STUDY PROTOCOL

A Phase II Study to Evaluate the Efficacy of IdeS (IgG endopeptidase) to Desensitize Transplant Patients with a Positive Crossmatch Test

Sponsors protocol ID: 15-HMedIdeS-06

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1. List of abbreviations and definition of terms

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ABMR	Antibody mediated rejection
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
APTt	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
ATGAM	Anti thymocyte globuline derived from horse
AUC	Area under serum concentration-time curve
BMI	Body mass index
BP	Blood pressure
BW	Body weight
CKD	Chronic kidney disease
CL	Clearance of drug from plasma/serum
C_{max}	Maximum serum concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CRF	Case report form (electronic/paper)
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common toxicity criteria for adverse events
CV	Coefficient of variation
CXM	Crossmatch test
DD	Deceased donor
DSMB	Data and safety monitoring board
DSA	Donor specific antibodies
EBV	Epstein-Barr virus
ECG	Electrocardiogram
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Food and drug administration
GCP	Good clinical practice
GODT	Global observatory on donation and transplantation

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IA	Immuno adsorption
ICF	Informed consent form
ICH	International conference on harmonization
IdeS	Immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*
IRB	Institutional review board
IVIg	Intravenous immunoglobulin
LD	Living donor
MedDRA	Medical dictionary for regulatory activities
MFI	Mean fluorescence intensity
NOAEL	No observed adverse effect level
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PI	Principal investigator
PK	Pharmacokinetics
PK (INR)	Prothrombin complex (internationally normalized ratio)
PLEX	Plasma exchange
PPS	Per protocol set
PRA	Panel reactive antibody
SA	Single antigen
SAB	Single antigen beads
SAE	Serious adverse event
SAR	Serious adverse reaction
SAP	Statistical analysis plan
SOC	System organ class
SPA	Solid phase immunoassay
Ss	Steady state
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
t_{max}	Time to maximum plasma concentration
V_z	Apparent volume of distribution
V_{ss}	Volume of distribution at steady state

1 Important medical procedures

1.1 Medical emergencies contacts

The principal investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such.

Name	Role in the study	Mail address & telephone number
[redacted]	Principal investigator	[redacted]
[redacted]	Principal investigator	
[redacted]	Principal investigator	
[redacted]	Medical Safety Officer	
[redacted]	Clinical Research Manager	mailto: [redacted]

1.2 Overdose

An overdose is a dose in excess of the dose specified for each cohort of the protocol. There are no data on overdosing of IdeS. There is no known antidote but depletion of IgG can be restored with intravenous immunoglobulin (IVIg). In the event of an overdose the patient should be monitored closely and treated symptomatically. This should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF
- An overdose without associated symptoms is only reported in the patient file

2 Introduction

2.1 Disease and patient population

Renal transplantation is the preferred treatment choice for patients with end stage kidney disease since it increases survival and patient quality of life and results in substantial savings in health care costs compared to dialysis (Montgomery, Zachary et al. 2005). In 2010, 23585 kidney transplantations were performed in Europe whereof 18890 within the EU-countries. The corresponding numbers in US was 17610 kidney transplantations and worldwide approximately 73000 kidney transplantations were performed (data from the Global Observatory on Donation and Transplantation (GODT).

Approximately one third of patients waiting for kidney transplantation are sensitized to human leukocyte antigen (HLA) (Iyer, Nikkel et al. 2014) and sensitization hampers the

identification of a suitable donor. As many as 15% of the listed patients are highly sensitized (calculated PRA ≥80) and it has been reported that less than 15% of the sensitized patients in US are transplanted each year despite high priority on the waitlist (Yabu, Pando et al. 2013). The presence of HLA donor specific antibodies (DSAs) is a direct contraindication to transplantation because of the risk of hyper-acute antibody-mediated rejection with acute allograft loss. For transplant candidates who have antibodies, which react against a wide range of HLA it can be difficult to find a donor against whom they have no antibodies. This is true both for patients waiting for a deceased donor kidney and for those within a paired donation program who have an available live donor against which they have DSAs. Consequently, sensitized patients have an extended waiting time for transplantation and a U.K. study demonstrated that the waiting time increased from 788 days for patients with no or low grade of sensitization to 2232 days (> 6 years) for highly sensitized patients (Fuggle and Martin 2008). Along the same line, Yabu *et al.* reported that less than 15% of the highly sensitized patients in the US were transplanted per year, despite high priority (Yabu, Pando et al. 2013).

Data demonstrate that desensitization followed by transplantation of patients with DSA is clearly associated with short- and long-term survival benefits compared to staying in dialysis (Montgomery, Lonze et al. 2011, Vo, Petrozzino et al. 2013, Orandi, Garonzik-Wang et al. 2014, Orandi, Luo et al. 2016). In addition, the patient's quality of life is dramatically increased and there are substantial cost-savings associated with desensitization compared to dialysis (Vo, Petrozzino et al. 2013).

In a study performed at John Hopkins Hospital, Baltimore, over 11 years (Montgomery, Lonze et al. 2011) a total of 211 patients underwent HLA-incompatible live-donor kidney transplantation following desensitization, with HLA incompatibility defined as DSA detected by crossmatch test or multiplex assay (Luminex). In the treatment group, Kaplan-Meier estimates of patient survival were 90.6% at 1 year, 85.7% at 3 years, 80.6% at 5 years, and 80.6% at 8 years, as compared with rates of 91.1%, 67.2%, 51.5% and 30.5%, respectively, for patients in dialysis-only group. The rate of ABMR after desensitization and transplantation has been reported to be 22%, most of which responded to treatment with plasmapheresis (Montgomery, Warren et al. 2012, Iyer, Jackson et al. 2013). Among patients in the desensitization group who had positive crossmatches on the complement-dependent cytotoxicity assay (CDC crossmatch), survival rates were 87.7% at 1 year, 82.0% at 3 years, 78% at 5 years and 78.0% at 8 years, as compared with rates of 92.2%, 67.0%, 49.7% and 27.1%, respectively, in the dialysis-only group. Patients were matched comprehensively based on cPRA, age, blood group, number of renal replacement, race, sex, and the presence or absence of diabetes.

Recently, a five-year outcome study in 535 living donor kidney transplants with a positive crossmatch (Orandi, Garonzik-Wang et al. 2014) was reported. In 102 patients with a positive complement dependent crossmatch test the 5-year survival was 70.7%, which is comparable to 78.0% reported by the Johns Hopkins group.

Although many sensitized patients have been successfully transplanted using current desensitization protocols there are patients on the kidney transplant waitlist who have previously undergone desensitization unsuccessfully or in whom effective desensitization will be highly unlikely.

2.2 Current treatment

In order to increase the likelihood in finding a suitable allograft and transplanting the highly sensitized patients, there are two main approaches (Morath, Opelz et al. 2012), paired donation or desensitization. These approaches may be combined.

Paired donation programs offer opportunities for sensitized patients to receive organs from donors to whom they have little or no DSA, with comparable outcomes to un-sensitized patients (Bray, Nolen et al. 2006). While 16% of the registered population in the Canadian Blood Services Living Donor Paired Exchange National Registry had PRA between 80% and 96%, they accounted for 24% of those transplanted. On the other hand, those with cPRA of 97% or greater make up 32% of the Registry population but accounted for only 10% of transplants (Cole 2015). Highly sensitized patients may remain on the waiting list for several years.

Over the past decade, novel desensitization protocols have been developed to enable patients with high levels of anti-donor antibodies to receive a transplant with acceptable five-year outcomes (Montgomery, Lonze et al. 2011, Orandi, Garonzik-Wang et al. 2014). There is no standardized or approved protocol for desensitization; however, a few protocols have been developed and tested in clinical settings (Vo, Wechsler et al. 2008). All of these protocols use techniques to remove antibodies, either through high-dose intravenous immunoglobulin (IVIg) or plasma-exchange (PLEX)/immunoadsorption (IA) often combined with low-dose IVIg (Montgomery, Zachary et al. 2000, Vo, Wechsler et al. 2008). In addition, some protocols use rituximab in order to inhibit the synthesis of IgG (Vo, Wechsler et al. 2008). The desensitization protocols are often combined with induction therapy using steroids and anti-thymocyte globulin (ATG), anti-CD52 (e.g. alemtuzumab) and/or anti-IL2R antibody (e.g. basiliximab or daclizumab) in order to prevent acute cellular rejections in high-risk patients. PLEX, IA and IVIg treatments have the disadvantage of requiring rigorous planning since they involve repeated treatments over a long period of time. Therefore, these treatments are difficult to apply when transplanting patients with deceased allografts.

2.3 IdeS

Immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* (IdeS) is an IgG specific endopeptidase. Cleavage of IgG generates one $F(ab')_2$- and one homodimeric Fc-fragment and efficiently neutralizes Fc-mediated activities of IgG (HMed doc. No. 2012-003) (von Pawel-Rammingen, Johansson et al. 2002, Wenig, Chatwell et al. 2004, Vincents, von Pawel-Rammingen et al. 2004). IdeS-mediated IgG degradation constitutes a novel therapeutic principle for the treatment of IgG-driven human diseases.

Hansa Medical AB has performed *in vitro* studies and clearly demonstrated that IdeS effectively cleaves purified IgG as well as IgG in serum from human and rabbit. IdeS is very specific in that no other substrate has been found [redacted] In addition, IdeS treatment rapidly and substantially cleaved anti-HLA IgG in serum from sensitized CKD grade 5 patients *in vitro* [redacted]. The reactivity to individual HLA-antigens were reduced below the critical Mean Florescence Intensity (MFI) acceptable for transplantation and a positive crossmatch test was turned into negative. IdeS offers a unique and powerful approach for removing the impenetrable immunology barrier HLA antibodies present and would allow life-saving transplants to patients who are currently not eligible for kidney transplantation.

2.4 IdeS clinical studies

A phase I study first in man single ascending dose study [redacted] showed that IdeS was safe and well tolerated [redacted] The study demonstrated that IdeS could be administered [redacted] with a favourable safety profile. It also showed that IdeS could effectively reduce the levels of plasma IgG and that newly synthesised IgG was not detectable until [redacted] after dosing. [redacted], IdeS completely cleaved the pool of plasma IgG [redacted] The data clearly shows that a single dose of IdeS is superior to both plasmapheresis and immunoadsorption with respect to efficiency and rate of plasma IgG reduction. [redacted] The adverse events that were reported, none of which were reported as serious, were as anticipated from the biological nature of the drug. [redacted]
All adverse events were mild or moderate.

One phase II study was completed at Uppsala University Hospital, Sweden in March 2015. The study was a single arm study with ascending doses of IdeS in 8 CKD patients on the kidney transplantation waiting list. The patients enrolled were diagnosed with CKD, in dialysis and on the waiting list for a kidney transplant. However, transplantation was not part of the study protocol. The treated patients had antibodies against multiple HLA antigens with pre-dose MFIs between 6000 and 25000 as measured by SAB (Luminex) assay. There were two dose groups, 0.12 and 0.25 mg/kg body weight (BW) given once or twice within 48 hours. The study showed that one or two doses of IdeS at 0.25 mg/kg BW in the majority of the patients resulted in HLA antibody levels, acceptable for transplantation, measured as an MFI (LABScreen) less than 1100 within 24 hours from dosing. In addition, in all patients having a significant pre-dose panel-reactivity the percentage PRA was reduced already one hour after IdeS treatment. It was also concluded that in the majority of patients the CDC crossmatches were converted to negative already one hour after a single dose of IdeS (0.12 or 0.25 mg/kg BW) and the crossmatches remained negative for one week. There were a total of five SAEs reported in the study of which four were classified as probable or possible related to study drug. Three of the SAEs were infections. Two phase II studies using IdeS in sensitized patients prior to transplantation are currently ongoing in Uppsala, Sweden and Los Angeles, US.

In a phase II study in patients diagnosed with asymptomatic antibody-mediated Thrombotic Thrombocytopenic Purpura (TTP) with low ADAMTS13 activity, safety and tolerability were assessed after patients receiving a single intravenous dose of IdeS. A secondary objective was to investigate IdeS efficacy in significantly increasing ADAMTS13 activity and decreasing ADAMTS13 antibody levels. Inclusion was prematurely terminated after inclusion of two patients who both showed signs of serum sickness (further described in section 2.6).

2.5 Study rationale and discussion on overall study design

This study will include patients on the kidney transplant waitlist who have previously undergone desensitization unsuccessfully or in whom effective desensitization will be highly unlikely. Patients in whom effective desensitization is highly unlikely are defined as patients who have been accepted into a desensitization program but have not been transplanted within a year despite the opportunity of desensitization and paired donation. Consequently, these patients have one of the highest unmet medical needs in transplantation today. A randomized controlled study in this patient population is not feasible as the potential control treatments have already been tried unsuccessfully or judged as highly unlikely to succeed.

The study will assess IdeS efficacy and safety in removing DSAs and thereby convert a positive crossmatch test to negative. The primary endpoint is conversion of the crossmatch test following IdeS therapy and hence the patients may serve as their own controls. The patients included will have an available deceased or live donor allograft with a positive crossmatch test at study entry.

For these patients there is no available treatment for a control arm and the study is therefore open labeled, single arm. There will be a total of 15-20 (7-13 with live donors and 7-13 with deceased donors) patients included in the study. The first 3 patients in this study will receive a kidney from a deceased donor. Patients will receive one dose of 0.25 mg IdeS/kg BW on study day 0 with the possibility of an additional IdeS dose within two days. This dosing schedule was used in the completed phase II study in highly and moderately sensitized CKD patients described above and was found to be, effective and safe in removing DSAs [redacted] However, it is desirable to find a dose, which is effective in all patients after a single dose in order to minimize time to transplantation especially for the deceased donor setting where a short cold ischemic time is critical. Therefore, there will be a possibility to escalate the dose to 0.5 mg/kg BW after evaluation of safety in the first 3 patients. Patients will receive IVIg on day 7 and anti-CD20 on day 9 after IdeS treatment. In addition, induction therapy with ATGAM at time of transplantation or anti-CD52 (Campath) on day 4 will be given.

There is evidence that low dose IVIg, given after DSA reduction with PLEX, suppresses endogenous antibody production and prevents DSA rebound. Additionally, after transplantation in the context of antibody reduction from plasmapheresis and low dose IVIg or high dose IVIg plus anti-CD20, most patients will experience a durable reduction in DSA but not third party HLA antibody. Thus, on about day 7 after IdeS dosing, IgG begins to return. From previous studies it has also been demonstrated that healthy subjects and some patients develop antibodies to IdeS at this time and there is no experience from administering a second dose of IdeS with a longer interval than 2 days. The current understanding of antibody depletion and reconstitution suggests that the rebound of DSA will be prevented or blunted by treatment with high dose IVIg given at about day 7 after IdeS treatment. At this point the IdeS activity is expected to be non-detectable or very low and not to affect the pharmacological effects of IVIg. Furthermore, the potential donor specific anamnestic response would likewise be reduced or prevented by memory B-cell depletion with the anti-CD20 antibody rituximab. With the donor antigens expressed on the graft the same phenomenon of donor specific B-cell unresponsiveness may be observed that is seen in the majority of patients desensitized with plasmapheresis and low dose IVIg. DSA is expected to remain low, whereas, third party antibody, including vaccine antibodies, will recover to normal levels (Stegall, Dean et al. 2009).

Based on the current knowledge, including experience from completed and ongoing clinical studies, it is expected that IdeS will inactivate IgG across all compartments allowing a rapid and potent reduction of donor specific antibody (DSA) to a level acceptable for transplantation.

2.6 Risk/benefit and ethical assessment

Patients included in this study have both a wide breadth of sensitization and high reactivity to common HLA antigens. Transplantation is not possible using current standards for desensitization due to antibodies creating a positive crossmatch test. These patients are so strongly sensitized that even with paired donation it is highly unlikely to identify a donor with a genotype that would allow desensitization with a reasonable likelihood of success. In addition, some of the patients will have failed on earlier attempts of desensitization. Eligible patients will either be on the waitlist for a deceased allograft or have an identified live donor. However, in both groups transplantation is not indicated due to antibodies creating a positive crossmatch test. Sensitized patients have an increased risk of ABMR associated with negative long-term graft outcome. From previous studies it is known that the ABMR frequency in the highly sensitized patient population is between 25-39% after desensitization (Abu Jawdeh, Cuffy et al. 2014). There are currently no approved treatments for ABMR but in the event of ABMR the patient will be treated according to best clinical practice. This may include plasmapheresis, IVIg, complement inhibitors and anti-CD20 antibodies. The risk for ABMR and graft loss should be weighed against the morbidities, low quality of life and increased mortality associated with long term dialysis. Data demonstrate that transplantation following desensitization is clearly associated with short- and long-term survival benefits compared to staying in dialysis (Montgomery, Lonze et al. 2011, Vo, Petrozzino et al. 2013, Orandi, Garonzik-Wang et al. 2014, Orandi, Luo et al. 2016). In addition, the patient's quality of life is dramatically increased after successful transplantation and there are substantial cost-savings associated with desensitization and subsequent transplantation compared to long-term dialysis (Vo, Petrozzino et al. 2013).

The patients included in the study will receive premedication with glucocorticoids (methylprednisolone) and antihistamines (loratadine) before each IdeS infusion in order to minimise the risk of infusion reactions. Patients with live donors will be screened for anti-IdeS IgE antibodies as part of the eligibility criteria and if positive they will not be included. Patients and healthy subjects who have been previously treated have formed antibodies to IdeS that persist for some months and then decline, the importance of which if unknown. In addition mild and reversible proteinuria has been detected in healthy subjects treated with IdeS.

It has been demonstrated that IdeS at therapeutic levels can cleave antibody-based drugs and IVIG, which are administered as part of treatment of transplant patients in this study. These therapies are administered at appropriate intervals after IdeS therapy in which the plasma level of IdeS is expected to have minimal or no effect on these drugs.

Since IdeS effectively removes the IgG pool, there may be an increased risk of infection. In order to minimise the risk for bacterial infections all patients treated with IdeS will receive prophylactic antibiotics until IgG levels are back to acceptable levels. Patients will be screened for viruses (Hepatitis B, C and HIV, CMV, EBV and BKV) and on-going infections and patients having clinical signs of on-going infections at the time of

enrolment will not be included in the study. Patients will be hospitalised for at least 7 days and closely monitored for infections and after that instructed to contact the principal investigator immediately if they have any sign of infection. There will be a physician specialized in infectious diseases available for medical advice in case of a patient showing signs of infection. In case of infection in a patient with low IgG plasma levels, intravenous immunoglobulin may be indicated.

The doses of 0.25 mg/kg and 0.5 mg/kg BW are well covered by the NOAEL [redacted] patients in the completed phase II study in Sweden were exposed to a total dose of 0.5 mg/kg BW. [redacted]

For this patient category the risk/possibility of becoming pregnant is extremely small due to their disease state. However, as an extra safety measure, the requirement for highly effective contraception is part of the inclusion criteria for this study. A pregnancy test will be done at screening and pre-dose IdeS for all women of childbearing potential.

Patients will be closely monitored for all adverse events and the second dose will only be given if the investigator considers it safe after evaluating adverse events and over all patient status after the first IdeS dose. The principal investigator must make sure that sufficient facilities and procedures are available to handle emergency situations during the study. The study sites have extended experience in phase I/II studies within transplantation and graft rejection treatment as well as handling biological drugs. The sites have adequate procedures in place to handle unexpected adverse reactions.

As described above in section 2.4 a phase II study in asymptomatic TTP patients, enrollment was stopped after two subjects showing signs of serum sickness. Previously, 27 patients without concomitant immunosuppression medications have been treated with IdeS and none of them showed signs of serum sickness. The sponsor cannot rule out that the underlying disease was a factor in the development of serum sickness in these two subjects. Based on all available safety information from non-clinical and clinical studies, the overall benefit/risk profile of IdeS still appears favorable.

3 Study objectives

3.1 Primary objective

- To assess the IdeS efficacy in creating a negative crossmatch test

3.2 Secondary objectives

- To determine DSA levels at multiple times (pre-dose, 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180) post IdeS treatment

- To determine time to creating a negative CDC crossmatch test

- To determine time to creating a negative FACS crossmatch test
- To evaluate safety parameters (adverse events, clinical laboratory tests, vital signs and ECGs) following IdeS treatment up to day 180
- To monitor kidney function after IdeS treatment as assessed by, filtration (eGFR), creatinine and proteinuria
- To establish the pharmacokinetic (PK) profile of IdeS
- To establish the Pharmacodynamic (PD) profile of IdeS (cleavage and recovery of IgG)
- To establish the immunogenicity profile of IdeS (ADA)

3.3 Primary endpoint

- Efficacy defined as IdeS ability to create a negative crossmatch test within 24 hours after IdeS dosing

3.4 Secondary endpoints

- DSA levels at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post IdeS treatment
- Time to creating a negative CDC crossmatch test
- Time to creating a negative FACS crossmatch test
- Safety parameters (adverse events, clinical laboratory tests, vital signs and ECGs)
- Kidney function after IdeS treatment assessed by, filtration (eGFR), creatinine and proteinuria up to 180 days post treatment
- Pharmacokinetic (PK) profile of IdeS up to day 14
- Pharmacodynamic (PD) profile of IdeS (cleavage and recovery of IgG) up to day 180 post IdeS
- Immunogenicity profile of IdeS by measuring anti-drug antibodies (ADA)

4 Study design

4.1 Overall study design and flowcharts

This is a phase II, open label exploratory study to assess the IdeS efficacy in creating a negative crossmatch test (CXM) in a total of 15-20 patients (7-13 with living donors and 7-13 with a deceased donor) who exhibit DSAs and have a positive crossmatch test to their available live or deceased donors. The first 3 patients in this study will receive a kidney from a deceased donor. The study will primarily examine the efficacy of IdeS in creating a negative CXM in these patients. Included patients will be treated with IdeS on day 0. If it is considered safe and the desired effect is not achieved (negative crossmatch) a second dose can be given within 2 days of the first infusion. In addition to IdeS patients

will be given high dose IVIg (2 g/kg BW, maximum of 140 g) on day 7 and anti CD20 (Rituximab) on day 9 as outlined in Figure 1. DSA levels will be monitored 2, 6, 24 and 48 hours and 7, 14, 21, 28, 64, 90, 120 and 180 days after the last IdeS dosing. Safety, including kidney function will be monitored at multiple time points up to 180 days after treatment. Pharmacokinetics, pharmacodynamics and anti-drug antibodies will be followed. For details on assessments see flow chart in Table 1. Patients who are not eligible for transplantation after IdeS treatment will not be transplanted and thus will not receive any induction therapy or immunosuppression. All patients who receive IdeS will also be asked to remain in the study and be followed up according to the study protocol even if they are not transplanted. In addition, patients who lose their graft during the course of the study will remain in the study and be followed up according to the study protocol.

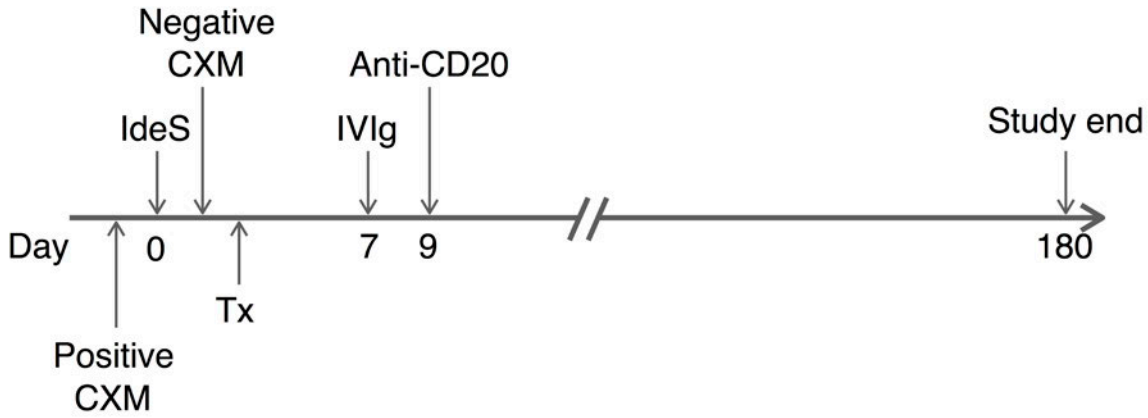


Figure 1. Overall treatment schedule. CXM=crossmatch test, Tx=transplantation.

Table 1. Study flow chart: Screening to Day 180 after IdeS infusion

Study visit	1	2	3	4	5	6	7	8	9	10	11	12
Day	Screening -28-0	0-2	3-6	7	9	14	21	28	64	90	120	180
Assessment /Time window				+/- 1 d	+ 2 d	+/- 2 d	+/- 3 d	+/- 3 d	+/-7 d	+/-7 d	+/-14 d	+/-14 d
Informed Consent	X											
Demographics and medical/surgical history	X	X										
Inclusion/exclusion	X	X										
Physical examination	X											X
Weight	X	X				X						
Height	X											
Vital signs	X	X		X[c]				X		X	X	X
Body temperature	X	X										
CDC and FACS	X	X[a]										
DSAs	X	X		X[c]		X	X	X	X	X	X	X
Pregnancy test (serum)	X	X[h]										X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
ECG	X											X
Drug infusion		X										
Safety laboratory	X	X		X[c]		X	X	X	X	X	X	X
HIV and hepatitis	X											
P-creatinin, (eGFR)		X		X[c]		X	X	X	X	X	X	X
Proteinuria						X		X	X	X	X	X
U-protein electrophoresis		X[d]	X[d]	X[d]	X[d]							
PK sampling		X	X[f]	X[c]	X[g]	X						
PD sampling (IgG)		X		X[b]	X[g]	X	X	X	X			X
ImmunoCAP IgG (ADA)		X		X[b]		X	X	X	X	X	X	X
ImmunoCAP IgE	X											
Virus screen (BK-, EBV, CMV-PCR)	X					X		X	X	X		
Methylprednisolone Loratadine		X										
Rituximab					X[e]							
High dose IVIg				X[i]								
Kidney biopsy		X[j]										X

Check concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

Day 0 is the IdeS dosing day
[a]For LD patients the screening crossmatch test must be repeated pre-dose
[b]PD (IgG) and ADA samples will be taken pre- and post-dose IVIg on day 7
[c]This assessment will be done prior to IVIg infusion
[d]24 hour urine collections for protein electrophoresis will be performed daily until day 9
[e]Rituximab can be given day 9-11 if a longer time window is required for practical reasons
[f]PK will be drawn at 96 hours ±4h
[g]PD (IgG) and PK samples will be drawn prior to Rituximab infusion on day 9-11
[h]If a female patient has been hospitalized between screening visit and visit 2, a pregnancy test at screening visit will suffice and a pregnancy test at visit 2 is not required
[i]If deemed necessary by the investigator this dose may be split into two doses administered over days 6-8
[j]a biopsy will be performed on the donor graft prior to transplantation (for DD transplantations)

Table 2. Study flow chart:0/Pre-dose to 48 h after IdeS infusion. Time-points after dosing (0) relates to START of infusion.

Study visit	2					
Day	0/ Pre-dose	Dosing	2h	6h	24h	48 h
Assessment /Time window	≤60 min	0	+/- 15 min	+/- 30 min	+/- 2h	+/- 2h
Demographics and medical/surgical history	X					
Inclusion/exclusion criteria	X					
Weight	X					
Vital signs (BP & pulse respiratory frequency)	X		X	X	X	X
Body temperature	X		X	X	X	X
CDC and FACS CXM	X		X	X	X	
DSAs	X		X	X	X	X
Pregnancy test (serum)	X[c]					
Adverse events	X	X	X	X	X	X
Drug infusion		X				
Safety laboratory tests	X		X	X	X	X
P-creatinin, eGFR					X	X
U-protein electrophoresis					X[b]	X[b]
PK sampling	X		X	X	X	X
PD sampling (IgG)	X		X	X	X	X
ImmunoCAP IgG (ADA)	X					X
Methylprednisolone Loratadine[a]	X					
Check concomitant medication	X		X	X	X	X

Assessments will be repeated from the pre-dose timepoint if a second dose of IdeS is given.

[a]Pre-medication with methylprednisolone and loratadine will be repeated before the second IdeS dose

[b]24 hour urine collections for protein electrophoresis will be performed daily until day 9.
[c]If a female patient has been hospitalized between screening visit and visit 2 a pregnancy test at screening visit will suffice and a pregnancy test at visit 2 is not required

4.2 Decision criteria for dose escalation, inclusion of living donor transplants and study termination

The first three patients enrolled in the study will receive a kidney from a deceased donor. The starting dose in this study is 0.25 mg/kg BW given once or twice, with the possibility of a higher dose group of less than or equal to 0.5 mg/kg BW. The decision to escalate the dose and to include living donor transplants will be done after evaluation of the efficacy and safety. Efficacy will be evaluated with regards to IdeS' ability to create a negative crossmatch test in the first three patients within a timeframe suitable for transplantation. If a single dose of IdeS fails to produce a negative crossmatch in any of these patients a dose escalation will be justified based on efficacy. Before proceeding to the next dose group, a data and safety monitoring board (DSMB) will review available safety and tolerability data (see Table 3). Safety data collected up to and including the day 28 visit for the first three patients will be evaluated. The safety data will be compiled to a DSMB package and sent to all DSMB members before the DSMB meeting. The DSMB package and recommendation will also be sent to FDA before proceeding to a higher dose level and the inclusion of living donor transplants. [redacted] In addition, the DSMB will continuously monitor the study safety throughout the study. If an unacceptable number of serious side effects or graft losses are observed the DSMB can recommend premature termination of the study.

Table 3. The following safety variables will be contained in the DSMB safety data package

Clinical chemistry	**Coagulation**	**Clinical safety data**
P-IgG	PK (INR)	Adverse events
P-ALP	P-APTT	Vital signs
P-ALT		eGFR
P-AST		
P-Bilirubin, total	**Hematology**	**Urine**
P-Glucose	B-Hemoglobin	Protein electrophoresis
P-Sodium	B-Differential analysis of leucocytes	Protein spot
P-CRP	B-Thrombocytes	
P-Albumin		
P-Urea		
P-Triglycerides		
P-Creatinine		
P-Creatinine phosphokinase		

4.3 Data safety monitoring board

The Data and Safety Monitoring Board (DSMB) will monitor participant safety, data quality and evaluate the progress of the study. The constitution, activities and reports of the DSMB shall be governed by the FDA's "Guidance for Clinical Study Sponsors: Establishment and Operation of Clinical Study Data Monitoring Committees" (detailed in a study specific DSMB charter). Both documents will be distributed to all DSMB members.

The DSMB will be an external group of experts, independent of the sponsor and consist of at least three physicians of which one will be the DSMB chairman.

5 Patient selection criteria

5.1 Screening

To be eligible for the study patients have to meet all inclusion criteria and no exclusion criteria. If the patient has been screened and meets all inclusion and no exclusion criteria and does not receive the dose within 28 days, for reasons such as the patient did not receive an organ offer within the time frame etc., the patient may be rescreened. No other rescreening is allowed. The re-screening procedure will be the same as the previous screening visit with the exception for the virology tests which do not have to be repeated if not more than 6 months old. Medical history and concomitant medication will be updated if applicable. Re-screened patients will keep the original screening number.

5.2 Inclusion criteria

1. Male or female age 18-70 years at the time of screening
2. Patients on the kidney transplant waitlist who have previously undergone desensitization unsuccessfully or in whom effective desensitization will be highly unlikely. The breadth and strength of sensitization will predict an extremely low likelihood of successful desensitization or kidney paired donation.
3. Patients with a live or deceased donor with a positive crossmatch test.
4. Patient must be able to understand and sign the informed consent.

5.3 Exclusion criteria

1. Previous treatment with IdeS
2. Previous high dose IVIg treatment (2 g/kg BW) within 28 days prior to IdeS treatment.
3. Lactating or pregnant females
4. Women of child-bearing age who are not willing or able to practice FDA-approved forms of contraception.
5. HIV-positive patients
6. Patients with clinical signs of HBV or HCV infection
7. Patients with active tuberculosis
8. A significantly abnormal general serum screening lab result according to the investigator's judgement. Hgb cannot be < 6.0 g/dL. Laboratory safety results from within 3 days before screening can be used
9. Severe other conditions requiring treatment and close monitoring, e.g. cardiac failure ≥ NYHA (New York Heart Association) grade 3, unstable coronary disease or oxygen dependent COPD
10. Individuals deemed unable to comply with the protocol
11. Patients with clinical signs of CMV or EBV infection
12. Patients with a history of major thrombotic events, patients with active peripheral vascular disease or patients with proven hypercoagulable conditions
13. Patients should not have received investigational drugs within 4 half-lives (or similar)

14. Known allergy/sensitivity to IdeS infusions
15. Patients who have a live donor and test positive for ImmunoCAP anti-IdeS IgE

5.4 Withdrawal criteria

5.4.1 Criteria for discontinuation from the study

Patients may be discontinued from study treatment and assessments at any time. The patient is free to discontinue his/her participation in the study at any time and for any reason, without prejudice to further treatment. If a patient is withdrawn from the study by the investigator due to adverse events he/she will not be replaced. Patients who withdraw for reasons other than adverse events may be replaced.

The study may be stopped prematurely if:

1. DSMB recommend that the study should be terminated

2. Findings that, at the discretion of Principal Investigator(s) and/or Sponsor, indicate that further dosing should be stopped

5.4.2 Procedures for discontinuation of a patient from the study

A patient who discontinues after study drug administration will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, he/she will be seen and assessed by an investigator(s). Adverse events will be followed. If possible, patients who discontinue from the study before completion should undergo the assessments and procedures scheduled for the end of study follow up visit. Patients who, for a medical reason, cannot comply with the protocol procedures will be followed by best procedure to retrieve safety and efficacy data.

If the study is prematurely terminated, the Sponsor will promptly inform the investigators and the regulatory authorities of the termination and the reason(s) for the termination. The IRBs/IECs will also be promptly informed and provided the reason(s) for the termination either by Sponsor or investigators, depending on local requirements. All patients, those in the study at the time for termination as well as those that have completed the study, will be informed about the study termination and the reason(s) for it by their respective investigator.

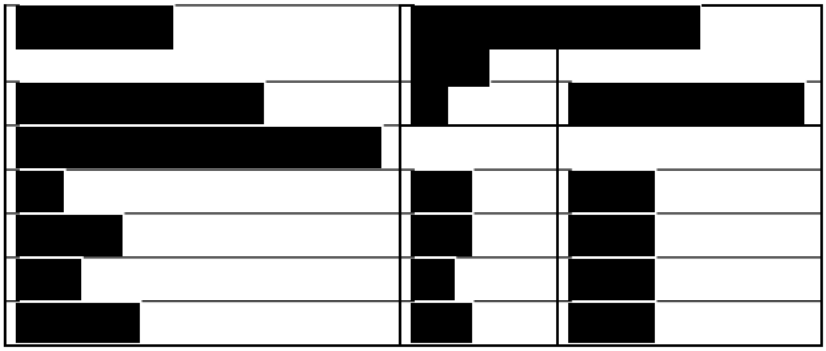
6 Study conduct

6.1 Study treatment

6.1.1 IdeS

IdeS is a clear colorless liquid. It is formulated at 10 g/L in PBS and intended for intravenous administration after dilution. Refer to Table 4 for composition.

[redacted]



6.1.2 Storage and handling

All patients will receive treatment with IdeS. IdeS will be supplied to the hospital pharmacy [redacted] in 15 mL vials, each containing 7 mL IdeS packed into cartons containing 10 vials each. Vials should be kept dark at – 20°C. IdeS infusion solution will be prepared at the study unit. Administration will be performed using an infusion syringe or infusion bag with a filter containing infusion set and an infusion pump. Details on preparation, labeling and administration of IdeS are described in the pharmacy manual.

6.1.3 Drug accountability and compliance check

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF. Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, date and time of administration of the investigational product will be checked by the monitor at monitoring visits.

It is the principal investigators/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

1. Deliveries are correctly received by a responsible person (e.g. pharmacist or designated study personnel)

2. Deliveries are recorded

3. Study treatments are handled and stored safely and properly

4. The study drug provided for this study will be used only as directed in the study protocol

5. The study personnel will account for all drugs dispensed and returned. Any discrepancies must be documented, investigated and appropriately resolved

6. At the end of the study, the pharmacy personnel will account for all unused drugs and for appropriate destruction/return of all unused drugs to the sponsor for destruction. Certificates of delivery, destruction and return must be signed by a study team member

6.1.4 Administration of investigational drug

Intravenous IdeS will be administered over at least 15 minutes. The first 3 patients will receive one dose of 0.25 mg/kg BW IdeS on study day 0. If it is considered safe and the desired effect is not achieved (negative crossmatch test) after the first dose, an additional IdeS infusion can be given within 2 days of the first infusion. The dose schedule may be increased to 0.5 mg/kg BW given once or twice after the first 3 patients have been tested. The decision to escalate the dose will be done after evaluation of safety and efficacy as described in section 4.2.

6.1.5 Desensitization protocol

In addition to treatment with IdeS, patients will be treated with high dose IVIg 10% solution 2 g/kg BW (max 140g for >70kg) 7 days after IdeS treatment and 1 g rituximab (anti-CD20) 9 (-11) days after IdeS treatment. If deemed necessary by the investigator the IVIg dose may be split into two doses administered over days 6-8.

6.1.6 Premedication

Patients will receive premedication with glucocorticoids (methylprednisolone, 250 mg intravenously) and antihistamines (loratadine 10 mg orally or an equipotent antihistamine) before each IdeS infusion.

6.1.7 Prophylactic antibiotic

All patients will receive prophylactic antibiotics or sulpha according to clinical practice at each site from the start of IdeS treatment until serum IgG level is back within normal range.

6.1.8 Induction therapy

Induction therapy can be used if indicated. Sites are allowed to use either ATGAM (anti thymocyte globuline derived from horse) or Alemtuzumab (anti-CD52 antibody). Rabbit ATG cannot be used since it is efficiently cleaved by IdeS. Alemtuzumab can be given 4 days after IdeS at the earliest, based on limited experience. If alemtuzumab is used as induction therapy on day 4, pulse steroid treatment can be used up to day 4 to prevent T-cell mediated rejection.

6.1.9 Immunosuppressing agents

Patients will be treated with immunosuppressing agents according to clinical practice at each study center.

6.1.10 Other concomitant medication

Supportive therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. All concomitant medication, including premedication and prophylactic antibiotics must be recorded on the concomitant medication page in the CRF.

6.2 Study procedures described per visit

Visit 1 (Screening day -28 to day 0)

At the screening visit each subject will be informed about the study and after signing the informed consent form assessments for eligibility will commence. Eligibility evaluation, collection of concomitant medication, demographic data (age, sex, race, height, weight and BMI) and medical and surgical history is performed. A full physical examination, height and weight measurements, vital signs including resting blood pressure, pulse, respiratory

frequency, 12-lead resting ECG and body temperature is done. Additionally blood sampling for serology (HIV, hepatitis, BK, EBV and CMV), pregnancy test and clinical chemistry, hematology as well as blood samples for analysis of DSAs, CDC- and FACS-CXM and anti-IdeS IgE antibody analysis (ImmunoCAP) will be collected.

Visit 2 (days 0-2)
Patients found eligible at the screening visit will be included in the study. At visit 2 the eligibility check will be repeated within 60 min from IdeS dosing. A pregnancy test will be taken. If a female patient has been hospitalized between screening visit and visit 2, a pregnancy test at screening visit will suffice and a pregnancy test at visit 2 is not required. In addition methylprednisolone and loratadine will be administered predose to prevent infusion reactions. Vital signs, body temperature, safety laboratory sampling, pharmacokinetic and pharmacodynamics sampling will be performed pre-dose, 2 h, 6 h, 24 h and 48 h post IdeS infusion. In addition blood sampling for DSAs will be drawn at pre-dose, 2 h, 6 h, 24 and 48 h. Blood sampling for CDC- and FACS-CXM will be done at pre-dose, 2 h, 6 h, and 24 h. Any effort should be made to obtain crossmatch test for all time-points indicated in the study flowcharts. If this is not possible due to logistics on specific sites, the sponsor can allow a smaller number of time-points to be evaluated. However, as a minimum one crossmatch test pre-dose and one post-dose IdeS must be performed to allow evaluation of the primary endpoint. ADA will be sampled at pre-dose and 48 h post IdeS infusion. P-creatinine will be measured at 24 h and 48 h post IdeS infusion and eGFR will be calculated. Repeat 24 hour urine collections will be performed day 1-9 for urine protein electrophoresis analysis. AEs and concomitant medication will be recorded in the CRF throughout the visit. AEs that occur in the time period prior to administration of the study drug should be recorded as part of the patient's medical history but will not be considered a treatment emergent adverse event (TEAE) unless directly related to study procedures (e.g. hematoma secondary to laboratory testing) or it meets the definition of an SAE. A kidney biopsy on the donor kidney will be performed in deceased donor patients.

Visit 3 (day 3-6)
Twenty-four- (24)-hour urine collections will be performed daily, day 1-9, for urine protein electrophoresis analysis. AE and concomitant medication will be assessed. PK will be drawn at 96 hours ±4h.

Visit 4 (day 7)
At visit 4 high dose IVIg (2 g/kg BW) will be administered. Prior to IVIg dosing the following assessments are made: vital signs, blood sampling for analysis DSAs, safetylaboratory parameters, PK, PD, ADA and P-creatinine. The eGFR will be calculated. Additional samples for PD and ADA will be drawn after the IVIg infusion. If the IVIg dose is split into two doses given over two days the sampling will be performed before and after the first dosing. Repeat 24 hour urine collections will be performed day 1-9 for urine protein electrophoresis analysis. AE and concomitant medication will be assessed.

Visit 5 (Day 9)
At visit 5 the patient will be dosed with rituximab. In addition a blood sample for PK and PD analysis will be drawn. Repeat 24 hour urine collections will be performed day 1-9 for urine protein electrophoresis analysis. AE and concomitant medication will be assessed.

Visit 6 (day 14)
At visit 6 the patient will be assessed for body weight, AEs and concomitant medication. Blood sampling for analysis of DSAs, safety laboratory tests, P-creatinine/eGFR, PK, PD, ADA and virus screen for BK, EBV and CMV will be drawn. Urine will be obtained for analysis of proteinuria.

Visit 7 (day 21)
Blood sampling for assessment of DSAs, safety laboratory parameters, PD, ADA and P-creatinine/eGFR will be drawn. In addition AEs and concomitant medication will be assessed.**Visits 8 and 9 (day 28 and 64)**

At visits 8 and 9 the patient will be assessed for AEs and concomitant medication. Blood sampling for analysis of DSAs, safety laboratory tests, PD, ADA, P-creatinine/eGFR and virus screen for BK, EBV and CMV. Urine will be obtained for assessment of proteinuria. At visit 8 vital signs will also be assessed.

Visits 10 and 11 (day 90 and 120)
At visits 10 and 11 the patient will be assessed for vital signs, AEs and concomitant medication. Blood sampling for analysis of DSAs, safety laboratory tests, ADA and P-creatinine/eGFR. At visit 9 a blood sample for virus screen (BK, EBV and CMV) will also be drawn. Urine will be obtained for assessment of proteinuria.

Visit 12 (day 180, end of study)
A follow-up visit will be performed 180 +/- 14 days following IdeS infusion. This will be considered the end of study for the patient. At this visit the patient will be assessed for vital signs, ECG, AEs and concomitant medication. Blood sampling for analysis of DSAs, pregnancy test, safety laboratory tests, P-creatinine/eGFR, PD and ADA will be performed and e GFR calculated. Urine will be obtained for assessment of proteinuria and a physical examination will be performed. A kidney biopsy will be performed to assess kidney status.

6.3 Safety reporting
It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

6.3.1 Definition of adverse events
An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Relationship to the study drug will be deemed as not related, unlikely, possible or probable. An undesirable medical condition can be symptoms (e.g. nausea and chest pain), signs (e.g. tachycardia and enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings and electrocardiograms).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Pre-treatment adverse event:

A pre-treatment adverse event is any untoward medical occurrence arising or observed between signing of informed consent and the first administration of the IMP.

Treatment emergent adverse event:

A treatment emergent adverse event is any AE occurring after the administration of the IMP and within the time of the follow up period or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after administration of the IMP and within the time of the follow up period.

6.3.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE or suspected adverse reaction (SAR) that is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization. Regular dialysis treatment in or outside hospital is not included
- Hospitalization for transplantation is not considered an SAE
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Life-threatening event: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

Hospitalization for inpatient hospitalization or prolongation of existing hospitalization. In this study the following will not qualify as an SAE. Elective treatment of a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization for study drug dosing and observation as required by protocol is not considered an SAE. Admittance to an emergency room for observation without being

admitted to the hospital may be considered to be an AE but is not considered as an SAE. However, complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Regular dialysis treatment in or outside hospital is not considered an AE or SAE.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyskrasias or convulsions that do not result in inpatient hospitalization, or the development or drug dependency or drug abuse.

SAEs should be followed until the event resolves, stabilizes, or returns to baseline. If the patient is discontinued from the study prior to resolution/stabilization of the SAE, then the patient will be followed as part of the SAE/pharmacovigilance system.

6.3.3 Recording of adverse events

In clinical studies, an AE/SAE can occur at any time after signing of the informed consent until the end of the study, including run-in or washout periods, even if no study treatment has been administered, e.g. and AE can be related to a procedure in the protocol.

AEs will therefore be collected on the AE CRF from the time of signing of the informed consent and throughout the study period including the follow-up period. However, AEs that occur in the time period between informed consent and administration of the trial drug should be recorded as part of the patient's medical history, but will not be considered a treatment emergent adverse event (TEAE) unless directly related to study procedures (e.g. hematoma secondary to laboratory testing) or it meets the definition of an SAE.

6.3.4 Variables

The following variables will be recorded in the CRF for each AE; description of the AE, the date and time (if applicable) when the AE started and stopped, intensity according to Common Toxicity Criteria grade (CTCAE v.4.03), seriousness of the AE, causality rating, action taken with regard to investigational product, if AE caused patient to discontinue the study and outcome.

For each reported AE the investigator will assess a causal assessment of the relationship of the event to study procedures and/or IdeS using the following criteria.

- **Unrelated;** applicable to an AE that occurs when the subject was not exposed to study treatment or another cause is obvious:
    - The AE does not meet the above criteria
    - There is sufficient information that the etiology of the AE is not related to the study drug
- **Unlikely to be related**: applicable to an AE that meets the following criteria:
    - Does not follow a reasonable temporal sequence from dosing of IdeS

  - May readily have been produced by the patient's clinical state, environmental, or toxic factors, or other therapy administered to the patient

- **Possibly related:** applicable to AEs where connection with IdeS dosing appears unlikely but cannot be ruled out. Applicable to AEs where:
  - It follows a reasonable temporal sequence following dosing of IdeS
  - It follows a known pattern of response to dosing of IdeS (based on animal studies)
- **Probably related:** applicable to AEs that are considered, with a high degree of certainty, to be related to IdeS. Applicable to AEs where:
  - It follows a reasonable temporal sequence from dosing of IdeS
  - It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy
  - It follow a known pattern of response to IdeS (based on animal data)

For SAEs, causal relationship will also be assessed for any study procedure.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: Have you had any health problems since you were last asked? or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms for example: congestive heart failure rather than low ejection fraction, rales and dyspnea. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom not part of the diagnosis will be recorded separately, for example: congestive heart failure and conjunctivitis.

6.3.6 Adverse Events based on examinations and tests

If laboratory values are judged as clinically significant and/or a treatment has been given for a medical event it will be captured as AEs and if SAE criteria is fulfilled they will also be an SAE.

If vital signs give clinical signs/symptoms and/or require a treatment then they will be captured as AEs and if SAE criteria is fulfilled they will also be SAEs.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE and if SAE criteria is fulfilled it will also be an SAE.

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g. anemia *versus* low hemoglobin value).

6.3.7 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator until stabilization, for as long as medically indicated or the overall clinical outcome of the patient is known, unless the patient is documented as "lost to follow-up". All SAEs should be followed until the event resolves, stabilizes, or returns to baseline. If the patient is discontinued from the study prior to resolution/stabilization of the SAE, then the patient will be followed as part of the SAE/pharmacovigilance system.

Reasonable attempts to obtain this information must be made and documented. Sponsor retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.8 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF. SAEs will be recorded from the time of admission to the clinic on day 0.

All Serious Adverse Events (SAE) must be reported, whether or not considered related to the study drug, on a separate SAE Report Form. All SAEs will be recorded in the Case Report Form. An assigned CRO will be responsible for reporting all SAEs to regulatory authorities and ethics committees in accordance with ICH Good Clinical Practice and local regulations. As soon as the Investigator is aware of a potential SAE he/she should contact the safety CRO appointed by the sponsor by fax or e-mail and in any case *no later than 24 hours* after the knowledge of such a case. At the time of initial reporting the investigator must provide as a minimum requirement, patient number, birth date, nature of the SAE and a preliminary assessment of causality.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform the sponsor and monitor of any follow-up information on a previously reported SAE immediately but no later than within 24 hours of when he or she becomes aware of it. The monitor or sponsor will advise the investigator/study site personnel how to proceed.

The SAE reporting procedures are detailed in the study specific Safety Management Plan. This plan is an agreement between the sponsor and [redacted].

6.3.9 Reporting of suspected unexpected serious adverse events (SUSARs)

A suspected serious adverse reaction is any serious adverse event for which there is a reasonable possibility that the investigational product caused the adverse event. A serious adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

SUSAR MedWatch reports **WILL NOT** be filled out for any prolonged hospital admissions or readmissions that are related to expected complications of the patients' primary

disease (CKD). For example, prolonged admissions for dialysis or readmission for fluid overload as a consequence of CKD since this this is an expected complication of the patients' disease state and not related to study drug. These events will be adjudicated by the PI. Otherwise, all SUSAR MedWatch reports will be submitted to the IRB, study sponsor and FDA.

SUSARs with an outcome of death or are life threatening must be reported to the relevant regulatory authorities within 7 calendar days, all other SUSARs must be submitted within 15 calendar days. The SUSAR reporting procedures are detailed in the study specific Safety Management Plan. This plan is an agreement between the sponsor, and [redacted] will notify the appropriate regulatory agency(ies) of any SUSARs on an expedited basis and in accordance with applicable regulations. Sponsor will notify all participating site Investigators. In addition the sponsor is responsible for informing all investigators in all ongoing studies involving IdeS about all SUSARs.

It is the responsibility of the site Investigator to promptly notify the IRB and other appropriate institutional regulatory bodies of all unexpected serious adverse reactions involving risk to human subjects as per their applicable requirements.

6.3.10 Procedures in case of pregnancy

Pregnancy is an exclusion criteria and a pregnancy test is performed twice before the study drug is infused; at the screening visit and prior to infusion of the IMP. A pregnancy test is also performed at the last study visit.

If a patient becomes pregnant during the follow up phase of the study, the patient will continue in the study according to study protocol, if possible. A Pregnancy Report Form must be sent by Principal Investigator to sponsor (or designee) at the latest within 24 hours of learning of the pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be followed up on the Pregnancy Report Form even after the patient has completed or discontinued the study. Sponsor (or designee) will follow up on pregnancy outcome 4 weeks after the projected due date.

Pregnancy itself is not considered an AE or SAE, but any event occurring during pregnancy that meets serious criteria must be reported to sponsor and will be handled as a SAE. Spontaneous abortions, congenital abnormalities/birth defects are always considered to be a SAEs and will be reported and followed up in accordance with other SAEs. Any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the study drug by the investigator will be reported to the sponsor (or designee).

6.4 Study assessments

6.4.1 Recording of data

The principal investigator will provide the sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to sponsor in the CRF and in all required reports. The study assessments are described in the sections below and the timing of these assessments are detailed in the study flow charts (Table 1 and Table 2). It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. Pre-dose assessments may be performed up to 60 minutes prior to dosing.

The timing priority order at a particular time point is:

1. Blood samples for PK and PD
2. Samples for DSA, CDC and FACS CXM
3. Vital signs
4. Safety laboratory samples
5. Additional laboratory samples

Pre-dose assessments may be performed up to 60 minutes prior to dosing.

6.4.2 Screening and demography procedures

Each patient will undergo a screening between 28 and 0 days prior to admission.

6.4.3 Patient care after end of study

After study completion, all study patients will be followed up regularly and interdisciplinary (by nephrologist and transplant surgeons) according to the center's follow-up routines for transplanted patients. The frequencies of outpatient visits will be adjusted individually to the state of patient health and transplant function.

6.5 Laboratory efficacy assessments and evaluation of primary endpoint

Timing of laboratory efficacy parameters (CDC and FACS crossmatch tests and DSA analysis) is given in the study flow charts 1 and 2 (Table 1 and Table 2). The date and time of collection will be recorded on the laboratory requisition form and in the CRF. Samples will be labelled, stored and shipped as detailed in the laboratory manual.

6.5.1 Analysis of crossmatch tests

Evaluation of the primary endpoint will be analyzed using the crossmatch test. CDC and flow cytometry (FACS) crossmatch test will be performed at the time points indicated in the study flowcharts (Table 1 and Table 2).

6.5.2 Determination donor specific antibodies (DSAs) and complement fixation

Samples for determination of DSAs will be analyzed in immunoglobulin (Ig) G single antigen solid-phase immunoassay (SA-SPA) for antibodies to HLA class I and class II. The assay allows determination of the mean fluorescence intensity (MFI) of antibodies in patient serum reacting to an array of individual HLA immobilized to beads. In addition, anti-HLA antibodies with complement fixation ability by detection of C1q will be analyzed in a SAB assay. Determination of DSAs will be performed at a central laboratory.

6.6 Clinical safety assessments

6.6.1 Physical examination

For timing of individual examinations refer to the study flow chart 1. A complete physical examination will be performed at screening and day 180 and include an assessment of the following: general appearance, head and neck, lymph nodes, abdomen, musculo-skeletal, cardiovascular, respiratory and gross neurological examination.

6.6.2 Height and weight

Regarding the timing for assessments of height and weight refer to the study flow charts 1 and 2 (Table 1 and Table 2). Measurements should be taken without shoes. Body mass index will be calculated from the height and weight. The timing of individual measurements is indicated in the study flow chart (Table 1 and Table 2).

6.6.3 ECG

ECG 12-lead will be taken after 10 minutes rest at screening and on day 180.

6.6.4 Vital signs

Vital signs, blood pressure, pulse and respiratory frequency will be measured as outlined in the study flow charts 1 and 2 (Table 1 and Table 2). At dosing, blood pressure and pulse will be recorded pre-dose, 2, 6, 24 and 48 hours post-dose. In addition, the patients will be monitored with oximetry during the infusion and the following 24 hours.

6.6.5 Other safety assessments

Body temperature will be measured as specified in the study flow charts at screening and study visit 2 (Table 1 and Table 2). At visit 2/dosing, body temperature will be recorded pre-dose, 2, 6, 24 and 48 hours post-dose.

6.6.6 Kidney biopsy

A kidney biopsy will be performed at visit 2 on deceased donor kidneys and at visit 12 on living and deceased donor kidneys (Table 1). If standard of care kidney biopsies are performed for any reason, e.g. suspected rejections, a de-identified copy of the kidney biopsy report will be collected.

6.7 Laboratory safety assessments

Timing of laboratory efficacy parameters is given in the study flow charts 1 and 2 (Table 1 and Table 2). The date and time of collection will be recorded on the laboratory requisition form and in the CRF. Samples will be labelled, stored and shipped as detailed in the laboratory manual.

6.7.1 Clinical chemistry, hematology, coagulation and virology

The following blood samples for determination of clinical chemistry, hematology, coagulation and total IgG in plasma will be taken:

Table 5. Clinical chemistry, hematology, coagulation and virology

P-IgG, total	P-PK(INR)
P-ALP	P-APTt
P-ALT	**Hematology**
P-AST	B-Hemoglobin
P-Bilirubin, total	B-Differential analysis of leucocytes
P-Glucose	B-Thrombocytes

P-Sodium	
P-CRP	***Virology**
P-Albumin	B-HIV
P-Urea	B-Hepatitis B surface antigen
P-Triglycerides	B-Hepatitis C antibodies
P-Creatinine	
P-Creatinine phosphokinase	

*Virology samples for HIV and hepatitis will be taken at screening. Test results not older than 6 months can be used.

Additional laboratory variables can be performed if judged appropriate by the investigator.

6.7.2 Viral surveillance

Samples will be taken in all patients as outlined in the study flow chart for BK-, EBV and CMV-PCR for early diagnosis of viral activations/reactivations and early treatment, respectively. Extra samples should be taken if indicated. At screening, results not older than 6 months can be used.

6.7.3 Pregnancy test

Serum B-HCG will be determined at screening, pre-dose and on day 180 using validated standard methods

6.7.4 Determination of kidney function

Evaluation of kidney function will be done based on P-creatinine analysis and calculation of filtration rate (eGFR). Proteinuria tests (spot urine/creatinine) will be performed at the time points indicated in the study flowcharts. In addition 24 hour urine collections for electrophoresis analysis of proteins will be performed daily starting after transplantation and up to day 9. The amount of urine per 24 hour will be measured and two samples will be taken from the collection. One sample will be analyzed at the hospital laboratory and one sample will be stored and analyzed later if deemed necessary.

6.8 Pharmacokinetics and pharmacodynamics

6.8.1 Determination of drug concentration in biological samples

Samples for determination of IdeS levels in serum (PK) will be performed at the time points indicated in the study flowcharts and analyzed by [redacted]

6.8.2 Determination of IgG levels in serum

Samples for determination of IgG levels in serum (PD) will be performed at the time points indicated in the study flowcharts and analyzed by [redacted],

England. Samples will also be qualitatively analyzed by gel electrophoresis for IgG integrity by [redacted]

6.9 Anti-drug antibody analysis

Venous blood samples for determination of anti-drug antibodies (ADA) will be taken at the times presented in the study flow charts (Table 1 and Table 2) and analyzed by [redacted]. Determination of anti-IdeS IgG antibody concentrations in serum will be performed using anti-IdeS ImmunoCAP. At screening anti-IdeS IgE antibodies will be drawn. This will be used for research purpose for patients with deceased donors and as part of the eligibility criteria for patients with live donors.

The normal range of anti-IdeS IgG antibodies is <2-78 mg/L (HMed Doc. No. 2012-041). Patients who are not back within the normal ADA range at study completion will be asked to come back for a follow up ADA sampling at 12 months. The results from the 12 months ADA samples will be reported separately.

7 Biological sampling procedures

7.1 Handling, storage and destruction of biological samples

Samples will be used or disposed after analyses. A detailed description on sample collection, handling and shipping will be provided in a separate laboratory manual.

7.1.1 Pharmacokinetic, pharmacodynamic and anti-drug antibody samples

Samples will be disposed after the clinical study report has been finalized, unless retained. [redacted] Study samples may be stored on behalf of the sponsor for a maximum of four years after completion of the study report.

7.2 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The principal investigator keeps full traceability of collected biological samples from the patients while in storage at the center until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed.

Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

7.3 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analyzed and documented.

The principal investigator:

- will ensure that patient withdrawal of informed consent is notified immediately to sponsor

- will ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destructed and the action documented.

- will ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, sponsor will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

8 Ethical and regulatory requirements

8.1 Ethical conduct of the study

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

8.2 Patient data protection

The informed consent form (ICF) will incorporate wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An ethical review board must approve the final study protocol, including the final version of the ICF and any other written information to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable ethical review board, and to the study site staff. The opinion of the ethical review board must be given in writing.

Sponsor must approve any modifications to the ICF that are needed to meet local requirements.

No patient will be enrolled in the study, the final study protocol, and the final version of the informed consent form are approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by sponsor.

Sponsor will provide ethical review boards and principal investigators with safety updates/reports according to local requirements.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the ethical review board according to local regulations and guidelines.

8.4 Informed consent

The principal investigator(s) at the centers will:

- Ensure that the patient is given full and adequate oral and written/read information about the nature, purpose, possible risk and benefit of the study.
- Ensure that the patients are notified that they are free to discontinue the study at any time.
- Ensure that the patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Obtain and document the patient's signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed informed consent form is stored in the Investigator's Study File.
- Ensure a copy of the signed informed consent form is given to the patient.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the principal investigator and sponsor.

If there are any changes to the study protocol, then these changes will be documented in a study protocol amendment.

The substantial amendment(s) must be submitted to regulatory authorities and approved by the ethical review board before implementation. Local requirements must be followed for amended protocols and approval obtained if required. Sponsor will distribute any subsequent amendments and new versions of the protocol to the principal investigator.

If a protocol amendment requires a change to a center's informed consent form, sponsor and the center's ethical review board must approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the ethical review board.

8.6 Audits and inspections

The investigator(s)/institution will permit study-related monitoring, audits, IRB/IEC review, a regulatory inspection(s), providing direct access to source data/documents and give permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g., domestic and foreign regulatory authorities, sponsor´s monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements(s) to maintain the confidentiality of patients´ identities and sponsor´s proprietary information.

Authorized representatives of sponsor or a regulatory authority may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator will contact sponsor immediately if contacted by a regulatory agency about an inspection at the center.

8.7 Archiving of Investigator Study File and Study Master File

The investigator is responsible for maintaining all records, which enable the conduct of the study at the site to be fully understood, in compliance with ICH-GCP. The study documentation including all the relevant correspondence should be kept by the investigator for at least 10 years after the study report is final. No study documents may be destroyed without prior written agreement between the investigator and Hansa Medical AB. Should the investigator elect to assign the study documents to another party, or move them to another location, Hansa Medical AB must be notified.

Hansa Medical AB will archive the Study Master File in accordance with ICG-GCP and applicable regulatory requirements.

9 Study management

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of sponsor to visit the investigational study site for a site initiation visit to:

- Determine the adequacy of the facilities to give the sponsor information about whether the study centre has knowledge, enough time, a sufficient patient pool, and sufficient training to manage the study in a good way in terms of patient inclusion, patient handling, data and overall study management.

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of sponsor or its representatives. This will be documented in a site initiation visit report and in the clinical study agreement between sponsor and the investigator

Before the first patient is entered into the study, a sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilised.

The principal investigator will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, a sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the CRFs, and investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will be done using print outs of records for each patient.
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the patient.

The sponsor and the CRO will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.3 Source data

Refer to the source data document for location of source data.

9.4 Study agreements

The principal investigator must comply with all the terms, conditions, and obligations of the clinical study agreement for this study. In the event of any inconsistency between this clinical study protocol and the clinical study agreement, the clinical study protocol will prevail.

Agreements between sponsor and the principal investigator must be in place before any study-related procedures can take place, or patients be enrolled.

9.5 Insurance

All patients in the study are covered by an insurance held by Hansa Medical AB.

9.6 End of study

The end of the study is defined as "the last visit of the last patient".

10 Data handling

10.1 Case Report Forms

A CRF/eCRF will be provided by a CRO. If an eCRF is chosen the system should be validated in accordance with regulatory and system requirements.

10.2 Source data

The source data document will provide information on the location of source data.

10.3 Data management

All data management procedures will be outsourced to a CRO [redacted] Activities will be specified in a Data management Plan prepared by the CRO and reviewed and approved by the Sponsor. The plan will be issued before data collection begins and will describe all functions, processes and specifications for data collection, cleaning and validation.

For medical coding of AEs, medical history and concomitant medication the most recent versions of MedDRA and WHO Drug will be used. The coding will be outsourced to a third party. When all data has been processed, queries resolved, medical coding completed and any issues from review of protocol violations and data listings resolved, the data base will be locked and any further update will be denied.

11 Evaluation and calculation of pharmacokinetic and pharmacodynamics variables

11.1 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the serum concentration data for IdeS will be performed at the appointed CRO on behalf of sponsor. The actual sampling times will be used in the parameter calculations. Concentration-time raw data and pharmacokinetic parameters will be calculated for each individual as well as reported per received dose(s).

[redacted] the area under the curve to infinite time (AUC), the terminal half-life ($T_{1/2}$), clearance (CL), volume of distribution at steady-state (V_{ss}) and volume of distribution during the elimination phase (V_z). In addition the maximum plasma concentration (C_{max}) and the time of occurrence of C_{max} (T_{max}) may be obtained directly from the experimental data.

12 Statistical methods and sample size

Prior to clean file a Statistical Analysis Plan (SAP) with details on statistical analysis and data presentation will be written.

12.1 Description of analysis sets

The safety analysis set will consist of all patients that received any amount of study medication.

The Full Analysis Set (FAS) will consist of all patients in the safety set that has a measurement of anti-HLA antibody level within 24 hours from dosing.

The Per Protocol Set (PPS) will be defined by the PK analyst.

The final criteria for the PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol violations/deviations are available.

12.2 Methods of statistical analyses

12.2.1 General principles

No formal statistical hypothesis testing will be performed in this study. Data will be presented by actual dose received.

12.2.2 Patient characteristics

The following demographic variables will be summarized: age, sex, race, height, weight and BMI for all dose groups as appropriate.

Medical/surgical histories and medications taken before screening will be listed including comments and coded fields.

Baseline assessments of safety variables (ECG, vital signs, and laboratory parameters) will be listed by dose groups as appropriate.

12.2.3 Safety and tolerability

All safety and tolerability data will be listed as specified in the SAP.

Adverse events will be collected for each patient from visit 1 until follow-up. Serious adverse events will be recorded from the time when informed consent is obtained (Visit 1) until the follow-up visit.

The following summaries of AEs will be given by treatment and in total:

The number of patients who had any AEs, SAEs, AEs that led to withdrawal, AEs related to study drug and AEs with severe intensity.

If the number of AEs is sufficiently large, summaries will be presented by PT (Preferred term) and SOC (System organ class) according to MedDRA vocabulary.

Severity, time of onset, duration, action taken, concomitant therapy started and patient outcome of the AEs will be given in data listings only. AEs which were reason for premature discontinuation of study drug will be listed separately.

Furthermore, SAEs and AEs that led to withdrawal will be listed separately.

12.2.4 Efficacy on DSA, CDC CXM and FACS CXM

CDC crossmatch results (positive or negative and when applicable titer) before and after IdeS treatment will be determined for each patient and presented in listing sorted by treatment, patient, and time-point. In addition, time to conversion of crossmatch will be calculated.

FACS crossmatch results (positive or negative and when applicable channel shift) before and after IdeS treatment will be determined for each patient and presented in listing sorted by treatment, patient, and time-point. In addition, time to conversion of crossmatch will be calculated.

HLA antibodies including DSA will be measured with SAB assays. Summary statistics of MFI values for DSA and for all HLA for each patient will be produced by time point, including min, 10th percentile, median, 90th percentile, and max. In addition, patient listings of MFI values for DSA and all HLA for all patients will be produced.

12.2.5 Pharmacokinetics
Pharmacokinetic (PK) variables will be summarized using appropriate descriptive statistics (e.g. n, geometric mean, harmonic mean for $t_{1/2}$, coefficient of variance (CV), min, median, max) by treatment group.

12.2.6 Pharmacodynamics
All data associated with the efficacy of IdeS in cleaving IgG will be presented using listings for each dose group. If feasible, the data will be explored graphically.

12.2.7 Anti-drug antibodies
All anti-IdeS antibody data will be presented using listings.

12.3 Determination of sample size
Sample size is not based on formal statistical considerations. Due to the nature of the primary endpoint of the study it is expected that data from 15-20 patients should suffice to achieve the objectives of the study. Also, the sample size is in line with experience from previous similar Phase II studies with other compounds to obtain adequate safety, tolerability and PK data to achieve the objectives of the study.

13 Publication policy

13.1 Clinical Study Report
The results from this study will be reported in a clinical study report (CSR) within one year after completion of the last patient. This will be prepared by Hansa Medical AB and submitted for comments and signature to the signatory investigator(s).

13.2 Confidentiality and Ownership of data
Any confidential information relating to the IMP or the study, including any data and results from the study will be the exclusive property of Hansa Medical AB. The investigator and any other persons involved in the trial will protect the confidentiality of the proprietary information belonging to Hansa Medical AB.

13.3 Publication and Public Disclosure

13.3.1 Publication Policy
At the end of the study, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Hansa Medical AB.

Any external Contract Research Organisation or laboratory involved in the conduct of this study has no publication rights regarding the study.

13.3.2 Public Disclosure Policy
The study will be uploaded to the EudraCT database.

14 References

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