



Clinical trial results:

A Phase II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous IdeS after Administration of Ascending Doses in Chronic Kidney Disease Patients

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-005417-13 |
| Trial protocol | SE |
| Global end of trial date | 13 February 2015 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 04 May 2019 |
| First version publication date | 18 April 2019 |
| Version creation reason | • Changes to summary attachments Removed attached appendices. |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | 13-HMedIdeS-02 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02224820 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Hansa Biopharma AB |
| Sponsor organisation address | Scheelevägen 22, Lund, Sweden, 223 63 |
| Public contact | Clinical Trials Information, Hansa Biopharma AB, clinicalstudyinfo@hansabiopharma.com |
| Scientific contact | Clinical Trials Information, Hansa Biopharma 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 | 25 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 February 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 February 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To find an IdeS dosing scheme which in the majority of the patients results in HLA antibody levels which are acceptable for transplantation. This will be measured as an MFI less than 1100 as measured in a single antigen bead (SAB) assay, within 24 hours from dosing

Protection of trial subjects:

Dosing was staggered with at least 7 days between patients in the group. The investigator decided the number of doses for each patient (max 2) and the decision was based on both safety and efficacy. There were to be 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.

Dose escalation to a higher group was to be based on safety and efficacy evaluation of previous dose groups. Proceeding to a higher dose group always required that the previous full group (2-4 patients) was evaluated by the Data Monitoring Committee (DMC).

Background therapy:

Patients were premedicated with the corticosteroid methylprednisolone (Solu-Medrol®) and the antihistamine loratadine (Loratadin®) before IdeS infusions.

All patients received prophylactic antibiotics until their serum total IgG was 3 g/L or more.

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 10 June 2014 |
| 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: 8 |
| Worldwide total number of subjects | 8 |
| EEA total number of subjects | 8 |

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) | 7 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was performed at Uppsala University Hospital in Sweden. Enrolled patients were diagnosed with Chronic Kidney Disease in dialysis and on the waiting list for a kidney transplant. Patients were recruited between 10-Jun-2014 and 12-Dec-2014.

Pre-assignment

Screening details:

In total, 10 patients were assessed for eligibility. Eight (8) patients were enrolled and started treatment.

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 | Group 1 |

Arm description:

0.12 mg/kg of IdeS once or twice within 48 hours

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

Dosage and administration details:

0.12 mg/kg milligram(s)/kilogram intravenously once or twice within 48 hours

| | |
|------------------|---------|
| Arm title | Group 2 |
|------------------|---------|

Arm description:

0.25 mg/kg IdeS once or twice within 48 hours

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

Dosage and administration details:

0.25 mg/kg milligram(s)/kilogram intravenously once or twice within 48 hours

| Number of subjects in period 1 | Group 1 | Group 2 |
|---------------------------------------|---------|---------|
| Started | 3 | 5 |
| Completed | 3 | 4 |
| Not completed | 0 | 1 |
| Adverse event, non-fatal | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 8 | 8 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn - gestational age < 37 wk | 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) | 7 | 7 | |
| From 65 to 84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 50.5 | | |
| standard deviation | ± 11.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Male | 3 | 3 | |
| Female | 5 | 5 | |
| Weight | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 74.5 | | |
| standard deviation | ± 14.5 | - | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 172.3 | | |
| standard deviation | ± 9.7 | - | |

Subject analysis sets

| | |
|----------------------------|-----------------|
| Subject analysis set title | SAS |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set (SAS) included all patients that received any amount of study medication.

| | |
|----------------------------|---------------|
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set (FAS) consisted of all patients in the safety analysis set (SAS) who had a measurement of anti-HLA antibody level within 24 hours from dosing.

The FAS was used for presenting efficacy data.

| | |
|----------------------------|--------------|
| Subject analysis set title | PPS |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per protocol set (PPS) was intended to consist of all patients who received at least one dose of IdeS and had evaluable PK data, and was determined by the PK analyst. The full criteria for the PPS, regarding protocol deviations that warranted exclusions, was specified when all data on protocol violations/deviations were available.

