Study protocol: GOOD-IDES-01, **13 February 2018**

An Open-Label Phase II Study in anti-GBM disease (Goodpasture's disease) with Adverse Renal Prognosis to Evaluate the Efficacy and Safety of IdeS --GOOD-IDES

Short title: IdeS --GOOD-IDES

Protocol Version: 3.3 AT
EudraCT number: 2016-004082-39
Sponsor protocol number: GOOD-IDES-01

Hansa Medical AB, protocol number: 15-HMedIdeS-10
Partial funding: Hansa Medical AB, P.O. Box 785 SE-220 07, Lund, SWEDEN

Coordinating Principle Investigator (CPI) and Sponsor

Division of Drug Research
Department of Medical and Health Sciences
Linköping University
SE-581 83 Linköping
SWEDEN

Title page

Study Title:	An Open-Label Phase II Study in anti-GBM disease (Goodpasture's disease) with Adverse Renal Prognosis to Evaluate the Efficacy and Safety of IdeS --GOOD-IDES
Protocol Number:	GOOD-IDES-01
Investigational Product:	HMED-IdeS
Indication:	Anti-GBM-disease (Goodpasture's disease)
Sponsor:	Linköping University
Development Phase:	II
EudraCT number	2016-004082-39
[redacted]	[redacted]

Abbreviations

AAV	ANCA-associated vasculitis
ACR	Albumin/Creatinine Ratio
ADA	Anti-IdeS antibodies
AE	Adverse Event
ANCA	Anti-neutrophil cytoplasm antibody
BW	Body weight
CPI	Coordinating Principle Investigator
CRF	Case report form
CYC	Cyclophosphamide
DD	Deceased donor
DSMB	Data Safety Monitoring Board
DSUR	Developmental Summary Update Report
EC	Ethics Committee
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-Linked Immunosorbent Assay
ESRD	End-stage renal disease
GBM	Glomerular Basement Membrane
GC	Glucocorticoids
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	Goodpasture's disease
HLA	Human Leukocyte Antigen
ICH	The International Council for Harmonisation
IMP	Investigational Medicinal Product
IgG	Immunoglobulin G

IdeS	IgG-degrading enzyme of Streptococcus pyogenes
IMP	Investigational medicinal product
KDIGO	Kidney Disease, Improving Global Outcomes
LD	Living donor
MDRD	The Modification of Diet in Renal Disease equation
PLEX	Plasma Exchange
RA	Regulatory Authority
SAE	Serious Adverse Event
SUSAR	Suspected unexpected Serious Adverse Reaction
TB	Tuberculosis
TRALI	Transfusion related Acute Lung Injury

Contact information

Investigators		Site
Sweden	[redacted] Department of Nephrology, University Hospital, SE-581 85 Linköping[redacted]	**01**
	[redacted] Department of Nephrology M99 Clinical Science, Intervention and Technology, Karolinska University Hospital, SE-141 86 Stockholm,[redacted]	**02**
	[redacted] Department of Nephrology, Faculty of Medicine, Lund University, University Hospital, SE-221 85 Lund,[redacted]	**03**
	[redacted] Department of Nephrology, Uppsala University Hospital, entr 30, 5th floor 75185, Uppsala,[redacted] Co-investigator [redacted], Department of Nephrology, University Hospital, SE-75185 Uppsala,[redacted]	**04**
	[redacted] Department of Nephrology, Sahlgrenska University Hospital, SE-413 45 Gothenburg,[redacted] Co-investigator [redacted] Department of Nephrology, Sahlgrenska University Hospital, SE- 413 45 Gothenburg[redacted]	**05**
Denmark	[redacted] Department of Department of Nephrology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark,[redacted]	**06**
	[redacted] Department of Renal Medicine, Aarhus University Hospital, Palle Juul-Jensen Boulevard 99, DK-8200 Aarhus N, Denmark,[redacted] Co-investigator,[redacted] Department of Renal Medicine,	**07**

	Aarhus University Hospital, Palle Juul-Jensen Boulevard 99, DK-8200 Aarhus N, Denmark. [redacted]	
Austria	[redacted] Division of Nephrology, Department of Internal Medicine Medical University of Graz Auenbruggerplatz 15, A-8036 Graz, [redacted] [redacted] Medical University of Vienna Department of Internal Medicine III Division of Nephrology and Dialysis Waehringer Guertel 18-20, A-1090 Vienna, [redacted] [redacted] Universitätsklinik für Innere Medizin IV, [redacted] Co.investigator [redacted] Department of Internal Medicine IV (Nephrology and Hypertension), Anichstraße 35, A-6020 Innsbruck, [redacted] Co-investigator, [redacted], Innsbruck [redacted] [redacted] Innere Medizin III (Nephrologie und Dialyse) Akademisches Lehrkrankenhaus Feldkirch, Carinagasse 47, A-6800 Feldkirch [redacted]	**<u>08</u>** **<u>09</u>** **<u>10</u>** **<u>11</u>**
Czech Republic	[redacted] Department of Department of nephrology, First Faculty of Medicine and General Teaching Hospital, U Nemocnice 2, 121 08 PRAHA 2, CZECH REPUBLIC and Charles University in Prague, Prague, CZ, Czech Republic, [redacted] Co-investigator, [redacted], Department of Nephrology Nephrology, Internal Medicine (General Medicine) Charles University in Prague , Prague (1. LF), [redacted]	
UK	[redacted] Department of Medicine, Imperial College London, London, UK	

	[redacted] Co-investigator, [redacted], Department of Medicine, Imperial College London, London, UK, [redacted] [redacted] [redacted] Division of Nephrology, Department of Medicine, University of Cambridge, Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge, UK. [redacted] Co-investigator, [redacted] Addenbrookes Hospital, UK [redacted] [redacted] UCL Centre for Nephrology, Royal free Hospital, Rowland Hill Street, London NW3 2PF. [redacted] [redacted] Department of Renal Immunobiology, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT [redacted] Co-investigator, [redacted], Institute of Inflammation and Ageing College of Medical and Dental Sciences University of Birmingham, UK. [redacted] [redacted]	
France	[redacted] Department of Nephrology, Hemodialysis, Apheresis, and Transplantation, CHUGA (centre hospitalier universitaire Grenoble-Alpes), [redacted] [redacted] Centre Hospitalier Régional Universitaire de Lille, Nephrology Service, Chr lille, Hop calmette chr lille, boulevard du pr leclercq 59000 Lille, [redacted]	
Netherlands	[redacted] Department of Nephrology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, [redacted]	

Research staff

Sweden:

Project coordinator (Linköping): [redacted]

Study coordinator (Linköping): [redacted]

Study coordinator (Uppsala): [redacted]

Back-up study coordinator (Uppsala): [redacted]

Study coordinator (Stockholm): [redacted]

Study coordinator (Lund): [redacted]

Study coordinator (Göteborg): [redacted]

Denmark:

Study coordinator (Copenhagen): [redacted]

Study coordinator (Aarhus): [redacted]

Austria:

Study coordinator (Graz) [redacted]

Study coordinator (Wien): [redacted]

Study coordinator (Innsbruck): [redacted]

Study coordinator (Feldkirch): [redacted]

UK:

Study Coordinator (London): [redacted]

Study Coordinator, [redacted]

Czech Republic:

France:

Study monitoring:

Copenhagen, Aarhus: [redacted]

Sweden: [redacted]

Graz, Wien: [redacted]

Innsbruck, Feldkirch: [redacted]

Laboratory contact:

Division of Drug Research Department of Medical and Health Sciences Linköping University SE-581 83 Linköping, SWEDEN

Hansa Medical AB, P.O. Box 785 SE-220 07, Lund, SWEDEN

[redacted]

Hansa Medical:

[redacted]

Clinical Research Manager

Hansa Medical AB

Scheelevägen 22, P.O Box 785

SE-220 07 Lund, Sweden

[redacted]

[redacted]

Web: www.hansamedical.com

[redacted]

Director Clinical Operations

Hansa Medical

[redacted]

[redacted]

Visiting address:
Scheelevägen 22
223 63 Lund, Sweden
Postal address:
P.O. Box 785
220 07 Lund, Sweden

AE/SAE reporting:

Contact Information:

CRO: [redacted]

e-mail: [redacted]

Table of Contents

1. Study synopsis

Name of Sponsor	**Name of Active Ingredient**	**Study number:**
[redacted] Linköping university	HMedIdeS	2016-004082-39

Title

An Open-Label Phase II Study to Evaluate the Efficacy and Safety of IdeS in anti-GBM disease (Goodpasture's disease) with Adverse Renal Prognosis --GOOD-IDES

Investigators

[redacted]

Study centers

Multi-center (up to15 sites), in 4-6 countries (Sweden, Denmark, UK, Czech Republic, France, Austria)

Study period	**Phase of development**
24 months	Phase II

Aim

The aim of this study is to evaluate the treatment with IdeS in anti-GBM disease

Objectives

The primary objective of this study is to evaluate the safety and tolerability of IdeS in patients with severe anti-GBM (Glomerular Basement Membrane) disease on background of standard care consisting of pulse-methylprednisolone, oral prednisolone and intravenous cyclophosphamide combined with plasma exchange (PLEX).

The primary efficacy objective is to evaluate the efficacy of an IdeS based regimen to salvage independent renal function defined as no need for dialysis at 6 months and after IdeS treatment.

