Clinical trial results:
A PHASE II PILOT STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PHARMACODYNAMICS AND PHARMACOKINETICS OF IDES IN ASYMPTOMATIC ANTIBODY-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) PATIENTS WITH LOW ADAMTS13 ACTIVITY

Summary

EudraCT number	2016-000249-30
Trial protocol	GB
Global end of trial date	25 January 2017

Results information

Result version number	v1 (current)
This version publication date	04 May 2019
First version publication date	04 May 2019

Trial information

Trial identification

Sponsor protocol code	15-HMedIdeS-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02854059
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hansa Biopharma AB (former name Hansa Medical AB)
Sponsor organisation address	Scheelevägen 22, Lund, Sweden, 223 63
Public contact	Clinical Trials Information, Hansa Biopharma AB (former name Hansa Medical AB), clinicalstudyinfo@hansabiopharma.com
Scientific contact	Clinical Trials Information, Hansa Biopharma AB (former name Hansa Medical AB), clinicalstudyinfo@hansabiopharma.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	02 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2017
Global end of trial reached?	Yes
Global end of trial date	25 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess safety and tolerability of single intravenous doses of IdeS in patients diagnosed with asymptomatic antibody-mediated thrombotic thrombocytopenic purpura (TTP) with low ADAMTS13 activity

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

An internal monitoring committee (IMC) at Hansa Biopharma AB (former name Hansa Medical AB) was established to review safety and tolerability data after the first 3 patients had been dosed and before potential dose escalation. Additionally, if at any time during the study, 2 or more patients had experienced a grade 3 (according to the common terminology criteria for adverse events [CTCAE] v 4.0) related adverse event (AE), the IMC had to be convened. Safety data (clinical chemistry, haematology, coagulation and AEs) collected up to and including day 14 was to be evaluated. Furthermore, efficacy data (ADAMTS13 activity, ADAMTS13 antibodies and CD19) were also planned to be evaluated by the IMC.

Background therapy:

Patients received premedication with paracetamol, hydrocortisone and antihistamine before study drug infusions as well as a 2-week regimen of prophylactic antibiotics (penicillin V or alternatively ciprofloxacin in case of allergy to penicillin), starting pre-dose.

Evidence for comparator:

N/A

Actual start date of recruitment	23 September 2016
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	United Kingdom: 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	0

wk	
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)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was a single centre study. 6 patients were planned: 3 patients to recieve 0.25 mg/kg of IdeS and a potential dose escalation to 0.5 mg/kg for additional 3 patients.
Two patients were recruited between 25-Sep-2016 and 11-Nov-2016. The study ended prematurely 25-Jan-2017.

Pre-assignment

Screening details:

The study included adult patients diagnosed with acquired TTP with ADAMTS13 levels of ≤10% in clinical remission and with measurable or previously confirmed ADAMTS13 antibodies.
2 patients were included and completed the study. The study was discontinued prematurely as an non-favourable risk-benefit profile was observed in the first 2 patients.

Pre-assignment period milestones

Number of subjects started	2
Number of subjects completed	2

Period 1

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

Arms

Arm title	Group 1 (overall trial)

Arm description:

Single i.v. infusion of IdeS (0.25 mg/kg).

After review of the initial results from the study that demonstrated a non-favourable risk-benefit profile in the first 2 patients who received single i.v. infusion of IdeS (0.25 mg/kg), the study was prematurely discontinued.
The potential dose escalation to i.v. infusion of IdeS (0.5 mg/kg) did not occur.

Arm type	Experimental
Investigational medicinal product name	IdeS
Investigational medicinal product code	IdeS
Other name	HMed-IdeS, IgG endopeptidase
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single 30-minute i.v. infusion of IdeS (0.25 mg/kg).

Number of subjects in period 1	Group 1 (overall trial)
Started	2
Completed	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	2	2	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	1	1	
Male	1	1	
Race Units: Subjects			
Black or African American	1	1	
White	1	1	

End points

End points reporting groups

Reporting group title	Group 1 (overall trial)

Reporting group description:

Single i.v. infusion of IdeS (0.25 mg/kg).

After review of the initial results from the study that demonstrated a non-favourable risk-benefit profile in the first 2 patients who received single i.v. infusion of IdeS (0.25 mg/kg), the study was prematurely discontinued.
The potential dose escalation to i.v. infusion of IdeS (0.5 mg/kg) did not occur.

Primary: Safety assessed as Adverse Events

End point title	Safety assessed as Adverse Events[1]

End point description:

Data on AEs were obtained if spontaneously reported by the patient, if reported in response to an open question from the study personnel or if revealed by observation.
A treatment emergent AE (TEAE) was defined as any AE occurring after administration of the IMP and within the time of the residual drug effect period (i.e. 30 days after IMP administration).
Severity was graded based on CTCAE version 4.0.

End point type	Primary

End point timeframe:

AEs were collected from subject signing the ICF until end of study visit, incl the follow-up period (=Day 64).
AEs reported in EudraCT include TEAEs and post-treatment AEs, i.e. all AEs occurring after admin of the IMP until end of study.

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: Because of the premature termination of the study and since the sponsor will no longer pursue the indication, the analyses as described in the protocol were not performed. Instead, data collected for the 2 enrolled subjects were listed and presented graphically.