The PPS was used for the pharmacokinetics (PK) and pharmacodynamics (PD) evaluations.

| Reporting group values | SAS | FAS | PPS |
|--|--------|--------|--------|
| Number of subjects | 8 | 8 | 7 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn - gestational age < 37 wk | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days - 23 months) | 0 | 0 | 0 |
| Children (2 - 11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 7 | 7 | 6 |
| From 65 to 84 years | 1 | 1 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 50.5 | 50.5 | 51.1 |
| standard deviation | ± 11.9 | ± 11.9 | ± 12.7 |
| Gender categorical Units: Subjects | | | |
| Male | 3 | 3 | 3 |
| Female | 5 | 5 | 4 |
| Weight Units: kilogram(s) | | | |
| arithmetic mean | 74.5 | 74.5 | 71.4 |
| standard deviation | ± 14.5 | ± 14.5 | ± 12.5 |
| Height Units: cm | | | |
| arithmetic mean | 172.3 | 172.3 | 172.7 |
| standard deviation | ± 9.7 | ± 9.7 | ± 10.4 |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | Group 1 |
| Reporting group description: 0.12 mg/kg of IdeS once or twice within 48 hours | |
| Reporting group title | Group 2 |
| Reporting group description: 0.25 mg/kg IdeS once or twice within 48 hours | |
| Subject analysis set title | SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety analysis set (SAS) included all patients that received any amount of study medication. | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The full analysis set (FAS) consisted of all patients in the safety analysis set (SAS) who had a measurement of anti-HLA antibody level within 24 hours from dosing. The FAS was used for presenting efficacy data. | |
| Subject analysis set title | PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per protocol set (PPS) was intended to consist of all patients who received at least one dose of IdeS and had evaluable PK data, and was determined by the PK analyst. The full criteria for the PPS, regarding protocol deviations that warranted exclusions, was specified when all data on protocol violations/deviations were available. The PPS was used for the pharmacokinetics (PK) and pharmacodynamics (PD) evaluations. | |

Primary: Mean fluorescent intensity of less than 1100 within 24 hours

| | |
|---|---|
| End point title | Mean fluorescent intensity of less than 1100 within 24 hours ^[1] |
| End point description: The primary endpoint in the study was efficacy defined as the IdeS dosing scheme resulting in HLA antibody levels acceptable for transplantation. It was analyzed using serial analysis for antibodies. Results from the single antigen bead (SAB) HLA assay were combined with results from the complement fixating anti-HLA assay (C1q). The acceptance criterion for transplantation was defined as a mean fluorescence intensity (MFI) of <1100, within 24 h from dosing. A responder was defined as a patient for whom all pre-dose MFI values that were >1100 had the 90th percentile MFI <1100 within 24 h after IdeS treatment. | |
| End point type | Primary |
| End point timeframe: From IdeS dosing up to 24 h after IdeS administration: (i) single antigen bead (SAB) HLA: pre-dose, 1h, 2h, 6h, and 24h post-dose (ii) complementing fixating anti-HLA assay (C1q): pre-dose, 1h and 24 h post-dose | |

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 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. Either resolve this issue or provide a justification.

| End point values | Group 1 | Group 2 | FAS | |
|-----------------------------|-----------------|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 5 ^[2] | 8 ^[3] | |
| Units: Number of responders | | | | |
| SAB HLA | 0 | 3 | 3 | |
| C1q | 3 | 3 | 6 | |

Notes:

[2] - The C1q analysis included 3 patients only due to high background for 1 p and dose interrupted for 1p

[3] - The C1q analysis included 6 patients only due to high background for 1 p and dose interrupted for 1p

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

| | |
|-----------------|--------|
| End point title | Safety |
|-----------------|--------|

End point description:

A summary of reported Adverse Events (AE)s from the study is included.

Please refer to the "Adverse Event" section for details on the specific AEs reported from this clinical study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

AEs were collected from the time-point the patient was admitted to the clinical trial unit and throughout the study including the follow-up period (i.e. up to day 64).

| End point values | Group 1 | Group 2 | SAS | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 5 | 8 | |
| Units: Number of AEs | | | | |
| Adverse Events | 23 | 53 | 76 | |
| Related Adverse Events | 8 | 19 | 27 | |
| Serious Adverse Events | 1 | 4 | 5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of IdeS: Cmax

| | |
|-----------------|--------------------------|
| End point title | PK profile of IdeS: Cmax |
|-----------------|--------------------------|

End point description:

Cmax = Maximum observed plasma concentration of IdeS following dosing (non-compartmental analysis)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Immediately before IdeS dosing up to 21 days

| End point values | Group 1 | Group 2 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 4 | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | 2.24 (± 0.08) | 6.39 (± 1.02) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of IdeS: tmax

| | |
|--|--------------------------|
| End point title | PK profile of IdeS: tmax |
| End point description: | |
| Tmax = Time of occurrence of Cmax (non-compartmental analysis) | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately before IdeS dosing up to 21 days | |

| End point values | Group 1 | Group 2 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 4 | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 0.92 (± 0.93) | 0.94 (± 0.77) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of IdeS: AUC

| | |
|--|-------------------------|
| End point title | PK profile of IdeS: AUC |
| End point description: | |
| AUC = Area under the plasma concentration vs time curve from time 0 to infinity (non-compartmental analysis) | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately before IdeS dosing up to day 21 | |

| End point values | Group 1 | Group 2 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 4 | | |
| Units: h x µg/mL | | | | |
| arithmetic mean (standard deviation) | 110 (± 27) | 487 (± 30) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of IdeS: t1/2

| | |
|--|--------------------------|
| End point title | PK profile of IdeS: t1/2 |
| End point description: t1/2 = Terminal half-life (non-compartmental analysis) | |
| End point type | Secondary |
| End point timeframe: Up to day 21 | |

| End point values | Group 1 | Group 2 | PPS | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 4 | 7 | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 54 (± 7) | 135 (± 111) | 100 (± 90) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Profile of IdeS: CL

| | |
|---|------------------------|
| End point title | PK Profile of IdeS: CL |
| End point description: CL = Clearance (non-compartmental analysis) | |
| End point type | Secondary |
| End point timeframe: Immediately before IdeS dosing up to 21 days | |

| End point values | Group 1 | Group 2 | PPS | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 4 | 7 | |
| Units: mL/h/Kg | | | | |
| arithmetic mean (standard deviation) | 1.14 (± 0.32) | 0.66 (± 0.33) | 0.86 (± 0.39) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Profile of IdeS: Vz

| | |
|---|------------------------|
| End point title | PK Profile of IdeS: Vz |
| End point description: Vz = Volume of distribution during the elimination phase (non-compartmental analysis) | |
| End point type | Secondary |
| End point timeframe: Immediately before IdeS dosing up to 21 days | |

| End point values | Group 1 | Group 2 | PPS | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 4 | 7 | |
| Units: L/kg | | | | |
| arithmetic mean (standard deviation) | 0.088 (± 0.015) | 0.092 (± 0.019) | 0.090 (± 0.016) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PD Profile of IdeS: Cleavage of IgG

| | |
|---|-------------------------------------|
| End point title | PD Profile of IdeS: Cleavage of IgG |
| End point description: The efficacy of IdeS treatment on IgG was investigated using an enzyme-linked immunosorbent assay (ELISA) at different time-points after dosing. This assay determines the sum of intact IgG and single chain cleaved IgG (scIgG) in serum. In addition a turbidimetric assay and a qualitative sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis were done (results not included). The mean concentration of IgG at selected timepoints after dosing is presented to follow the progress of the IgG cleaving process. Individual IgG concentrations at all time-points are listed in Appendix 16.2, List 16.2.6.7. | |
| End point type | Secondary |
| End point timeframe: 1 dose: pre-dose, 14min, 0.5, 1, 2, 4, 6, 8, 24, 48, 72h, 7, 14, 21, 28, and 64d after dosing 2 doses: 1st dose as above until 24h, then pre-2nd dose, 14min, 0.5, 1, 2, 4, 6, 8, 24, 48, 72h, 7, 14, 21, 28, and 64d after dosing | |

| End point values | Group 1 | Group 2 | | |
|--|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 4 ^[4] | | |
| Units: microgram(s)/millilitre | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| Concentration pre-1st dose | 11000 (6800 to 13800) | 9300 (7900 to 10700) | | |
| Concentration at 6h (1st dose) | 2200 (1000 to 4100) | 130 (37 to 300) | | |
| Concentration at 24h (1st dose) | 610 (350 to 940) | 23 (5 to 41) | | |
| Concentration at 6h (2nd dose) | 43 (14 to 58) | 13 (5 to 25) | | |
| Concentration at 24 h (2nd dose) | 21 (14 to 26) | 5 (5 to 5) | | |

Notes:

[4] - Please observe that 2 patients only received 2 doses

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of IdeS: Anti-drug antibodies (ADAs)

| | |
|-----------------|---|
| End point title | Immunogenicity of IdeS: Anti-drug antibodies (ADAs) |
|-----------------|---|

End point description:

The serum concentration of anti-IdeS IgG was measured.

The number of patients with anti-IdeS IgG present at screening and 64 days after IdeS dosing are presented together with the number of patients that had a peak concentration of anti-IdeS IgG on day 14 after dosing.

Individual anti-IdeS IgG concentrations at all sampling time-points are listed in Appendix 16.2, List 16.2.6.6.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 dose: Screening, pre-dose, 24h after dose, 5d, 7d, 14d, 21d, 28d, and 64 d after dose

2 doses: Screening, pre-dose, 24h after 1st dose, 24 h after 2nd dose, 5d, 7d, 14d, 21d, 28d, and 64d after dose

| End point values | Group 1 | Group 2 | PPS | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 4 | 7 | |
| Units: Number of patients | | | | |
| ADAs at Screening | 3 | 4 | 7 | |
| ADAs at Day 64 | 3 | 4 | 7 | |
| Peak concentration of ADAs at Day 14 | 2 | 4 | 6 | |

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:

Samples were analyzed for complement dependent cytotoxicity (CDC) against a panel of T- and B-cells to determine the level of panel reactivity (PRA) in percentage (%).

Number of patients with a reduction in T/B PRA (%) 1 hour after IdeS dosing is presented.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 dose: pre-dose, 1h, 2h, 6h, 24h, 7d, 14d, 28d, and 64d after dosing

2 doses: pre-dose, 1h, 2h, 6h, 24h after first dose, then 1h, 2h, 6h, 24h, 7d, 14d, 28d, and 64d after second dosing

| End point values | Group 1 | Group 2 | PPS | |
|------------------------------------|-----------------|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 4 ^[5] | 7 ^[6] | |
| Units: Number of patients | | | | |
| Reduced T/B PRA 1 h after 1st dose | 3 | 4 | 7 | |
| Reduced T/B PRA 1 h after 2nd dose | 3 | 2 | 5 | |

Notes:

[5] - Please note that 2 patients only had 2 doses of IdeS

[6] - Please note that 5 patients only had 2 doses of IdeS

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of IdeS: Alpha t1/2 and Beta t1/2

| | |
|-----------------|--|
| End point title | PK profile of IdeS: Alpha t1/2 and Beta t1/2 |
|-----------------|--|

End point description:

2-compartment analysis

Alpha t1/2 = half-life for the distribution phase

Beta t1/2 = half-life for the elimination phase

Harmonic mean values were calculated for alpha and beta half-lives as $\ln 2 / \text{mean alpha}$ and $\ln 2 / \text{mean beta}$, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Immediately before IdeS dosing up to 21 days

| End point values | Group 1 | Group 2 | PPS | |
|--|---------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 ^[7] | 4 ^[8] | 7 ^[9] | |
| Units: hour | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| Alpha t1/2 | 4.03 (2.38 to 7.77) | 6.26 (3.22 to 11.2) | 5.06 (2.38 to 11.2) | |
| Beta t1/2 | 53.7 (47.2 to 59.8) | 88.9 (49.2 to 301) | 69.3 (47.2 to 301) | |

Notes:

[7] - Harmonic means are presented rather than arithmetic means

[8] - Harmonic means are presented rather than arithmetic means

[9] - Harmonic means are presented rather than arithmetic means

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of IdeS: Vss

| | |
|---|-------------------------|
| End point title | PK profile of IdeS: Vss |
| End point description: | |
| Vss = Volume of distribution during steady state (non-compartmental analysis) | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately before IdeS dosing up to 21 days | |

| End point values | Group 1 | Group 2 | PPS | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 3 | 4 | 7 | |
| Units: L/kg | | | | |
| arithmetic mean (standard deviation) | 0.083 (± 0.014) | 0.084 (± 0.019) | 0.083 (± 0.015) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Results in FACS crossmatch test against available donor cells

| | |
|--|---|
| End point title | Results in FACS crossmatch test against available donor cells |
| End point description: | |
| Samples were analyzed for reactivity against T and B lymphocytes from available donors using flow-cytometry. | |
| FACS crossmatch test was performed only for the one patient that was kidney transplanted during the course of the study. | |
| End point type | Secondary |
| End point timeframe: | |
| 6h and 24h after each dose of IdeS | |

| End point values | Group 1 | Group 2 | PPS | |
|--|-------------------|-------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 1 ^[10] | 0 ^[11] | 1 ^[12] | |
| Units: Number of patients | | | | |
| Positive T and B crossmatch 6h after 1st dose | 1 | | 1 | |
| Negative T and B crossmatch 6h after 1st dose | 0 | | 0 | |
| Positive T and B crossmatch 24h after 1st dose | 1 | | 1 | |
| Negative T and B crossmatch 24h after 1st dose | 0 | | 0 | |
| Positive T and B crossmatch 6h after 2nd dose | 0 | | 0 | |
| Negative T and B crossmatch 6h after 2nd dose | 1 | | 1 | |
| Positive T and B crossmatch 24h after 2nd dose | 0 | | 0 | |
| Negative T and B crossmatch 24h after 2nd dose | 1 | | 1 | |

Notes:

[10] - 1 patient only was transplanted. There were no available donor cells for the other patients.

[11] - There were no available donor cells for the other patients.

[12] - 1 patient only was transplanted. There were no available donor cells for the other patients.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of admission until last visit, 64 days after treatment

Adverse event reporting additional description:

Adverse events included all clinical laboratory tests, vital signs and ECGs judged as clinically significant.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group 2 |
|-----------------------|---------|

Reporting group description:

0.25 mg/kg IdeS once or twice in 48 hours

| | |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

Reporting group description:

0.12 mg/kg IdeS once or twice within 48 hours

| | |
|-----------------------|---------------------|
| Reporting group title | Safety analysis set |
|-----------------------|---------------------|

Reporting group description:

The safety analysis set (SAS) included all patients that received any amount of study medication.

| Serious adverse events | Group 2 | Group 1 | Safety analysis set |
|---|----------------|----------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 1 / 3 (33.33%) | 4 / 8 (50.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 3 (33.33%) | 2 / 8 (25.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Group 2 | Group 1 | Safety analysis set |
|---|-----------------|-----------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | 3 / 3 (100.00%) | 8 / 8 (100.00%) |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 3 (33.33%) | 2 / 8 (25.00%) |
| occurrences (all) | 1 | 1 | 2 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Feeling cold | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Feeling hot | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Infusion site pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 3 (66.67%) 2 | 2 / 8 (25.00%) 2 |
| Pyrexia subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 2 | 0 / 3 (0.00%) 0 | 2 / 8 (25.00%) 2 |
| Immune system disorders Kidney transplant rejection subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 1 | 1 / 8 (12.50%) 1 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 | 1 / 8 (12.50%) 1 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 3 (33.33%) 1 | 2 / 8 (25.00%) 2 |
| Aspartate aminotransferas increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | 1 / 3 (33.33%) 1 | 2 / 8 (25.00%) 3 |
| Blood phosphorus increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 | 1 / 8 (12.50%) 1 |

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|---|---------------------|---------------------|---------------------|
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Donor specific antibody present subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 | 1 / 8 (12.50%) 1 |
| Infusion related reaction subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Cardiac disorders | | | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 3 (33.33%) 1 | 1 / 8 (12.50%) 1 |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Nervous system disorders | | | |
| Dizziness postural subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 2 |
| Headache subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | 1 / 3 (33.33%) 1 | 2 / 8 (25.00%) 3 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Tremor subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 3 (0.00%) 0 | 1 / 8 (12.50%) 1 |

| | | | |
|--|----------------|----------------|----------------|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 3 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Leucocytosis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 3 (33.33%) | 2 / 8 (25.00%) |
| occurrences (all) | 1 | 1 | 2 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye disorders | | | |
| Scleral haemorrhage | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 3 (66.67%) | 2 / 8 (25.00%) |
| occurrences (all) | 0 | 2 | 2 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 3 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|----------------|----------------|----------------|
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Infections and infestations | | | |
| Herpex simplex infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Influenza | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 3 (33.33%) | 2 / 8 (25.00%) |
| occurrences (all) | 1 | 1 | 2 |
| Oral candidas | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 3 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 3 (33.33%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 2 | 4 |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28767349>