The secondary objectives of this study include assessment of:

1. Renal function 3 months
2. Change in eGFR during the study period;
3. Number of days with anti-GBM antibodies above a toxic level (i.e. >30 ELISA units)
4. Disappearance of hematuria, days from start of treatment;
5. Change in proteinuria during the study measured as u-albumin/creatinine ratio in morning void;
6. Number of PLEX needed;
7. Changes in renal histology (optional)
8. Anti-IdeS antibodies (ADA)
9. Pharmacokinetics, Pharmacodynamics (IgG degradation)

Rationale

Patients with anti-GBM disease presenting with advanced renal injury (p-creatinine above 500 μmol/L) have a very poor renal prognosis. Less than 10% survive with independent renal function. The pathogenic process is driven by IgG autoantibodies directed against the glomerular basement membrane. The antibodies attract neutrophils to the site of injury and to complement activation mediated by the Fc-portion of the molecule. IdeS specifically cleave human IgG of all four subclasses, while all other plasma proteins are left undigested. A single injection clears circulating levels of IgG completely and levels of newly synthesized IgG cannot be detectable until two weeks after dosing. PLEX is known to alter the course of anti-GBM disease but each session clears less than a third of total body IgG. Consequently it takes several days of PLEX to reach non-toxic levels of circulating autoantibodies, and PLEX has no effect on membrane bound autoantibodies. In animal experiments IdeS can also cleave IgG that has bound to the basement membrane preventing subsequent glomerular injury as well as complement activation and neutrophil influx. It is probable that fast cleavage of all toxic antibodies including those already bound, would halt the inflammatory process and lead to a better prognosis.

Methodology

This is a pilot study to test the safety, tolerability, and efficacy of IdeS in severe anti-GBM disease.

All patients with anti-GBM disease confirmed by the combination of hematuria and circulating anti-GBM antibodies are eligible for inclusion provided they have an eGFR < 15 ml/min/1.73 m^2 and that they are not anuric (i.e. having voided >200 ml urine during the last 48 hours). Standard treatment including PLEX may have been started but patients will be excluded if anti-GBM is below a level considered as toxic by the treating physician.

Screening procedures will include demographics, medical history, medication history, physical examination and vital signs, serum pregnancy test for women of childbearing potential, serum chemistry, hematology, urinalysis, viral screening (HCV, HBV, HIV), chest x-ray and estimated glomerular filtration rate (eGFR) assessment.

A renal biopsy is not necessary to be included in the study. But if not done before inclusion, a biopsy should be performed as soon as possible after anti-GBM antibodies have reached a non-toxic level. An optional renal biopsy could be performed to assess the effect of IdeS treatment on kidney histology.

On Day 1 of the study patients will be given a single intravenous infusion of IdeS (0.25 mg IdeS/kg BWt). Anti-GBM antibodies will be measured with decreasing frequency through the study. PLEX will be performed when necessary to keep the anti-GBM levels below a level considered as a toxic level at each participating center. PLEX should not be issued the first 36 hours following the infusion of IdeS.

Glucocorticoids (GC) therapy starts with intravenous methylprednisolone given as 3 daily pulse doses. Each pulse dose may be between 0.5 g and 1 g. Any dose given prior to inclusion in the study should be subtracted from the total dose. Oral prednisolone therapy shall commence after stopping methylprednisolone. Dosing will be given according to local practice, a preferential range is listed in Table 2. Prophylaxis against peptic ulcers and osteoporosis will be given based on the investigators decision in each individual case.

Cyclophosphamide (CYC) either intravenous pulses or daily oral will be prescribed for at least 13 weeks in patients with independent renal function, but may be withdrawn earlier

in patients considered to have reached end-stage renal disease (ESRD). A starting dose of 10 mg/kg/pulse will be used for pulse CYC (maximum 1.0 g/dose) or 1.5 mg/kg/day for oral CYC (maximum 150 mg/day) with reductions made for age. Pulse CYC will be administered intravenous at a frequency of every two weeks for the first 3 doses then every 3 weeks thereafter. Modifications to dose and frequency will be made in the case of leucopenia. Full blood counts will be performed regularly. Concomitant use of mesna is optional and left to the discretion of the investigator and local practice.

Number of Patients

Up to approximately 15 male or female patients with anti-GBM disease will be enrolled in this study.

Questionnaire about the feasibility at each site and the availability of patients with anti-GBM disease with Adverse Renal Prognosis for the last 5 years will be evaluated before sites will be included.

Main Criteria for Inclusion

1. Anti-GBM antibodies detected by Enzyme-Linked Immunosorbent Assay (ELISA) above a level that is considered toxic by the investigator. Patients double-positive for anti-GBM and ANCA may be entered in the trial, but only if their level of anti-GBM antibodies fulfil the criteria above.
2. eGFR < 15 ml/min/1.73 m^2 (by MDRD equation) or if the patient is non-responsive to standard treatment, and has lost >15 ml/min/1.73 m^2 after start of treatment.
3. Haematuria on dipstick and/or urinary sediment.
4. Male or female patients aged at least 18 years; Female patients of childbearing potential may participate if highly effective contraception is used during the study.
5. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
6. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination, and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to be of clinical significance, may be entered into the study.

Main Criteria for Exclusion

1. Anuria for more than 48 hours (less than 200 ml)
2. Dialysis dependency for more than 5 days (maximum 3 sessions before signing informed consent)
3. Moderate to severe pulmonary haemorrhage as defined in the protocol
4. Pregnant
5. Symptomatic congestive heart failure (NYHA class 2-4) requiring prescription medication or clinically evident peripheral edema of cardiac origin
6. Myocardial infarction, unstable angina or stroke within 3 months prior to screening
7. Ongoing bacterial infection requiring antibiotic therapy or viral infection with

Hepatitis B, C or HIV; or active tuberculosis as indicated by chest x-ray.

8. Patients should not have received investigational drugs within 30 days prior to screening or within 4 half-lives (whichever is longer); and
9. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

Test Product

HMED-IdeS, administered intravenously once per subject.

Duration of Treatment and Observation

HMED-IdeS will be given as a single infusion over 30 minutes. Within 36 hours after the HMED-IdeS infusion no PLEX should be given. After that patients will be treated according to standard of care and followed according to the protocol for 6 months.

Safety Assessments

Safety assessments include adverse events, evaluation for lung haemorrhage, physical examination abnormalities, vital signs, and clinical laboratory tests (including blood chemistry, complement analysis, haematology, and urinalysis). Safety assessment will also include occurrence of infections.

Physical examination including vital signs will be performed at screening, day 1, day 7, day 29, day 93 and end of study at day 180. Visits to the research nurse/site coordinator will be made at other times, in accordance with the study visit plan Appendix 1.

The patients will be closely monitored for all adverse events. The principal investigator must make sure that sufficient facilities and procedures are available to handle emergency situations during the study. The hospitals should have adequate procedures in place to handle unexpected adverse reactions.

Efficacy Assessments

Efficacy assessments include:

1. Independent renal function measured as no need for chronic renal replacement therapy
2. eGFR by Modification of Diet in Renal Disease (MDRD) formula based on serum creatinine;
3. Albuminuria measured as first morning urinary Albumin/Creatinine Ratio (ACR);
4. Haematuria based on urine sticks
5. Histological changes in a second biopsy (optional).

Laboratory Markers

Plasma samples will be collected for analysis both at local (at site) and at central laboratory on Days 1, 3, 7, 10, 15, 22, 29, 50, 93, 135 and 180 (end of study) for laboratory marker measurements for example anti-GBM, CRP and inflammatory cytokine and chemokine levels. Urine samples will also be collected on Days 1, 7, 15, 50, 93 and 180 (end of study) for biomarker assessments including for example complement fragments, inflammatory chemokine and cytokine levels. Blood and urine samples will be sent on the same day for analysis at local laboratories for safety surveillance. Samples for central

laboratory will be frozen at site and sent during the study period (for more detailed information see section 6.5.7 and study visits, Appendix 1).

Statistical Methods

Historical data indicate that when using standard therapy only 7% of patients fulfilling the inclusion criteria of this study survive with independent renal function. If the experimental therapy raises this figure to 50 %, 15 patients are needed (power 0.98). The corresponding figures for a response rate of 40 % or 30 % and would then have a power of 0.92 and 0.77 respectively. Chi square ($\chi 2$) calculations (alt. Fisher's exact test), at significance level p=0.05, will be used to compare changes proportions dialysis independent patients. For the other endpoints (2-6) descriptive statistics will be used.

To compare patients treated for anti-GBM disease under similar conditions, matched historical controls will be used in each site that includes patients to the study. The variables to be matched will be age and gender.

Demographics and Baseline Characteristics

All subject baseline characteristics and demographic data (age, sex, weight, height, smoking status, viral test results, eGFR, proteinuria (ACR), physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications at study entry will be listed by study center and subject number, and will also be summarized.

Safety Analysis

The primary safety endpoint is incidence of adverse events or disease progression in the lungs.

Other safety endpoints include:

- Change from screening in all safety laboratory parameters;
- Change from screening in vital signs;

All clinical safety and tolerability data will be listed by subject and will be summarized. Treatment-emergent adverse events will be listed and summarized by System Organ Class, by relatedness and by maximum severity. Serious adverse events and adverse events leading to withdrawal will be listed and summarized. Individual vital signs and change from baseline in vital signs will be listed by subject, and study visit, and summarized descriptively. Laboratory data (actual values and change from baseline) will be listed by subject and study visit. Abnormal laboratory values will be flagged.

Efficacy Analysis

The primary efficacy endpoint is proportion of patients with independent renal function at 6 months.

Other efficacy endpoints include:

1. The proportion of subjects with independent renal function, defined as no need for dialysis at 3 months, as compared to historical controls.

2. Renal function at 3 and 6 months expressed as eGFR and as change in GFR from baseline;
3. Number of days with anti-GBM antibodies above a toxic level (i.e. >30 ELISA units) measured at a central laboratory using the Wieslab anti-GBM kit;
4. Disappearance of haematuria, measured in days from start of treatment;
5. Change in proteinuria during the study measured as u-albumin/creatinine ratio in morning void;
6. Number of PLEXs needed;
7. Renal histology measurements and changes in renal histology if a second renal biopsy is performed;
8. Anti-IdeS antibodies (ADA)
9. Pharmacokinetics, Pharmacodynamics (IgG degradation)

2. Background and Rationale

Anti-glomerular basement membrane (anti-GBM) disease also called Goodpasture's disease (GP) is included among immune complex small vessel vasculitis [1]. The definition of anti-GBM disease is a vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary haemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.

Anti-GBM disease is a serious autoimmune disease characterized by rapidly progressive glomerulonephritis and the presence of anti-GBM antibodies. The antibodies can be found both in the circulation and deposited in the lungs and the kidneys where they mediate damage through the activation of complement and recruitment of inflammatory cells. When untreated, the vast majority of patients progress to end-stage renal disease (ESRD) or die due to pulmonary haemorrhage. However, if the disease is detected early and treatment that reduces levels of anti-GBM antibodies is instituted, it is possible to alter the prognosis and preserve renal function [2, 3]. Unfortunately, many patients with anti-GBM disease are diagnosed late, at which time not even aggressive regimens combining extensive plasma exchange (PLEX) and immunosuppressive therapy lead to restored renal function [3-5]. Actually, the prognosis for anti-GBM disease is much worse than for other forms of autoantibody-associated rapidly progressive glomerulonephritis. In the Plasma Exchange for Renal Vasculitis (MEPEX) study, from the European Vasculitis Society (EUVAS), 59% (81/137) of the patients with antineutrophil cytoplasmic antibody-associated systemic vasculitis (AAV) presenting with above 500 µmol/L in serum creatinine had regained independent renal function at 3 months after the start of therapy [6]. In a recent study 20 % (11/53.7) of anti-GBM patients with such renal function at diagnosis had autonomous renal function at 12 months[McAdoo, submitted]. When combining all studies published since 1990 only 7 % of patients with creatinine >500 and/or dialysis dependency had such an outcome [7]. Today, standard therapy for anti-GBM disease consists of the combination of steroids, cyclophosphamide and PLEX. There are several potential explanations for the discrepancy in outcome between AAV and anti-GBM disease, two such explanations are that the current anti-GBM therapy does not lower autoantibody levels quick enough and is unable to affect the autoantibodies already bound to the kidneys.

2.1 Description of IdeS and summary of findings from earlier studies

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 [8-11]. 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 [8].

A phase I study [redacted] showed that IdeS was safe and well tolerated in doses up to 0.24 mg/kg body weight (BW). [redacted]

Study 13-HMedIdeS-02 (EudraCT no. 2013-005417-13) was a single centre, single arm, dose finding, Phase II study in sensitized CKD patients assessing safety, tolerability, pharmacokinetics (PK) and efficacy of HMED-IdeS without intent to transplantation. However, patients were not removed from the transplant waitlist during the study. Included patients had a panel reactive antibody [PRA] >70% (n=7). All patients received the infusions: 0.25mg/kg once (n=2), 0.12mg/kg twice (n=3), or 0.25mg/kg twice (n=2) HMED-IdeS. Five serious adverse events (SAEs) were reported of which 4 were classified as probably or possibly related to the study drug. Those were 3 infections and 1 myalgia.

For all patients, >99% of plasma IgG was degraded within 48 hours after treatment with <1% plasma IgG detectable for up to 7 days. The HLA antibodies started to recover from day 7/8 and were back to pre-dose levels between day 14/15 and day 28. Efficacy of HMED-IdeS was also demonstrated on PRA crossmatch test in which PRA was reduced from 69% (range 11% to 100%) pre-treatment to 3% (range 0% to 21%) after treatment. The PRA decreased in all patients within one hour of treatment and remained low for approximately one week (Hansa Doc 2015-30).

The primary objective of the study was to find an HMED-IdeS dosing scheme which resulted in HLA-antibody levels acceptable for transplantation in the majority of patients. The acceptance criteria for transplantation was defined as a mean fluorescence intensity (MFI) of <1100, within 24 hours from HMED-IdeS dosing and the primary objective of the study was reached (Hansa doc. 2015-029). Two days after HMED-IdeS treatment, one patient was offered a cadaveric kidney that was crossmatch test positive prior to HMED-IdeS treatment and turned to negative after treatment. Transplantation was successful and the patient is doing well with very good kidney function >16 months after transplantation.

In the 2 completed studies, there was a total of 2 non-serious infusion related reactions with no reports of serious infusion related reactions reported in ongoing studies. Signs and symptoms associated with infusion related reactions included but were not limited to the following: dyspnoea, pharyngeal oedema, sinus tachycardia, chest discomfort and flushing. To date there have been no reports of anaphylactic or anaphylactoid reactions. All adverse events were mild or moderate.

Study 13-HMedIdeS-03 (EudraCT no. 2014-000712-34) was a single arm, Phase II study to assess safety and efficacy of HMED-IdeS given immediately prior to kidney transplantation in order to reduce DSAs in sensitized CKD patients awaiting deceased donor (DD) or living donor (LD) transplantation. The cut of level for inclusion was the same as in 13-HMedIdeS-02 3000 MFI with patients eligible for transplantation if crossmatch test was negative after IdeS treatment with acceptable antibody levels. 10 patients (2 LD, 8 DD) have been treated with single doses of 0.25 or 0.5 mg/kg HMED-IdeS along with standard immunosuppressive treatment, but no additional desensitizing agents. There have been no deaths and no study discontinuations due to adverse events (AEs). There were 26 SAEs reported by 8 patients. Five SAEs in 4 patients were considered treatment-related (abdominal infection, device related infection, pneumonia, sepsis, parvo virus). All patients experienced complete absence of complement binding antibodies within 1 hour of treatment, cleavage of all IgG within 6 hours of treatment and negative crossmatch test post-treatment, with initial recovery of IgG levels after 7-14 days. At the end-of-study the kidney function (creatinine and eGFR) was good in all patients and 9 out of the 10 patients the biopsy was normal. One patient showed signs of chronic ABMR at evaluation of the kidney biopsy on day 180. This study is completed with the last patient last visit performed in October 2016.

Study 14-HMedIdeS-04 (IND no. 124301) is an ongoing investigator initiated Phase I/II, single arm, exploratory study to assess safety, tolerability, and efficacy of HMED-IdeS given immediately prior to kidney transplantation to reduce DSAs in highly sensitized (PRA range 82-100%, all DSA+) CKD patients awaiting DD renal transplantation. Study 14-HMedIdeS-04 has enrolled 15 patients to date and all data presented are preliminary. All included patients were treated with a single dose of 0.24 mg/kg HMED-IdeS. There have been 15 SAEs reported in 10 patients to date. None of them were considered related to IdeS. There were no signs of increased incidence of infections. All patients showed efficient inactivation of IgGs and eradication of HLA antibodies as measured by Luminex at 6-24 hours post-HMED-IdeS infusion and all included patients were transplanted. Target inclusion is 20 patients.

Study 15-HMedIdeS-06 (IND no. 128074, EudraCT no. 2016-002064-13) is an ongoing Phase II study to evaluate the efficacy of HMED-IdeS to desensitize transplant patients with a positive crossmatch test. The study will enroll 15-20 patients (7-13 with LD and 7-13 with a DD) who exhibit DSAs and have a positive crossmatch test to their available live or deceased donor organs. The study will primarily examine the efficacy of IdeS in creating a negative crossmatch in these patients. Included patients will be treated with HMED-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 HMED-IdeS, patients will be given high dose IVIg (2 g/kg BW, maximum of 140 g) on day 7 and B-cell depleting agent anti-CD20 (Rituximab) on day 9. 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 HMED-IdeS dosing. Safety, including kidney function will be monitored at multiple time points up to 180 days after treatment. Pharmacokinetics, pharmacodynamics (PD) and anti-drug antibodies will be measured. To date 4 patients have been included, dosed and transplanted. So far there have been five SAEs in three patients, none related to IdeS.

Study 15-HMedIdeS-08 (EudraCT no. 2016-000249-30) is an ongoing Phase II study in patients diagnosed with asymptomatic antibody-mediated TTP with low ADAMTS13

activity. The primary objective is to monitor safety and tolerability after receiving single intravenous doses of IdeS. The secondary objective is to investigate IdeS efficacy in significantly increasing ADAMTS13 activity and decreasing ADAMTS13 antibody levels in patients with asymptomatic antibody-mediated TTP. In the current study this will be investigated in asymptomatic patients with reduced levels of ADAMTS13 activity and measurable levels of circulating ADAMTS13 antibodies.

Eligible patients must have ADAMTS13 activity levels less than 10% of normal levels. Each patient will receive one dose of 0.25 mg/kg BW IdeS. Following an evaluation of safety and efficacy in 3 patients dosed at 0.25 mg/kg, there will be a possibility to increase the dose to 0.5 mg/kg for the next 3 patients. The dose will be given as a single intravenous infusion over 30 minutes. So far, two patients have been dosed with 0.25 mg/kg. Both patients have experienced symptoms of serum sickness six days after IdeS administration. Follow up of the patients is currently ongoing. An overview of the ongoing and completed clinical studies is presented in Table 1.

Table 1. Clinical Studies

Study No./ Status	**Phase/ Subjects**	**Doses/ Follow up time**	**Main objectives**	**Comments**
11-HMedIdeS-01/ *Completed*	[redacted]	[redacted]	[redacted]	[redacted]
13-HMedIdeS-02/ *Completed*	II/ CKD Patients N=8	0.12 and 0.25 mg/kg BW given once or twice within 48 h	Efficacy in CKD patients defined as an HMED-IdeS dosing scheme resulting in HLA antibody levels acceptable for transplantation, within 24 hours from dosing. Safety in the transplantation setting.	Single arm with ascending doses. Primary efficacy endpoint reached. Safe and well tolerated.
13-HMedIdeS-03/ *Completed*	II/ Patients N=10	0.25 and 0.5 mg/kg 180 d	Safety in the transplantation setting. Efficacy defined as HLA antibody levels acceptable for transplantation.	Similar design as 13-HMedIdeS-02 but transplantation part of protocol. Deceased and living donors.
14-HMedIdeS-04/ *Ongoing* (Investigator initiated study)	II/ Patients N=10-20	0.25 and 0.5 mg/kg 180 d	Safety in combination with Cedars Sinai's "standard protocol" for desensitization of highly sensitized patients. Efficacy in preventing AMR.	Investigator sponsored IND (IND 124301). HMED-IdeS combined with rituximab and IVIg. Deceased donors.

15-HMedIdeS-06/ *Ongoing*	II/ Patients N=20	0.25 and 0.5 mg/kg Primary endpoint: 24h Safety: 180 d	Efficacy in creating a negative crossmatch test. Safety in the transplantation setting.	Deceased and living donors. Target population cannot be transplanted with current available methods for desensitization.
15-HMedIdeS-08/*Ongoing*	II/ Patients N=6	0.25 and possibly 0.5 mg/kg Safety and efficacy: 64 d	Safety and tolerability in patients with asymptomatic antibody-mediated TTP with low ADAMTS13 activity. Change from baseline in ADAMTS13 activity and antibody (IgG and $F(ab')_2$)	Pilot study to investigate IdeS safety, tolerability and efficacy in patients diagnosed with asymptomatic antibody-mediated TTP with low ADAMTS13 activity

BW=body weight, h=hours, d=days, TTP Thrombotic Thrombocytopenic Purpura

2.2 Potential risks and befits to human subjects

The Data and Safety Monitoring Board (DSMB) will follow the progress and outcome of the study including patient safety.

A single dose of 0.25 mg/kg BW has been selected for this study. The primary efficacy objective of the study is to evaluate the efficacy of an IdeS based regimen to salvage independent renal function defined as no need for dialysis at 3 and 6 months after IdeS treatment. A single of dose of 0.24 or 0.25 mg/kg is the dose that has been administered to the majority of renal transplant patients and has been shown to be highly effective in degrading donor specific antibodies with a favorable risk benefit profile.

The phase I study in healthy subjects did not identify any dose limiting factors even at the highest tested dose (0.24 mg/kg BW) and CKD patients in a completed phase II study (13-HMedIdeS-02) in Sweden were exposed to a total dose of 0.5 mg/kg BW with acceptable safety profile. In another recently completed study in Sweden (13-HMedIdeS-03) to evaluate the safety, tolerability, efficacy and pharmacokinetics of intravenous ascending doses of IdeS in kidney transplantation the first 5 patients in the study received a dose of 0.25 mg/kg BW and next 5 patients received a dose of 0.5 mg/kg BW, respectively. Both dose levels were well tolerated. More information on the design of the study is found in the Investigators Brochure and in section 2.1 above.

[redacted] an evaluation of the female and male reproductive organ in rabbit and dog were performed as part of the pivotal toxicological studies. In conclusion, there were no observations considered related to IdeS treatment on the female and male reproduction organs neither in rabbit nor dog. In order to avoid pregnancies the requirement for highly effective contraception is part of the inclusion criteria for this study. In addition, a pregnancy test will be performed prior to dosing and approximately at monthly intervals throughout the study, see appendix 1, Study visit plan.

A pilot toxicology study in beagle dogs, showed that repeated IV administration of 2 mg/kg BW or 20 mg/kg BW IdeS to Beagle dogs can result in clinical signs resembling an immune-mediated anaphylactic shock that correlates with high levels of anti-IdeS

antibodies. However, injection of IdeS did not increase the serum levels of total IgE. In completed and ongoing clinical studies two non-serious infusion related reactions, which included the following signs and symptoms: dyspnoea, pharyngeal oedema, sinus tachycardia, chest discomfort and flushing, were reported. Non clinical toxicology studies identified a no observed adverse effect level (NOAEL) of 2.0 mg/kg BW.

In an ongoing study in asymptomatic patients with Thrombotic thrombocytopenic purpura (TTP), two subjects developed signs and symptoms of serum sickness about 6 days after receiving a single dose of 0.25 mg/kg BW. In one of the patients there was laboratory evidence of consumption of complement. Both subjects responded well to treatment with corticosteroids. Neither of the patients was receiving immunosuppressive therapy at the time of presentation. All renal transplant patients who have been treated with IdeS received immunosuppressive therapy post infusion and no signs of serum sickness have been observed in any of these patients. This indicates that the risk of serum sickness is low in patients receiving immunosuppression following IdeS therapy. Patients in the current study will be treated with prednisolone and cyclophosphamide which should mitigate the risk of serum sickness.

Some patients may have pre-existing antibodies to IdeS subsequent to streptococcal infections. As a precaution patients included in the study will receive premedication with hydrocortisone and antihistamine (chlorphenamine maleate) before IdeS infusion in order to mitigate the risk of infusion-related reactions. Patients and healthy subjects who have been previously treated have formed antibodies to IdeS that persist for some months and then decline. The relevance of this finding with respect to administering a second dose of IdeS is currently unknown. There is no experience giving a second dose of IdeS with a longer interval than approximately 30 hours. In this study only a single dose of IdeS will be administered. In addition, mild and reversible proteinuria has been detected in healthy subjects treated with IdeS.

In the IdeS studies in renal transplantation the IgG fragments resulting from IdeS cleavage of IgG do not appear to impair kidney function. The potential increased risk for patients with anti-GBM disease due to IgG fragments is unknown and renal function in patients will be closely monitored. 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 a two-week regimen of prophylactic antibiotics following IdeS dosing. Patients positive for viruses (Hepatitis B, C and human immunodeficiency virus [HIV]), tuberculosis and other active bacterial infections requiring antibiotics will be excluded from the study. Patients will be instructed to contact the principal investigator immediately if they have any sign of infection. In case of infection in a patient with low IgG plasma levels, intravenous immunoglobulin may be indicated if a patient with low levels of plasma IgG develops an infection.

It has been demonstrated in laboratory studies that IdeS cleaves biologics based on human IgG including; IVIg, basiliximab, rituximab, adalimumab, denosumab, belatacept and etanercept. IdeS also cleaves rabbit anti-thymocyte globulin (rATG) but not equine anti-thymocyte globulin (ATGAM). The optimal interval between HMedIdeS administration and these biologics have not been defined [8]. The concomitant use of these other biologics and IdeS will continue to be closely monitored in order to mitigate any changes in the efficacy of these biologics.

To date, there have been 3 reports of myalgia in completed studies, 1 was serious and unexpected and occurred in a patient with a previous history of myalgia after atorvastatin treatment and who was on chronic glucocorticoid treatment. An extensive workup including muscle biopsy, electromyograms and other muscle related biomarkers showed no abnormalities or explanation for the myalgia. The remaining 2 myalgias were non-serious. The non-serious cases resolved and the serious case was improving upon steroid tapering. Myalgias have been reported with treatment with other biologics such as IVIg and rituximab [13].

No local adverse reactions have been observed at the site of IdeS infusion.

The patients will be closely monitored for all adverse events. The principal investigators must make sure that sufficient facilities and procedures are available to handle emergency situations during the study. The included sites have experience in early phase studies and there are adequate procedures in place to handle unexpected adverse reactions. Measures for risk minimization are listed and discussed under section 4.9

2.3 Route of administration and dosage of IdeS

The present test product IdeS will be given as a single intravenous infusion of 0.25 mg/kg BW, during 30 minutes, as soon as the diagnosis has been set and inclusion criteria have been fulfilled and no exclusion criteria are met, in order to reduce the risk of IgG attack of the GBM.

2.4 Trial statement

The study will be conducted in accordance by this Protocol with the ethical principles that have their origin in the Declaration of Helsinki (2013), Good Clinical Practice, ICH-GCP, and all applicable regulatory requirements.

2.5 Target population

The current standard treatment of anti-GBM disease consisting of combining extensive PLEX and immunosuppressive therapy has poor outcome in patients presenting with a low GFR. Different studies have defined the adverse prognosis group in various ways. In this study adverse prognosis is defined as either an eGFR <15 ml/min/1.73 m^2 or poor response to standard therapy indicated by a fall in eGFR >15 ml/min/1.73 m^2 after start of standard therapy.

3. Objectives and Purpose

3.1 Primary Objectives

The primary objective of this study is to evaluate the safety and tolerability of IdeS in patients with severe anti-GBM (Glomerular Basement Membrane) disease on background of standard care consisting of pulse-methylprednisolone, oral prednisolone and intravenous cyclophosphamide combined with plasma exchange (PLEX).

The primary efficacy objective is to evaluate the efficacy of an IdeS based regimen to salvage independent renal function defined as no need for dialysis at 6 months and after IdeS treatment.

3.2 Secondary Objectives

1. Renal function 3 months
2. Change in eGFR during the study period;
3. Number of days with anti-GBM antibodies above a toxic level (i.e. >30 ELISA units)
4. Disappearance of hematuria, days from start of treatment;
5. Change in proteinuria during the study measured as u-albumin/creatinine ratio in morning void;
6. Number of PLEX needed;
7. Changes in renal histology (optional)
8. Anti-IdeS antibodies (ADA)
9. Pharmacokinetics, Pharmacodynamics (IgG degradation)

4. Trial design

This is an Open-Label Phase 2 Study to Evaluate the Efficacy and Safety of IdeS in anti-GBM disease (Goodpasture's disease, i.e. GP) with Adverse Renal Prognosis --GOOD-IdeS. The primary efficacy objective is to evaluate the efficacy of an IdeS based regimen to salvage independent renal function measured as no need for dialysis at 6 months after IdeS treatment. The primary safety objective of this study is to evaluate the safety and tolerability of IdeS in patients with severe anti-GBM disease on background of standard care consisting of pulse-methylprednisolone, oral prednisolone and intravenous cyclophosphamide (CYC) combined with plasma exchange (PLEX). The patients will be followed during 6 months according to the study visit plan, Appendix 1.

4.1 Overview

This trial will include patients with anti-GBM disease that meets the inclusion criteria consecutively. Since the incidence of anti-GBM disease is approximately one per million enrolments in the study is anticipated to be slow. For this reason multiple centres in several countries are planned.

4.2 Number of Centres

The study will be conducted in multiple centres in Europe. It is anticipated that enrolment will start in Sweden followed by Denmark, UK, Czech Republic, France and Austria, however this may change based on the availability of anti-GBM disease patients. If the inclusion of patients proceeds slowly more countries might be added.

4.3 Number of Participants

This study will aim to recruit 15 patients with anti-GBM disease over a period of 18 months from the start of the first country, Sweden. The enrolment rate of patients is expected to be slow and if at least 12 patients have been enrolled at 18 months, this will considered an acceptable number of participants to meet the objectives of this study.

4.4 Study Duration

Each patient will be followed for 6 months (180 days) after the intravenously given single study dose of IdeS at Day 1. During this 6 month period, a total of 10 follow-up

visits/blood tests with increasing intervals between visits will be conducted (see Appendix 1).

4.5 Trial Endpoints

4.5.1 Primary Endpoint

The primary efficacy endpoint is proportion of patients with independent renal function at 6 months.

4.5.2 Secondary Endpoints

The secondary endpoints of this study include assessment of:

1. The proportion of subjects with independent renal function, defined as no need for dialysis at 3 months, as compared to historical controls.
2. Renal function at 3 and 6 months expressed as eGFR and as change in GFR from baseline;
3. Number of days with anti-GBM antibodies above a toxic level (i.e. >30 ELISA units) measured at a central laboratory using the Wieslab anti-GBM kit;
4. Disappearance of haematuria, measured in days from start of treatment;
5. Change in proteinuria during the study measured as u-albumin/creatinine ratio in morning void;
6. Number of PLEXs needed;
7. Renal histology measurements and changes in renal histology if a second renal biopsy is performed;
8. Anti-IdeS antibodies (ADA)
9. Pharmacokinetics, Pharmacodynamics (IgG degradation)

4.6 Trial treatments

All patients will receive treatment with a single dose of HMED-IdeS at Day 1 (more details in 6.1.1 Storage and handling).

4.6.1 Plasma Exchange for Treatment of anti-GBM disease

PLEX was introduced for anti-GBM disease in the 1970-ties. Concurrently the prognosis of the disease improved considerably compared to historic control. There is, however, only one randomized study [15]. In this study, the PLEX group showed a better outcome, but the study was not well balanced with respect to severity. There are several studies showing that anti-GBM levels fall much faster with PLEX which together with studies showing that levels of circulating antibodies correlate with prognosis provide additional rationale for the use of PLEX in the treatment of anti-GBM disease.

4.6.2 The treatment of anti-GBM disease with Cyclophosphamide (CYC)

Cyclophosphamide (CYC) was introduced simultaneously with PLEX. [16] No clinical trials specifically addressing the use of CYC or dosing of CYC have been published. Experience from the field of ANCA associated vasculitis a disease with similar clinical features has been used to support the use of CYC in the treatment of anti-GBM disease. In animal models of anti-GBM disease the use of CYC has been shown to reduce autoantibody production [17].

4.6.3 The treatment of anti-GBM disease with Glucocorticoids

Glucocorticoids were introduced for the treatment of various inflammatory conditions in the 1950s. Their efficacy in anti-GBM disease has never been formally tested in

clinical trials, but there use is by expert opinion considered to be as indispensable. Steroid in the combination with CYC and PLEX is recommended treatment for anti-GBM disease according to the Kidney Disease, Improving Global Outcomes 2012 (KDIGO) guidelines [18].

4.7 Trial discontinuation

The study drug will only be given once therefor discontinuation of treatment after the first dose is not applicable in this study. However discontinuation of the infusion before completion is feasible for any safety reason. After the single infusion of IdeS is administered the regular treatment regimen for anti-GBM disease will follow. If patients at this stage wish to withdraw their consent, the planned extra visits and blood sampling included in the study will be stopped. Any collected samples can be destroyed upon the patient's request.

4.8 Data to be recorded

Since this study only will include a maximum number of 15 participants, a paper CRF will be used. Data will be recorded directly on the CRF and will be considered as source data. After the CRF is completed it will be scanned in and sent by email to the study coordinator in Linköping for entry into a database. Appropriate information about the study and information considered important for patients' treatment will also be entered in the patients' medical record.

4.9 Benefit risk assessment

Participants in this study may have a direct benefit from participation, if chronic dialysis for these patients could be avoided. The patients may also have a decreased risk for developing severe lung haemorrhage, which in this disease can start also after onset of severe renal disease. Furthermore, knowledge from this study can lead to opportunities to apply IdeS to other IgG-related autoimmune diseases. These potential benefits should be weighed against the potential risks.

Infections: As IdeS degrades all IgG in the body there is most probably an increased risk of infections during the period when IgG is low. The patients are still protected by their IgM and IgA, which is not cleaved by IdeS. An increased number of infections has not been seen in the phase I and II studies performed so far, but the risk must still be appreciated. To minimize risks patients with ongoing infections requiring antibiotics, chronic virus infections and active tuberculosis will not be allowed in the study. A Quatiferon® test or similar test for latent tuberculosis should be performed at screening, if a positive result is returned after start of treatment specialists in the treatment of tuberculosis should be contacted and appropriate actions taken. To mitigate the risk of infections it is recommended that all patients will be given prophylactic antibiotics until IgG levels return to acceptable values as judged by the investigator. The preferred drug is penicillin V (erythromycin if the patient is allergic to penicillin).

Infusion reactions: Mild to moderate infusion reactions have been noted in some patients and heathy subjects in the phase I and II studies. To reduce this risk premedication with Solu-Medrol 100 mg *i.v.* and 10 mg loratadine *p.o.* will be given before the IdeS infusion.

Unexpected reactions: Cases of serum sickness like reaction has been noted in another phase IIs study. The high doses of corticosteroid used in this study probably reduce this

risk. Analysis of complement components will be done as part of safety monitoring. There is a theoretical a risk that IdeS treatment can lead to a rebound of autoantibody production which can potentiate the disease. Anti-GBM levels will be closely monitored and PLEX should be instituted when (if) rebound occurs. Patients with severe lung haemorrhage that would be most vulnerable for such rebound are not allowed in the study. It is also possible that PLEX has other beneficial mechanisms than autoantibody removal, that IdeS treated patients will not benefit from.

[redacted] an evaluation of the female and male reproductive organ in rabbit and dog were performed as part of the pivotal toxicological studies. In conclusion, there were no observations considered related to IdeS treatment on the female and male reproduction organs neither in rabbit nor dog. In order to avoid pregnancies the requirement for highly effective contraception is part of the inclusion criteria for this study. The patients must be willing to accept birth control methods which are considered as highly effective birth control methods according to *CTFG (clinical trial facilitation group) guidance 2014: Recommendations related to contraception and pregnancy testing in clinical trials.* [18]

Such methods include [19]:

1) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - oral
   - intravaginal
   - transdermal
2) progestogen-only hormonal contraception associated with inhibition of ovulation:
   - oral
   - injectable
   - implantable
3) intrauterine device (IUD)
4) intrauterine hormone-releasing system (IUS)
5) bilateral tubal occlusion
6) vasectomised partner
7) sexual abstinence

In addition, a pregnancy test will be performed prior to dosing and approximately at monthly intervals throughout the study, see appendix 1, Study visit plan.

For risks associated with background medication, PLEX, Glucocorticoids and CYC, see section 8.5.

Overall the risks associated with the current protocol are considered smaller than the potential benefits for the participants.

5. Selection of Patients and Criteria for Discontinuation

The patients have the right to withdraw their consent of participating in the study at any time without giving any reason why and without affecting future care and treatment.

The Sponsor and the investigators reserve the right to discontinue the study at any time for safety reasons or other reasons jeopardizing the justification of the study. Such a termination will be implemented in a time frame that is compatible with the patient's wellbeing. If the study is prematurely terminated or suspended, the investigator will promptly inform the patients and assure appropriate therapy and follow-up. The Sponsor will notify the Regulatory Authorities and the Ethics Committee of any plans to terminate the study.

5.1 Subject inclusion criteria

1. Anti-GBM antibodies detected by ELISA above a level that is considered toxic by the investigator using local laboratory. Patients double-positive for anti-GBM and ANCA may be entered in the trial, but only if their level of anti-GBM antibodies fulfil the criteria listed above.
2. eGFR < 15 ml/min/1.73 m^2 (by MDRD equation) or if the patient is non-responsive to standard treatment, and has lost >15 ml/min/1.73 m^2 after start of treatment
3. Haematuria on dipstick and/or urinary sediment
4. Male or female patients aged at least 18 years; Female patients of childbearing potential may participate if highly effective contraception is used during the study, according to CTFG guidance [18], see also section 4.9 (pregnancy test should be performed before inclusion).
5. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
6. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination, and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to be of clinical significance, may be entered into the study.

5.2 Subject exclusion criteria

1. Anuria for more than 2 days (less than 200 ml during last 48 hours);
2. Dialysis dependency for more than 5 days (maximum 3 sessions before signing informed consent);
3. Ongoing moderate to severe pulmonary haemorrhage (or having ceased within the last two weeks), defined as requiring assisted ventilation, oxygen or blood transfusions.
4. Pregnancy.
5. Symptomatic congestive heart failure (NYHA class 2-4) and requiring prescription medication or clinically evident peripheral edema of cardiac origin;
6. Myocardial infarction, unstable angina or stroke within 3 months prior to screening;
7. Ongoing bacterial infection requiring antibiotic therapy or viral infection with Hepatitis B, C or HIV (up to 3 months old negative test results are accepted); or active tuberculosis as indicated by chest x-ray.
8. Patients should not have received investigational drugs within 30 days prior to screening or within 4 half-lives (whichever is longer); and

9. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

5.3 Subject withdrawal criteria

5.3.1 Criteria for discontinuation from the study

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuation can be:

1. Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment;
2. Risk to patients as judged by the investigator and/or sponsor;
3. Severe non-compliance to protocol as judged by the investigator and/or sponsor;
4. Incorrectly enrolled patients;
5. Patient lost to follow-up;
6. Adverse events;
7. Withdrawal of informed consent for the use of biological samples collected in the study.

Patients who are withdrawn from the study by the investigator due to AE will not be replaced. Patients who withdraw for reasons other than AE may be replaced. A replacement patient must be an eligible patient according to the protocol's inclusion/exclusion criteria and will follow the procedures described in this protocol.

5.3.2 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 AE. If possible, they will be seen and assessed by an investigator(s). AEs will be followed until they resolve, stabilize or the clinical outcome of the patient is ascertained. 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 contacted, e.g., telephone call, to retrieve safety and efficacy data.

5.3.3 Procedures after completion of the trial

Patients who have completed the trial are recommended to be monitored according to the KDIGO-guidelines [17] and according to local practice. Patients with anti-GBM disease require long term follow up and in selected patients maintenance therapy to avoid relapses is of value.

6. Treatment of Patients

6.1 Investigational Medicinal Product

IdeS is a clear colourless liquid. It is formulated at 10 g/L in phosphate buffered saline and intended for intravenous infusion after dilution.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6.1.1 Storage and handling

All patients will receive treatment with HMED-IdeS. HMED-IdeS will be supplied to site [redacted] in 7 mL vials packed into cartons containing 10 vials each. Vials should be kept in the dark at - 20°C. HMED-IdeS infusion solution will be prepared by the pharmacy or site staff 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, labelling and administration of HMED-IdeS are described in the pharmacy manual (provided by Hansa Medical).

6.2 Packaging and labelling

Packaging and labelling of the investigational medicinal product (IMP) will be performed in accordance with Good Manufacturing Practice (GMP) and national regulatory requirements. The IMP will be labelled according to Annex 13, EudraLex Volume 4 and national regulatory requirements.

6.3 Drug accountability and compliance check

The administration of all medication (including IMP) must be recorded in the appropriate sections of the case report form (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 study 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.

6.4 Administration of IMP

An intravenous dose of IdeS will be administered over 30 minutes. Each patient will receive a single dose of 0.25 mg IdeS/kg BW. Detailed instructions on preparation and administration are provided in the pharmacy manual. The infusion may be slowed down or stopped and restarted if required. This will be recorded in the CRF.

6.5 Concomitant Administration of other drugs

A single infusion with the IdeS will be given on top of the standard of care in the treatment of patients with anti-GBM disease. The treatment included in standard of care is Plasma exchange (PLEX), Glucocorticoids (GC) and Cyclophosphamide (CYC).

6.5.1 Plasma exchange (PLEX)

PLEX will be issued according to local practice, and will be given at a dose considered necessary to keep anti-GBM below a toxic level. Observe that the 36 hours after the IdeS infusion there should be no PLEX issued. Also after 36 hours there might be harmless IgG breakdown products circulating that gives false positive results on anti-GBM ELISA. This has to be taken into account when starting PLEX after IdeS treatment. A standard session usually consists of 60 ml/kg (based on actual body weight) using albumin (3% to 5% depending on local availability, with or without crystalloid) as a replacement solution.

The following parameters may be determined according to local practice: 1) PLEX may be performed by centrifugation or filter separation technique 2) Anticoagulation may be provided by citrate or by heparin but it is suggested that in patients with active bleeding regional citrate anticoagulation be utilized, 3) PLEX may be performed via a central venous catheter if patient is deemed unsuitable for peripheral venous access, the latter is strongly recommended, and 4) monitoring of coagulation parameters 5) PLEX dose may be reduced for PLEX related complications according to local best medical practice and indication and dose alteration noted for future analysis.

Local practice should be followed for patients with active bleeding including patients with known pulmonary haemorrhage or a bleeding episode from any source within the 24 hours prior to PLEX treatment. This may include fresh frozen plasma at the end of the exchange. This information will be recorded in the case report form.

NOTE: No PLEX should be done up to 36 hours after the IdeS infusion is administered.

6.5.2 Glucocorticoids (GC)

GC therapy shall commence with intravenous methylprednisolone. Intravenous methylprednisolone shall be given as 3 daily pulse doses. Each pulse dose may be between 0.5 g and 1 g at the local investigators discretion. Any dose given prior to inclusion in the study should be subtracted from the total dose. Additional pulses of methyl prednisolone can be given to curb resistant pulmonary haemorrhage

Oral GC therapy shall commence after stopping methylprednisolone. Oral GC therapy will consist of prednisolone. Dosing will be given according to local practice, preferentially within the range listed in Table 3, which indicates the local guidelines in Linköping for ANCA vasculitis (lower values) and the KDIGO guidelines for anti-GBM disease (higher values). All oral GC will be given as a single daily dose. Patients intolerant of oral medications or for who oral medications are contraindicated may be given an equivalent daily intravenous dose. Prophylaxis against peptic ulcers and osteoporosis will be given based on the investigators decision in each individual case.

Table 3. Recommended range of prednisone dosing

Week	<50 kg	50-75 kg	>75 kg
1	40-50	50-75	60-80
2	40-50	50-75	60-80
3	25-30	30-45	40-60
4	20-30	25-45	30-60
5-6	17.5-20	20-30	25-40
7-8	15-20	17.5-30	20-40
9-10	12,5-20	15-30	17,5-30
11-12	10-20	12.5-20	15-20
13-14	7.5-15	10-15	12.5-15
15-16	7.5-10	7.5-10	10
17-18	5-7.5	7.5	7.5-10
19-26	5-7.5	5-7.5	7.5-10

6.5.3 Cyclophosphamide (CYC)

Induction therapy with CYC will be prescribed for at least 13 weeks in patients with independent renal function, but may be withdrawn earlier in patients considered to have reached end-stage renal disease. As the experience of using either oral or intravenous routes of administration varies between centres and there is no apparent difference in efficacy or safety, the study protocol will allow the use of either oral or intravenous CYC.

A starting dose of 10 mg/kg/pulse will be used for pulse CYC (maximum 1.0 g/dose) or 1.5 mg/kg/day for oral CYC (maximum 150 mg/day) with reductions made for age. In patients responding well to therapy increases should be considered when eGFR is >30 ml/min/1.73m2. Oral CYC will be administered daily with the recommendation for morning administration of full dose, if tolerated. Pulse CYC will be administered intravenous at a frequency of every two weeks for the first 3 doses then every 3 weeks thereafter. Modifications to dose and frequency will be made in the case of leucopenia.

For patients undergoing PLEX, PLEX will not occur for at least 15 hours following an IV dose of CYC.

For patients receiving PLEX and daily CYC (oral or IV), on days when PLEX is performed, CYC will be given following PLEX. PLEX will not be performed for at least 12 hours following a dose of oral CYC.

Full (complete) blood counts will be performed according to local protocol but the following minimum is recommended: patients receiving oral CYC should have their blood count monitored weekly for the first four weeks and weekly for four weeks after any dose adjustment and every other week thereafter. Patients receiving pulse CYC should have their blood count monitored 10 to 14 days after each dose and within 1 day prior to each dose.

Concomitant use of mesna is optional and left to the discretion of the investigator and local practice.

6.5.4 Concomitant medication

Therapeutic IgG based drugs such as Rituximab will be cleaved by IdeS during 7 days following dosing therefore Rituximab treatment within 7 days prior to IdeS dosing is not allowed. Other concomitant medication may be administered at the discretion of the Investigator. All concomitant medication, including premedication and prophylactic antibiotics will be recorded in the CRF, together with the main reason for its prescription.

6.5.5 Premedication

Patients will receive premedication with Solu-Medrol 100 mg *i.v.* and 10 mg loratadine *p.o.* (or equivalent) before the IdeS infusion.

6.5.6 Prophylactic antibiotic

To mitigate the risk of infections it is recommended that all patients will be given prophylactic antibiotics until IgG levels return to acceptable values as judged by the investigator. The preferred drug is penicillin V (erythromycin if the patient is allergic to penicillin). Prophylactic medication against Pneumocystis jiroveci pneumonia (PCP) is strongly recommended, to be begun at day 15, in all patients who are not allergic to sulfamethoxazole or trimethoprim, pentacarinat inhalation can be an alternative. The prophylaxis should be continued for a minimum of 3 months and until prednisone doses are below 12.5 mg/day. Quantiferon® test or similar test for latent tuberculosis should be performed at screening, in case of positive tests results after start of treatment specialist in management of tuberculosis should be consulted and appropriate measures taken.

6.5.7 Laboratory Markers

Plasma samples will be collected for analysis both at local (at site) and at central laboratory in Linköping University Hospital, Sweden, at Hansa Medical AB in Lund, Sweden and [redacted] At screening and Day 1, 3, 7, 10, 15, 22, 29, 50, 93, 135 and 180 (end of study) anti-GBM (for clinical evaluation), Creatinine, Haematology, CRP and urinalysis will be measured. ANCA will be measured Day 1 and 29 and Total IgG and cystatin C will be assessed Day 1, 15, 29 and 180, IdeS concentration (PK) will be taken Day 1, 3,7,10 and 15. PD (IgG) will be assessed Day 1, 3,

7, 10, 15, 22, 29, 50 and 180, ImmunoCAP IgG (ADA) will be measured Day 1, 7, 15, 22, 29, 50, 93 and 180. Complement fragments will be taken at Day 1 and 180, and RNA and Anti-GBM (not for clinical evaluation) will only be taken on Day 1. In addition will serum and plasma samples for research be taken at Visit 2-11, to investigate various cytokines and chemokines and substances related to leukocyte activation and tissue damage, see Study Visit Plan Appendix 1. Anti-GBM samples will be sent both to local and central laboratory, in case of local for clinical evaluation of PLEX and in case of central as study variable. On Day 1 all laboratory samples should be taken before the infusion of IdeS. In addition; anti-GBM, serum, PK and PD (central lab.) should be taken at 2, 6 and 24 hours after start of the infusion of IdeS and anti-GBM (local lab.) should be taken at 6 hours after start of the infusion. Urine samples will also be collected on Days 1, 7, 15, 50, 93 and 180 (end of study) for biomarker assessments including for example complement fragments, inflammatory chemokine and cytokine levels. Blood and urine samples will be sent on the same day for analysis at local laboratories for safety surveillance. Samples for central laboratory will be frozen at site and sent during the study period.

7. Assessment of efficacy

7.1 Efficiency parameters

1. Independent renal function measured as no need for chronic renal replacement therapy.
2. eGFR absolute values and change in ml/min from start of therapy.
3. Change in proteinuria during the study measured as ACR in morning void.
4. Haematuria based on urine sticks, time to remission defined as a value <1+ (in arbitrary units, local laboratory).
5. Histological changes in a second biopsy (optional).

7.2 Method for timing, assessing, recording, and analysis of efficiency parameters

Assessing paragraph 1 (in 7.1) will be a Yes or No if patient is dependent on replacement therapy (haemodialysis or peritoneal dialysis) at the time of assessment (at 6 months primary and at 3 months secondary, after infusion with the IdeS). Assessing paragraph 2-5 will be performed by standard laboratory methods. To obtain reliable values, all blood samples should be taken before PLEX treatment at all sampling time points.

8. Assessment of Safety

8.1 Safety parameters

The primary safety endpoint is the incidence of AEs or disease progression in other organ systems than the kidneys such as the lungs (7.1.5). Other safety endpoints include: change from baseline in all safety laboratory parameters and/or change from baseline in vital signs.

8.2 Method for timing, assessing, recording, and analysis of safety parameters

Assessing safety parameters will be performed at visits; baseline and visit 1-4, 8 and 11 by recording the vital signs and assessing values in blood and urine comparing with

baseline and previous visits. The scheduled visits 5, 7, 9 and 10 can be replaced with telephone contact if the patient is feeling well and no AE occurred. In addition all visits considered necessary for routine clinical follow-up as decided by the investigator.

8.3 Definitions

8.3.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

8.3.2 Serious adverse event (SAE) or serious adverse reaction

Any untoward medical occurrence or effect that:
- results in death,
- is life-threatening
- requires hospitalization or prolongation of existing inpatients hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.
- important medical event

Life-threatening in the definition of a SAE or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.4 Expected adverse reactions

8.4.1 Plasma exchange

Plasma exchange is associated with the following adverse reactions, in 5-10% of procedures [6, 20]:
- Respiratory: dyspnea
- Cardiac: arrhythmias, hypotension
- Metabolic: hypocalcemia, metabolic alkalosis
- Hematologic: coagulation abnormalities, bleeding
- Infection: bacterial infections, catheter related blood stream infections, transmission of viral infections via blood products
- Dermatologic: urticaria
- Neurologic: paresthesia

Plasma exchange is also associated with the following severe adverse reactions, in 0.5% of procedures:
- Respiratory: acute respiratory distress syndrome, non-cardiogenic pulmonary edema transfusion-related acute lung injury (TRALI), pneumothorax, haemothorax
- Cardiac: arrhythmias, hypotension, arterial dissection, air embolism
- Haematological: bleeding, bleeding diathesis, venous thrombosis
- Infection: blood stream infections, sepsis

NOTE: A patient may for practical reasons have to stay in hospital during PLEX treatment, e.g. PLEX early morning and/or a long distance to the hospital. Such

hospitalisation or prolongation of hospitalization should not be reported as an SAE in this study.

8.4.2 Prednisone and prednisolone

Prednisone and prednisolone are associated with the following adverse drug reactions [21, 22]:
- >10%: Central nervous system: Insomnia, nervousness Gastrointestinal: Increased appetite, indigestion
- 1% to 10%: Central nervous system: Dizziness or lightheadedness, headache Dermatologic: Hirsutism, hypopigmentation Endocrine & metabolic: Diabetes mellitus, glucose intolerance, hyperglycaemia Neuromuscular & skeletal: Arthralgia Ocular: Cataracts, glaucoma Respiratory: Epistaxis Miscellaneous: Diaphoresis
- <1% (Limited to important): Cushing's syndrome, edema, fractures, hallucinations, hypertension, muscle-wasting, osteoporosis, pancreatitis, pituitary-adrenal axis suppression, seizures

Prednisone and Prednisolone are also associated with the following severe adverse reactions:
- Musculoskeletal: insufficiency fractures, avascular osteonecrosis
- Cardiovascular: premature atherosclerosis, myocardial infarction
- Gastrointestinal: ulceration and bleeding
- Central nervous system: psychosis
- Endocrine: hyperosmolar non-ketotic state, Addisonian crisis
- Miscellaneous: Bacterial infections, fungal infections, viral infections, ocular herpes zoster

8.4.3 Cyclophosphamide

Cyclophosphamide is associated with the following severe adverse reactions [23, 24]:
- Leucopenia and neutropenia
- Thrombocytopenia
- Anaemia
- Bacterial, viral and fungal infections
- Haemorrhagic cystitis
- Malignancies, especially bladder cancer and haematological malignancies

8.5 Reporting of AE and SAE

All AE and SAE have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All AEs and SAEs will be recorded in the CRF. SAEs will be recorded from the time of informed consent.

All SAEs must be reported, whether or not considered related to the study drug, on a separate SAE Report Form. An assigned CRO [redacted] 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 [redacted] 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, description of the SAE and a preliminary assessment of causality.

Contact Information:

CRO: [redacted]

e-mail: [redacted]

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 should 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]

8.6 Recording and evaluation of SAEs

Individual SAEs need to be recorded and to include expectedness assessment by the investigator and reported to the CPI, central study coordinator for evaluation immediately, and within 24 hours of the investigator becoming aware of the event. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event. The CPI has to keep detailed records of all SAEs reported to him by the investigators.

8.6.1 Assessment of severity

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

8.6.2 Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.
Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.
Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.
Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

8.7 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting as per each approving Regulatory Authority and Ethics Committee as applicable.

8.7.1 Who should report and whom to report to?

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 Reference Safety Information (RSI) in the investigator brochure or is not listed in the RSI at the specificity or severity that has been observed.

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 Safety Management Plan. This plan is based on agreement with [redacted]

It is the responsibility of the site Investigator to promptly notify the Ethics Committee and other appropriate institutional regulatory bodies of all SUSARs received involving risk to human subjects as per their applicable requirements.

8.8 Reporting adverse events and breaches

8.8.1 Reporting adverse events

The CPI, i.e. sponsor, is responsible for the prompt notification to all concerned investigator(s), the Research Ethics Committee and competent authority (Regulatory Authority) of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorization to continue the trial in accordance with current regulations. An annual report will be written to the Competent Authority and the Research Ethics Committee.

8.8.2 Reporting on breaches

The sponsor shall notify the competent authority and Ethics Committee about a serious breach of this protocol without undue delay but no later than seven days of becoming aware of that breach. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

8.9 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported until the end of the study.

8.10 Developmental Safety Update Report (DSUR)

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited competent authorities (i. e.

läkemedelsverket in Sweden) and ethics committee in accordance with existing EU regulations. This safety report consists of a list all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system. The report will also consist about the safety of the patients, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation, i.e., benefit-risk profile of the investigational drug.

8.11 Study Risk Assessment

A PI from each country will constitute an internal Data and Safety Monitoring Board (DSMB) for this trial. The DSMB will have teleconferences at regular intervals and will discuss if dose reductions, protocol amendments or early termination of the study should be necessary. A specific document is prepared for DSMB Procedures which also includes safety laboratory variables to be evaluated (Internal Data Safety Monitoring Board Procedures, vers.no 1). Data from this trial will be handled by the CPI and the study coordinator in Sweden with significant experience in conduct clinical trials. The CPI recognizes the responsibilities of data management with respect to the ethical practice of research and the adequate protection of human subjects. All study investigators are trained and certified in GCP standards. Additionally, all staff and investigators in this study who contact patients or their data or have the potential to handle patient data are required to be instructed in whom to provide documentation of GCP.

9. Statistical Considerations

All subject baseline characteristics and demographic data (age, sex, weight, height, smoking status, viral test results, eGFR, proteinuria, ACR, physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications at study entry will be listed by study center and subject number, and will also be summarized.

9.1 Sample Size Estimation

Since 1990, there are 11 case series published on anti-GBM disease with a total of 461 patients, the combined renal survival (patient alive and free from dialysis) among these historical controls at 6-12 months for patients with creatinine > 500 µmol/L was 7%. In a more recent not yet published study the renal survival was 20 % (11/53). In the present study we will also include patients that are refractory to standard therapy, justifying the 7 % figure to be used for the sample size estimation. If IdeS treatment would result in a survival rate similar to AAV (i.e. 50%) the study would have a power of 0.98 to detect a difference with a sample size of 15. If the survival rate instead would be 40 % or 30 % the power will be 0.92 and 0.77. If only 10 patients are recruited to corresponding figures would be 0.94 (50 %), 0.83 (40 %) and 0.65 (30 % survival).

The incidence of anti-GBM disease is estimated to 1 per million inhabitants per year. Of these, we estimate that about 65% will comply with the inclusion and exclusion criteria of the study protocol. We have an approximate catchment area of 35 million inhabitants. If half of those eligible for the study actually are included the study will be able to enroll about 15 participants over an 18 month period. See also under section 4.3 Number of Participants.

9.2 Outcome calculations

Chi square ($\chi 2$) calculations (alt. Fisher's exact test), at significance level p=0.05, will be used to compare the proportion patients without need for dialysis. The authors of the published series will be contacted in order to better define the comparison group. Patients with adverse renal prognosis in these studies will be defined as patients who are either oliguric, having started dialysis, having a creatinine of above 500 at diagnosis or progressing in spite of therapy. Only patients receiving standard therapy will be included in the final analysis.

In the secondary analysis (efficacy endpoint 2) changes in eGFR will be assessed using matched controls from two recent studies (Alchi and McAdoo). Patients will be matched for eGFR, sex, histology (percentage of crescents categorized), ANCA positivity and age (also in categories). Dialysis and death will be considered as eGFR of 0, as creatinine measurements do reflect dialysis efficacy rather than GFR in dialysis patients. Analysis will be performed using paired t-test at 3 and 6 months. Multiplicity will be corrected by post-hoc test (e.g. Bonferroni).

For the other endpoints (3-6) descriptive statistics will be used; these data are important mainly for the design and power calculations in future studies. Anti-GBM antibodies will be measured at a central laboratory. A toxic level is predefined as 30 ELISA units when using the Wieslab anti-GBM ELISA kit. Each plasma sample for visit 2-10 (day 93) will be defined as above or below this level. All days in between two samples will classified as above the toxic level if both samples are above the cut-off, and half of the days if one only of the samples is above cut off. The number of days with toxic levels will be expressed in median, interquartile range, box plots and as histograms.

The number of PLEX sessions will add up for each patient and expressed as median and interquartile range, box plots and as histograms. Disappearance of haemturia will be based on local laboratory dipsticks and the first study visit with a negative test (or trace amount) will be entered. Results will again be expressed as median and interquartile range, box plots and as histograms. Albumin/creatinine ratio will be analysed in the central laboratory at visit 4, 6, 9, 10 and 12. At each time point the value of that day will compared with the pre-treatment value for day 1, the result will expressed as the percentage which in turn will expressed as median and IQR for each day and presented graphically.

10. Study Monitoring

Monitoring of sites in Sweden and Denmark will be performed by [redacted] Linköping will be monitored by [redacted]. Sites outside Scandinavia will be monitored by independent staff contracted locally.

11. Procedures for Recruitment and for obtaining informed consent

Patients with suspected anti-GBM disease will usually be referred to a nephrology department. As soon as the diagnosis of anti-GBM disease is confirmed and the inclusion and exclusion criteria are met, the nephrologist who is responsible for the treatment of this patient will inform and ask the patient if he/she is interested in participating in the study. The study will be explained and written information will be provided. Patients

will be given one to three hours (or more if advise from relatives are needed) to consider their decision to participate after they have indicated that they agree to consider participation. The short time frame to consider participation is because it is important to start treatment as soon as possible with either study medication, i.e., IdeS, if the patient signs the informed consent or if not, PLEX. Patients who consent to participate will be asked to fill out the consent form. The treating nephrologist will also sign the consent form. The infusion of IdeS should be given within 48 hours after the signing of the informed consent.

Anti-GBM disease patients are usually hospitalized for several weeks with intensive treatment and initial daily PLEXs.

If an anti-GBM disease patient is not treated at any of the participating centres, the patient can be referred to such a centre if the patient wants to participate in the study.

12. Ethical Considerations

12.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

12.2 Protection against risks

Recruitment will occur through the investigators' clinical practices and from referring physicians. The Independent Ethics Committees of each participating country/center will provide ethical review and approval for this protocol as well as the consent forms to be used prior to study start or enrolment. Details of the goals of the research and the risk and benefits of the protocol will be reviewed with each potential study subject. Recruitment will occur by physicians, study nurses, and research coordinators.
Patients who decline to participate in any or all parts of the study will still have available the opportunity of evaluation by a nephrologist if they or their physician feels this is appropriate.
Strict patient confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the research team, no individually identifiable patient data will be distributed to non-research or care-giving team members.
In the event of adverse effects from the study, the full resources of the hospital will be available to intervene as medically necessary. Licensed physicians expert in the care of patients with vasculitis are available at all times at each study site.
To avoid possible worsening of ongoing infections, patients who have active antibiotic treatment because of ongoing infections will be excluded. To prevent new infections all included patients will receive antibiotic prophylaxis (see 6.5.6).

12.3 Trial Ethical Approval

Each national coordinator or local coordinator will apply for national or regional ethics approval. Site agreements will be contingent upon the provision of evidence that study personnel have completed GCP training.

13. Handling and Archiving of Data

The Sponsor is obligated to ensure that monitoring persons, ethics committees and competent authority have the right to have access to the source data. The Sponsor also ensures that patients agree that the above parties have access to their patient records. Source data is patient records and the study CRF, a source data list will be used. A subject identification code list will be created in order to trace data to the individual subject. The code will not be based on participants' initials or birth-date. The CPI and/or study coordinator will safeguard the key to the code to ensure patient confidentiality.

13.1 End of study report

The sponsor will notify the accredited drug authorities and ethics committee at the end of the study within a period of 90 days and a final report within 12 months. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited drug authorities and ethics committee within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study.

13.2 Archiving data

After completion of the study will all study data be archived for 15 years in a special storage area for this purpose.

14. Insurance

Products liability insurance will be held by Hansa Medical AB.

15. Funding

This trial is partly funded by the Hansa Medical AB, Lund, Sweden. The study is also funded by a grant from the Ingrid Asp Foundation in Linköping.

16. Reporting and Publishing

Results will be reported in scientific publications, as presentations at scientific conferences and also to the general population as popular science reports. As obligated, both the protocol and results will be publicly available.

Authors of these reports will preferably be active study investigators and researchers, from both academia and the funding company, Hansa Medical AB.

17. References

[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1e11.

[2] Hudson BG, Tryggvason K, Sundaramoorthy M. Alport's syndrome, Goodpasture's syndrome, and type IV collagen. N Engl J Med 2003; 348: 2543–2556

[3] Salama AD, Levy JB, Lightstone L. Goodpasture's disease. Lancet 2001; 358: 917–920

[4] Segelmark M, Hellmark T, Wieslander J. The prognostic significance in Goodpasture's disease of specificity, titre and affinity of anti-glomerular-basement-membrane antibodies. Nephron Clin Pract 2003; 94: c59–c68

[5] Yang R, Hellmark T, Zhao J. Levels of epitope-specific autoantibodies correlate with renal damage in anti-GBM disease. Nephrol Dial Transplant 2009; 24: 1838–1844

[6] Jayne DR, Gaskin G, Rasmussen N. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18: 2180–2188

[7] Hellmark, Segelmark. Anti-GBM disease; in Oxford Textbook of Medicine 6th edition, in press

[8] HMed doc. No. 2012-003

[9] von Pawel-Rammingen U, Johansson BP, Björck L. IdeS, a novel streptococcal cysteine proteinase with unique specificity for immunoglobulin G. EMBO J. 2002 ;21: 1607-1615.

[10] Wenig K, Chatwell L, von Pawel-Rammingen U, Björck L, Huber R, Sondermann P. Structure of the streptococcal endopeptidase IdeS, a cysteine proteinase with strict specificity for IgG. Proc Natl Acad Sci U S A. 2004;101:17371-17376.

[11] Vincents B, von Pawel-Rammingen U, Björck L, Abrahamson M. Enzymatic characterization of the streptococcal endopeptidase, IdeS, reveals that it is a cysteine protease with strict specificity for IgG cleavage due to exosite binding. Biochemistry. 2004; 43:15540-15549.

[12] HMed Doc. No. 2014-003

[13] Orbach et al., 2005, Rituximab Summary of Product Characteristics

[14] Alchi B, Griffiths M, Sivalingam M, Jayne D, Farrington K. Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort. Nephrol Dial Transplant. 2015;30:814-21

[15] Johnson JP, Moore J Jr, Austin HA 3rd, Balow JE, Antonovych TT, Wilson CB. Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine (Baltimore). 1985;64:219-227.

[16] Rossen RD, Duffy J, McCredie KB, Reisberg MA, Sharp JT, Hersh EM, Eknoyan G, Suki WN. Treatment of Goodpasture syndrome with cyclophosphamide, prednisone and plasma exchange transfusions. Clin Exp Immunol. 1976 Apr;24(1):218-22.

[17] Pusey CD, Bowman C, Peters DK, Lockwood CM. Effects of cyclophosphamide on autoantibody synthesis in the Brown Norway rat. Clin Exp Immunol. 1983;54:697-704.

[18] Anti-glomerular basement membrane antibody glomerulonephritis. Kidney International Supplements, Chapter 14 (2012) 2, 240-242.

[19] The Heads of Medicines Agencies, Clinical Trial Facilitation Group (CTFG), Key documents list, Guidance: Recommendations related to contraception and pregnancy testing in clinical trials, September 2014 |pdf http://www.hma.eu/ctfg.html

[20] Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. Am J Kidney Dis. 1994;23:817-827.

[21] Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006;54:628-634.

[22] Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, Kohler JA, Furst DE. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med. 1994 Feb;96(2):115-23.

[23] Walsh M, Faurschou M, Berden A, Flossmann O, Bajema I, Hoglund P, Smith R, Szpirt W, Westman K, Pusey CD, Jayne DR; European Vasculitis Study Group. Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis. Clin J Am Soc Nephrol. 2014;9:1571-1576.

[24] FASS, produktresume´ för Sendoxan
http://www.fass.se/LIF/product?nplId=19860613000150&userType=0