



## 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:

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**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              |
| <b>Arm title</b>             | 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.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>Number of adverse events reported in each treatment group.                               |                                  |
| End point type   | Primary                          |
| End point timeframe:<br>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:<br>Number of patients with HLA antibody levels acceptable for transplantation within 24 hours from dosing with IdeS. |  |
| End point type  | Secondary  |
| End point timeframe:<br>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:<br>Number of subjects having functioning kidney, assessed by serum creatinine, eGFR and kidney biopsy at day 180. |   |
| End point type   | Secondary   |
| End point timeframe:<br>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:<br>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, t<sub>1/2</sub>: terminal half-life

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic (PK) profile of IdeS, t <sub>1/2</sub> : terminal half-life |
|-----------------|---|

End point description:

Harmonic mean reported for t<sub>1/2</sub> 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 ( $\pm$ 16)   | 93 ( $\pm$ 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 ( $\pm$ 1.2) | 1.2 ( $\pm$ 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:<br>Time to 80% recovery of SAB-HLA |  |
| End point type  | Secondary                              |
| End point timeframe:<br>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:<br>Mean IgG cleavage scores at 24 hours post dosing with IdeS.<br>Summary of IgG cleavage scores:<br>0 = No intact IgG, scIgG or F(ab)2.<br>1 = F(ab)2.<br>2 = Mix of scIgG and F(ab)2.<br>3 = Only scIgG.<br>4 = Mix of intact IgG and scIgG.<br>5 = Only intact IgG. |  |
| End point type  | Secondary  |
| End point timeframe:<br>24 hours post dosing with IdeS  |  |

| <b>End point values</b>              | 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 ( $\pm$ 0)     | 1 ( $\pm$ 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 %

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |  |
| Psychiatric disorders  |                     |                     |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Investigations   |                     |                     |  |
| Blood creatine increased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 5 (20.00%)<br>1 | 2 / 5 (40.00%)<br>2 |  |
| Escherichia test positive<br>subjects affected / exposed<br>occurrences (all)            | 2 / 5 (40.00%)<br>2 | 0 / 5 (0.00%)<br>0  |  |
| Neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)           | 2 / 5 (40.00%)<br>2 | 0 / 5 (0.00%)<br>0  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)        | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Donor specific antibody present<br>subjects affected / exposed<br>occurrences (all)      | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |  |
| Haematocrit increased  |                     |                     |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Injury, poisoning and procedural complications<br>Post procedural haematoma<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)  | 2 / 5 (40.00%)<br>2 | 1 / 5 (20.00%)<br>1 |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 5 (40.00%)<br>2 | 3 / 5 (60.00%)<br>3 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 2 / 5 (40.00%)<br>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%) |  |
| Hepatobiliary disorders                | occurrences (all)                               | 0              | 1              |  |
|  | Vomiting  |                |                |  |
|  | subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 5 (20.00%) |  |
|  | occurrences (all)                               | 0              | 1              |  |
|  | Cholecystitis                                   |                |                |  |
|  | subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 5 (20.00%) |  |
|  | occurrences (all)                               | 0              | 1              |  |
|  | Cholelithiasis                                  |                |                |  |
| Skin and subcutaneous tissue disorders | subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 5 (20.00%) |  |
|  | occurrences (all)                               | 0              | 1              |  |
|  | Rash  |                |                |  |
|  | subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 5 (20.00%) |  |
|  | occurrences (all)                               | 0              | 1              |  |
|  | Proteinuria                                     |                |                |  |
|  | subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 5 (0.00%)  |  |
|  | occurrences (all)                               | 1              | 0              |  |
| Renal and urinary disorders            | 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<br>subjects affected / exposed<br>occurrences (all)              | 1 / 5 (20.00%)<br>0 | 0 / 5 (0.00%)<br>0  |  |
| Infections and infestations   |                     |                     |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)   | 3 / 5 (60.00%)<br>3 | 3 / 5 (60.00%)<br>7 |  |
| Sepsis<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 5 (20.00%)<br>1 | 2 / 5 (40.00%)<br>2 |  |
| Candida infection<br>subjects affected / exposed<br>occurrences (all)         | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>2 |  |
| Infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 5 (0.00%)<br>0  | 2 / 5 (40.00%)<br>2 |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 5 (20.00%)<br>1 | 1 / 5 (20.00%)<br>1 |  |
| Abdominal infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Adenovirus infection<br>subjects affected / exposed<br>occurrences (all)      | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |  |
| BK virus infection<br>subjects affected / exposed<br>occurrences (all)        | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Catheter site infection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 5 (0.00%)<br>0  |  |
| Cytomegalovirus infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 1 / 5 (20.00%)<br>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 | <p>Amendment 1, dated 26 Sep 2014</p> <ul style="list-style-type: none"><li>• 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.</li><li>• Results in cytotoxic cross-match test were added to the secondary endpoints.</li><li>• P-alkaline phosphatase (ALP) was added to the clinical chemistry variables since this variable was also required for safety evaluation.</li><li>• 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.</li><li>• The sampling time points for cross-match tests after IdeS administration were clarified.</li><li>• The time points for kidney biopsies were changed and it was clarified that patients who did not undergo transplantation would not have biopsies taken.</li><li>• The causality rating for AEs was changed to be consistent with the safety plan.</li><li>• The procedures for SAE and SUSAR reporting were changed to be consistent with the safety management plan.</li><li>• The principal investigator at Uppsala University Hospital was changed.</li><li>• One more site (Karolinska University Hospital) was added.</li></ul>  |
| 14 November 2015 | <p>Amendment 3, dated 20 Oct 2015</p> <ul style="list-style-type: none"><li>• Staggered dosing within dose groups removed.</li><li>• 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).</li><li>• Clarified on signature page of protocol that principal investigator at Uppsala University Hospital was the coordinating investigator for study.</li><li>• Known horse allergy added as an exclusion criterion.</li><li>• Requirement for a negative cross-match test before transplantation was removed.</li><li>• Screening window increased to include day 0, i.e. including the day of IdeS administration.</li><li>• 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.</li><li>• 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.</li><li>• Clarified viral surveillance (BK, EBV, and CVM) would be performed.</li><li>• 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.</li><li>• P-creatinine was added to the table describing the DMC safety data package</li><li>• Complement function variables would not be evaluated for clinical significance at each time point.</li><li>• Phenoxyethylpenicillin changed to 1 g OD instead of 1 g three times daily.</li><li>• Valaciclovir 500 mg three times daily was changed to valganciclovir 450 mg daily.</li><li>• Clarified that induction therapy would be given according to clinical practice.</li><li>• Additional time points added in the flow chart for analysis of SAB-C1q</li><li>• Complement function screening C3dg was removed</li><li>• Evaluation of causal relationship between SAEs and other medications apart from the IMP omitted</li><li>• Patients could be re-screened if IdeS had not been given within 28 days from first screening</li><li>• Info regarding Investigators from Karolinska University Hospital added</li></ul> |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported