection of trial subjects:

The protocol was approved by the Danish Medicines Agency (DMA) and the local ethics committee. The trial was conducted in accordance with good clinical practice. The Clinical Good Practice Unit, Aarhus, Denmark, were monitoring the trial including safety precautions. Oral and written informed consent were obtained prior to any trial events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with Placenta Previa verified by ultrasound in week 34-35, defined as cases where the placenta covered the internal os of the cervix, were enrolled after both oral and written consent to receive local treatment with recombinant, activated FVII during cesarean section. No known coagulative disease.

Pre-assignment

Screening details:

All pregnant women were screened for placenta previa in second trimester and in week 32 and finally in week 34-35 if suspicion. An elective Cesarean Section was planned.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placenta Previa patients

Arm description:

Patients presenting with a Placenta Previa in Week 34-35 undergoing a planned Cesarean Section were enrolled to receive local treatment with recombinant activated FVII at the placenta site.

Arm type	Experimental
Investigational medicinal product name	NovoSeven
Investigational medicinal product code	PR1
Other name	rFVIIa, recombinant activated Factor VII
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intrauterine use

Dosage and administration details:

1mg rFVIIa (NovoSeven, Novo Nordisk A/S, Bagsværd, Denmark) was dissolved in an enclosed 6-mL histidine solution and brought up to 246 mL with a sterile saline solution just a few minutes before use. As the carrier, a nonwoven abdominal swab (Barrier; Mölnlycke Health Care Aps, Allerød, Denmark) was soaked in this solution.

Arm title	Controls
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Arm description:

Patients undergoing a planned Cesarean Section for other reasons than Placenta Previa

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Placenta Previa patients	Controls
Started	7	5
Completed	5	5
Not completed	2	0
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Placenta Previa patients
Reporting group description: Patients presenting with a Placenta Previa in Week 34-35 undergoing a planned Cesarean Section were enrolled to receive local treatment with recombinant activated FVII at the placenta site.	
Reporting group title	Controls
Reporting group description: Patients undergoing a planned Cesarean Section for other reasons than Placenta Previa	

Reporting group values	Placenta Previa patients	Controls	Total
Number of subjects	7	5	12
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	0	0
Adults (18-64 years)	7	5	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	7	5	12
Male	0	0	0

End points

End points reporting groups

Reporting group title	Placenta Previa patients
Reporting group description: Patients presenting with a Placenta Previa in Week 34-35 undergoing a planned Cesarean Section were enrolled to receive local treatment with recombinant activated FVII at the placenta site.	
Reporting group title	Controls
Reporting group description: Patients undergoing a planned Cesarean Section for other reasons than Placenta Previa	
Subject analysis set title	Placenta previa patients before
Subject analysis set type	Safety analysis
Subject analysis set description: Blood samples collected before cesarean section in placenta previa group.	
Subject analysis set title	Placenta previa patients after
Subject analysis set type	Safety analysis
Subject analysis set description: Blood samples collected 15 minutes after removal of the placenta in placenta previa group.	
Subject analysis set title	Controls before
Subject analysis set type	Safety analysis
Subject analysis set description: Blood samples collected before cesarean section in control group.	
Subject analysis set title	Controls after
Subject analysis set type	Safety analysis
Subject analysis set description: blood samples collected 15 minutes after reæoval of the placenta in control group.	

Primary: Bleeding amount

End point title	Bleeding amount ^[1]
End point description: As soon as the placenta was removed, bleeding from the placenta site was assessed. A swab soaked in NovoSeven solution was placed at the bleeding placenta site for 2 min. Upon gently removal the placenta site was visualized and bleeding from the site reassessed. Total blood loss was estimated.	
End point type	Primary
End point timeframe: End of cesarean section	

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: We have used Mann-Whitneys test for unpaired data, see all informations in attached article from AJOG.

End point values	Placenta Previa patients	Controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: millilitre(s)				
median (full range (min-max))	490 (300 to 800)	400 (250 to 700)		

Statistical analyses

No statistical analyses for this end point

Secondary: FVII:clot

End point title FVII:clot

End point description:

FVII:clot will augment in case of augmentation of coagulation in the blood circulation

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: 1000 IU/L				
median (full range (min-max))	1.87 (1.72 to 2.04)	1.65 (1.58 to 1.87)	1.40 (1.09 to 1.95)	1.40 (1.13 to 1.91)

Statistical analyses

No statistical analyses for this end point

Secondary: Fibrinogen

End point title Fibrinogen

End point description:

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: micromole(s)/litre				
median (full range (min-max))	12.8 (6.5 to 18.1)	12.9 (11.6 to 16.6)	13.6 (12.9 to 14.8)	12.1 (11.1 to 14.2)

Statistical analyses

No statistical analyses for this end point

Secondary: APTT

End point title APTT

End point description:

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: second				
median (full range (min-max))	28 (25 to 30)	30 (25 to 31)	31 (28 to 35)	31 (29 to 35)

Statistical analyses

No statistical analyses for this end point

Secondary: INR

End point title INR

End point description:

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: None				
median (full range (min-max))	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	1 (1.0 to 1.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet count

End point title Platelet count

End point description:

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: Giga L				
median (full range (min-max))	235 (177 to 275)	216 (184 to 246)	206 (173 to 239)	176 (158 to 198)

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin

End point title Hemoglobin

End point description:

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: millimole(s)/litre				
median (full range (min-max))	7.9 (6.4 to 8.2)	7.2 (6.5 to 7.9)	7.6 (7.0 to 8.1)	7.2 (6.4 to 7.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombin generation, Lagtime

End point title Thrombin generation, Lagtime

End point description:

Thrombin generation, Lagtime is reduced when thrombin generation augments.

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: minute				
median (full range (min-max))	2.67 (2.67 to 3.00)	2.44 (2.33 to 3.00)	3.00 (2.33 to 3.33)	2.33 (2.33 to 3.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombin generation, Peak

End point title Thrombin generation, Peak

End point description:

Thrombin generation, Peak augments when Thrombin generation augments.

End point type Secondary

End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: nM				
median (full range (min-max))	163.53 (132.66 to 240.75)	206.98 (176.35 to 315.85)	188.43 (148.84 to 291.89)	279.66 (196.11 to 310.80)

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombin generation, ttpeak

End point title	Thrombin generation, ttpeak
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End point description:

Thrombin generation, ttpeak diminishes with augmentation in thrombin generation.

End point type	Secondary
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End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: minute				
median (full range (min-max))	8.56 (5.67 to 10.11)	6.44 (5.33 to 7.56)	7.11 (5.33 to 8.67)	5.11 (4.33 to 6.33)

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombin generation, ETP

End point title	Thrombin generation, ETP
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End point description:

Thrombin generation, endogenous thrombin potential (ETP) augments with augmentation in thrombin generation.

End point type	Secondary
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End point timeframe:

Blood samples from the systemic circulation were taken just before the Cesarean Section and 15 minutes after removal of the placenta.

End point values	Placenta previa patients before	Placenta previa patients after	Controls before	Controls after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	5
Units: NM x Minute				
median (full range (min-max))	1493 (1203 to 1908)	1574 (1417 to 2359)	1464 (1432 to 1584)	1470 (1323 to 1568)

Statistical analyses

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

24 hours after end Cesarean Section

Assessment type	Systematic
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Dictionary used

Dictionary name	GCP, SOP I02-13
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Dictionary version	F3
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Reporting groups

Reporting group title	Placenta Previa patients
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Reporting group description:

Patients with Placenta Previa undergoing planned Cesarean Section and receiving local treatment with recombinant, activated FVII solution at the placenta site.

Serious adverse events	Placenta Previa patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placenta Previa patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There were no reports of any sign of adverse effects after local application of recombinant, activated FVII at the placenta site.

In addition all blood samples drawn 15 minutes after end of cesarean section showed no signs of overspill of rFVIIa through the placenta site to the systemic circulation.

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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28219621>