End point values	Group 1 (overall trial)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Adverse events				
TEAEs	10			
Mild TEAEs (Grade=1)	7			
Moderate TEAEs (Grade=2)	1			
Severe TEAEs (Grade=3)	1			
Life-threatening TEAEs (Grade=4)	1			
Related TEAEs	4			
Serious TEAEs	2			
Post-TEAEs	2			
Mild Post-TEAE (Grade=1)	1			
Moderate Post-TEAE (Grade=2)	1			
Related Post-TEAEs	0			
Serious Post-TEAEs	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in ADAMTS13 activity

End point title	Change from baseline in ADAMTS13 activity

End point description:

ADAMTS13 is an enzyme which is inhibited in patients with TTP. The efficacy of IdeS on ADAMTS13 activity was measured througout the study as change from baseline.

End point type	Secondary

End point timeframe:

From day of dosing until end of follow up on day 64.

End point values	Group 1 (overall trial)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Participants				
Change in activity at any time after IdeS	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ADAMTS13 Antibody Levels (IgG and F(ab')2)

End point title	Change From Baseline in ADAMTS13 Antibody Levels (IgG and F(ab')2)

End point description:

The efficacy of IdeS on ADAMTS13 antibody cleaving was measured througout the study as change from baseline in ADAMTS13 antibody concentration.

End point type	Secondary

End point timeframe:

From day of dosing until end of follow up on day 64

End point values	Group 1 (overall trial)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Participants				
≥90% decrease 2-24h after IdeS	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Time for ADAMTS13 Activity to Return to Normal Levels

End point title	Time for ADAMTS13 Activity to Return to Normal Levels

End point description:

The ADAMTS13 activity in TTP patients is decreased. The efficacy of IdeS on ADAMTS13 activity was assessed throughout the study to identify the time-point of return to normal levels.

End point type	Secondary

End point timeframe:

From day of dosing until end of follow up on day 64

End point values	Group 1 (overall trial)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Participants				
Normal activity any time after IdeS	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pharmacodynamics as Measured by Level of IgG

End point title	Change From Baseline in Pharmacodynamics as Measured by Level of IgG

End point description:

IdeS cleaves IgG molecules. The concentration of uncleaved IgG in the patient's serum was measured throughout the study to determine change from baseline following IdeS administration.

End point type	Secondary

End point timeframe:

From day of dosing until end of follow up on day 64

End point values	Group 1 (overall trial)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Patients				
≥90% decrease 2-24h after IdeS	2			
≥90% decrease 3d after IdeS	1			
≥90% decrease 7-64d after IdeS	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of IdeS by Measuring Anti-drug Antibodies

End point title	Immunogenicity of IdeS by Measuring Anti-drug Antibodies

End point description:

Most humans have been infected with S. pyogenes which is the origin of IdeS. It was therefore expected that patients in this study might have antibodies against IdeS before being exposed to IdeS in the study. The concentration of ant-IdeS antibodies was measured before dosing and throughout the study.

End point type	Secondary

End point timeframe:

From day of dosing until end of follow up on day 64

End point values	Group 1 (overall trial)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Participants				
Presence of anti-IdeS before IdeS	2			
Elevated anti-IdeS at day 64	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from subject signing the ICF until end of study visit, incl the follow-up period (=Day 64).
AEs reported in EudraCT include TEAEs and post-treatment AEs, i.e. all AEs occurring after admin of the IMP until end of study

Adverse event reporting additional description:

Data on AEs were obtained if spontaneously reported by the patient, if reported in response to an open question from the study personnel or if revealed by observation.
A treatment emergent AE (TEAE) was defined as any AE occurring after administration of the IMP and within the time of the residual drug effect period (i.e. 30 days after IMP adminis

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Group 1 (overall trial)

Reporting group description:

Single i.v. infusion of 0.25 mg IdeS/kg body weight.
Initially 3 patients receiving a dose of 0.25 mg/kg body weight of IdeS and after safety evaluation, a potential dose escalation to 0.5 mg/kg for the remaining 3 patients. The study was terminated early by the sponsor following a review of the initial results from the study that demonstrated a non-favourable risk-benefit profile in the first 2 patients.

Serious adverse events	Group 1 (overall trial)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Serum sickness			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1 (overall trial)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		

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? Yes

Date	Interruption	Restart date
25 January 2017	After an internal review of initial results from the study in December 2016, it was decided that the study would be discontinued since a non-favourable risk-benefit profile was observed in the first 2 patients. Although IdeS effectively cleaved IgG antibodies, including a transient reduction in the anti-ADAMTS13 antibodies, an effect on ADAMTS13 enzyme activity was not demonstrated. Thus, the two unexpected events of serum sickness observed caused an overall non-favourable risk-benefit profile for treatment with IdeS in patients with antibody-mediated asymptomatic TTP. The study 15-HMedIdeS-08 was therefore discontinued on 25 Jan 2017 (date of last patient last visit).	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Because of premature study termination and since the sponsor will no longer pursue the indication, the analyses as described in the protocol were not performed. Instead, data collected for the 2 enrolled subjects were listed and presented graphically

Notes: