Clinical trial results:
A PHASE II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY AND PHARMACOKINETICS OF INTRAVENOUS ASCENDING DOSES OF IDES IN KIDNEY TRANSPLANTATION

Summary

EudraCT number	2014-000712-34
Trial protocol	SE
Global end of trial date	13 October 2016

Results information

Result version number	v1 (current)
This version publication date	28 October 2017
First version publication date	28 October 2017

Trial information

Trial identification

Sponsor protocol code	13-HMedIdeS-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02475551
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hansa Medical AB
Sponsor organisation address	Scheelevägen 22, Lund, Sweden, 22007
Public contact	Hansa Medical AB, Hansa Medical AB, +46 768581506,
Scientific contact	Hansa Medical AB, Hansa Medical AB, +46 768581506,

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	22 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2016
Global end of trial reached?	Yes
Global end of trial date	13 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the safety and tolerability of IdeS in renal transplantation

Protection of trial subjects:

To secure the safety of the patients, a cautious approach was chosen, employing staggered dosing with at least 7 days between patients within a dose group and at least 14 days between dosing of the first patient in a higher dose group and dosing of the last patient in the previous dose group. The requirement for staggered dosing within dose groups was removed (in protocol amendment 3) when a sufficient amount of safety data was available to assess that it was no longer necessary. In addition, increase to a higher dose group was controlled by the DMC that evaluated all safety data prior to each dose escalation.
No placebo group was included in the study since it could not be ethically justified to randomise patients with DSAs to placebo treatment. The presence of DSAs is a contraindication to transplantation due to the high risk of hyperacute and acute AMR.

Background therapy:

Induction therapy was given according to clinical practice at each site. If anti-thymocyte globulin (ATG) was indicated, ATGAM® (equine ATG [eATG]) was given since rabbit ATG (rATG) is cleaved by IdeS.

In addition to the medication that was administered as standard of care of kidney transplant patients, the following medication was required according to protocol:
Premedication: In order to prevent an anaphylactic reaction due to infusion of a biological IMP, the patients received premedication with methylprednisolone sodium succinate (Solu-Medrol®) 250 mg i.v. and 10 mg oral loratadine before each IdeS infusion.

Prophylactic Antibiotics: All patients received 1 g phenoxymethylpenicillin (Kåvepenin) once daily (OD) from the start of IdeS treatment until recovery of serum IgG level (>3 g/L) as antibiotic prophylaxis to prevent opportunistic infections due to low IgG levels.

Standard of Care Medication
The medication administered as standard of care of kidney transplant patients at the sites included; Prophylactic Antibiotics, Prophylaxis of Pneumocystis jirovecii, Viral Prophylaxis and Surveillance, and maintenance immunosuppression.

Evidence for comparator: -	
Actual start date of recruitment	04 June 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	Sweden: 10

Worldwide total number of subjects	10
EEA total number of subjects	10

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)	8
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 sites (departments of transplant surgery) in Sweden.

Pre-assignment

Screening details:

Screening of a patient could take place up to 28 days before first dosing on study day 0. If the patient met all inclusion and no exclusion criteria and was not dosed with IdeS within 28 days, for example because the patient did not receive an organ offer within this time frame, the patient could be re-screened.
12 patients screened , 10 enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	First dose group

Arm description:

Patients in the first dose group received one intravenous (i.v.) dose of 0.25 mg/kg IdeS over 15 minutes.

Arm type	Experimental
Investigational medicinal product name	HMED-IdeS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

One intravenous (i.v.) dose of 0.25 mg/kg over 15 minutes.

Arm title	Second dose group

Arm description:

The second dose group received one dose of 0.50 mg/kg after evaluation of the safety and efficacy in the first group.

Arm type	Experimental
Investigational medicinal product name	HMED-IdeS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

One intravenous (i.v.) dose of 0.50 mg/kg ideS over 15 minutes.

Number of subjects in period 1	First dose group	Second dose group
Started	5	5
Completed	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
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)	8	8	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	51.6		
standard deviation	± 13.7	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	3	3	

End points

End points reporting groups

Reporting group title	First dose group
Reporting group description:	
Patients in the first dose group received one intravenous (i.v.) dose of 0.25 mg/kg IdeS over 15 minutes.	
Reporting group title	Second dose group
Reporting group description:	
The second dose group received one dose of 0.50 mg/kg after evaluation of the safety and efficacy in the first group.	

Primary: Safety parameters

End point title	Safety parameters[1]
End point description:	
Number of adverse events reported in each treatment group.	
End point type	Primary
End point timeframe:	
From day -1 and throughout the study including the follow-up period until day 180 ± 7 days	

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: No formal statistical analysis were performed in this study. All endpoints were presented using descriptive statistics, individual patient listings and graphs.

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of Adverse Events	52	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy defined as the IdeS dosing scheme resulting in HLA antibody levels acceptable for transplantation within 24 hours from dosing

End point title	Efficacy defined as the IdeS dosing scheme resulting in HLA antibody levels acceptable for transplantation within 24 hours from dosing
End point description:	
Number of patients with HLA antibody levels acceptable for transplantation within 24 hours from dosing with IdeS.	
End point type	Secondary
End point timeframe:	
Within 24 hours from dosing with HMED-IdeS	

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of PRA levels in cytotoxic sera screen after IdeS treatment

End point title	Reduction of PRA levels in cytotoxic sera screen after IdeS treatment

End point description:

Number of patients who had a reduction of PRA levels up to 24 hours after dosing with IdeS. Data available only for 6 patients.

End point type	Secondary

End point timeframe:

Within 24 hours from dosing with IdeS

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: Number of subjects	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Result in FACS and cytotoxic crossmatch test after IdeS treatment

End point title	Result in FACS and cytotoxic crossmatch test after IdeS treatment

End point description:

Number of subjects crossmatch negative after IdeS treatment. Data available for 7 subjects as 3 missing post dose FACS and CDC CXM.

End point type	Secondary

End point timeframe:

Post IdeS treatment (between 2 and 24 hours)

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Number of subjects	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, Cmax: peak drug concentration

End point title	Pharmacokinetic (PK) profile of IdeS, Cmax: peak drug concentration

End point description:

End point type	Secondary

End point timeframe:

Up to 24 hours after dosing with IdeS

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: µg/L				
arithmetic mean (standard deviation)	5900 (± 1200)	9900 (± 890)		

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:

The overall average (SD) level of anti-IdeS IgG (ADA), ImmunoCAP (mg/L) at day 180.

End point type	Secondary

End point timeframe:

Day 180

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: mg/L				
arithmetic mean (standard deviation)	140 (± 190)	120 (± 180)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kidney function in patients who were transplanted

End point title	Kidney function in patients who were transplanted

End point description:

Number of subjects having functioning kidney, assessed by serum creatinine, eGFR and kidney biopsy at day 180.

End point type	Secondary

End point timeframe:

Day 180

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, Tmax: time to maximum serum concentration

End point title	Pharmacokinetic (PK) profile of IdeS, Tmax: time to maximum serum concentration

End point description:

End point type	Secondary

End point timeframe:

Up to 24 hours post dosing of IdeS

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Hours				
arithmetic mean (standard deviation)	0.70 (± 0.27)	0.29 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, AUC: area under the plasma concentration-time curve

End point title	Pharmacokinetic (PK) profile of IdeS, AUC: area under the plasma concentration-time curve

End point description:

End point type	Secondary

End point timeframe:

From time 0 to infinity.

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: µg×h/L				
arithmetic mean (standard deviation)	210000 (± 120000)	630000 (± 530000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, t½: terminal half-life

End point title	Pharmacokinetic (PK) profile of IdeS, t½: terminal half-life

End point description:

Harmonic mean reported for t½ rather than arithmetic mean

End point type	Secondary

End point timeframe:

During terminal phase of elimination.

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Hours				
arithmetic mean (standard deviation)	74 (± 16)	93 (± 50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, Clearance

End point title	Pharmacokinetic (PK) profile of IdeS, Clearance

End point description:

End point type	Secondary

End point timeframe:

Up to day 21.

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: mL/h/kg				
arithmetic mean (standard deviation)	1.7 (± 1.2)	1.2 (± 0.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, Vss: volume of distribution at steady state

End point title	Pharmacokinetic (PK) profile of IdeS, Vss: volume of distribution at steady state

End point description:

End point type	Secondary

End point timeframe:

Up to day 21.

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: L/kg				
arithmetic mean (standard deviation)	0.12 (± 0.054)	0.13 (± 0.042)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of IdeS, Vz: apparent volume of distribution

End point title	Pharmacokinetic (PK) profile of IdeS, Vz: apparent volume of distribution

End point description:

End point type	Secondary

End point timeframe:

Up to day 21.

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: L/kg				
arithmetic mean (standard deviation)	0.17 (± 0.080)	0.16 (± 0.069)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to recovery of total serum IgG

End point title	Time to recovery of total serum IgG

End point description:

Time to 80% recovery of Immunoglobulin G

End point type	Secondary

End point timeframe:

Up to day 180

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: Days				
arithmetic mean (standard deviation)	141 (± 26.9)	42.5 (± 29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to recovery of total HLA-antibody

End point title	Time to recovery of total HLA-antibody

End point description:

Time to 80% recovery of SAB-HLA

End point type	Secondary

End point timeframe:

Up to day 180

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: Days				
arithmetic mean (standard deviation)	87 (± 66)	23 (± 22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic (PD) profile of IdeS (cleavage of IgG)

End point title	Pharmacodynamic (PD) profile of IdeS (cleavage of IgG)

End point description:

Mean IgG cleavage scores at 24 hours post dosing with IdeS.
Summary of IgG cleavage scores:
0 = No intact IgG, scIgG or F(ab)2.
1 = F(ab)2.
2 = Mix of scIgG and F(ab)2.
3 = Only scIgG.
4 = Mix of intact IgG and scIgG.
5 = Only intact IgG.

End point type	Secondary

End point timeframe:

24 hours post dosing with IdeS

End point values	First dose group	Second dose group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: IgG cleavage scores				
arithmetic mean (standard deviation)	1 (± 0)	1 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From day -1 and throughout the study including the follow-up period until day 180 ± 7 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	0.25 mg/kg
Reporting group description: -	
Reporting group title	0.50 mg/kg
Reporting group description: -	

Serious adverse events	0.25 mg/kg	0.50 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	5 / 5 (100.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Donor specific antibody present			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphocele			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal artery stenosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (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: 0 %

Non-serious adverse events	0.25 mg/kg	0.50 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	
Vascular disorders			
Lymphocele			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Vena cava thrombosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 5 (0.00%)	4 / 5 (80.00%)	
occurrences (all)	0	5	
Kidney transplant rejection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			

Hydrothorax			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Escherichia test positive			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Neutrophil count increased			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Donor specific antibody present			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Haematocrit increased			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Tremor			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 5 (60.00%)	
occurrences (all)	2	3	
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Renal artery stenosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ureteric obstruction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Osteoporosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	
occurrences (all)	3	7	
Sepsis			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Candida infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Abdominal infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Adenovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
BK virus infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Catheter site infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Cytomegalovirus viraemia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Parvovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Postoperative wound infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Serratia infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Urosepsis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	4 / 5 (80.00%)	3 / 5 (60.00%)	
occurrences (all)	4	3	
Diabetes mellitus			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

Hyperkalaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hyperlipidaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2014	Amendment 1, dated 26 Sep 2014 •Inclusion criterion number 3 was changed to allow inclusion of patients who were more highly sensitised. This was done because preliminary data from an ongoing phase II study showed high efficacy also on highly sensitised patients and one patient in that study had been transplanted with a good result. •Results in cytotoxic cross-match test were added to the secondary endpoints. • P-alkaline phosphatase (ALP) was added to the clinical chemistry variables since this variable was also required for safety evaluation. • It was clarified that treatment with IdeS should be performed the day before transplantation for patients with a living donor and on the day of transplantation for patients with a deceased donor. • The sampling time points for cross-match tests after IdeS administration were clarified. • The time points for kidney biopsies were changed and it was clarified that patients who did not undergo transplantation would not have biopsies taken. • The causality rating for AEs was changed to be consistent with the safety plan. • The procedures for SAE and SUSAR reporting were changed to be consistent with the safety management plan. • The principal investigator at Uppsala University Hospital was changed. • One more site (Karolinska University Hospital) was added.
14 November 2015	Amendment 3, dated 20 Oct 2015 • Staggered dosing within dose groups removed . • Number of additional patients that could be included in each dose group increased from 2 to 6 additional patients (i.e. total 2-8 patients). • Clarified on signature page of protocol that principal investigator at Uppsala University Hospital was the coordinating investigator for study. • Known horse allergy added as an exclusion criterion. • Requirement for a negative cross-match test before transplantation was removed. • Screening window increased to include day 0, i.e. including the day of IdeS administration. • Flow charts were updated to specify that day 0 was the day of IdeS dosing and to clarify when pre-dose sampling was to be performed. • In the flow chart clarified that the pregnancy test did not have to be repeated pre-dose if the pregnancy test at screening had been performed within the last 24 hours prior to dosing. • Clarified viral surveillance (BK, EBV, and CVM) would be performed. • Previous virology screening (for HIV and hepatitis B and C) accepted if performed within 36 months prior to IdeS administration instead of only 6 months. • P-creatinine was added to the table describing the DMC safety data package • Complement function variables would not be evaluated for clinical significance at each time point. • Phenoxymethylpenicillin changed to 1 g OD instead of 1 g three times daily. Valaciclovir 500 mg three times daily was changed to valganciclovir 450 mg daily. • Clarified that induction therapy would be given according to clinical practice. • Additional time points added in the flow chart for analysis of SAB-C1q • Complement function screening C3dg was removed • Evaluation of causal relationship between SAEs and other medications apart from the IMP omitted • Patients could be re-screened if IdeS had not been given within 28 days from first screening • Info regarding Investigators from Karolinska University Hospital added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported