Clinical Study Protocol

A Randomized, Open-Label, Multi-Centre, Active Control Study Investigating the Efficacy and Safety of Imlifidase in Eliminating Donor Specific Anti-HLA Antibodies in the Treatment of Active Antibody-Mediated Rejection in Kidney Transplant Patients

Clinical Study Protocol No.:	16-HMedIdeS-12
Investigational Medicinal Product:	Imlifidase
Phase:	II
Version:	6.3_US
EudraCT Number:	2018-000022-66
IND Number:	128074
Name and Address of Sponsor:	Hansa Biopharma AB P.O. Box 785 SE-220 07 Lund Sweden

SYNOPSIS

Name of Sponsor/Company Hansa Biopharma AB (hereafter referred to as Hansa Biopharma)	
Title of the study A Randomized, Open-Label, Multi-Centre, Active Control Study Investigating the Efficacy and Safety of Imlifidase in Eliminating Donor Specific Anti-HLA Antibodies in the Treatment of Active Antibody-Mediated Rejection in Kidney Transplant Patients	
Co-ordinating Signing Principal Investigator Stanley C. Jordan, M.D.	
Study Site(s) Approximately 14 sites, in US, Europe and Australia will be included	
Planned study period First subject first visit: Q1 2019 Recruitment period: 35 months Last subject last visit: Q3 2022 Completion of the clinical study report: Q1 2023	**Clinical Phase** II

Background and Scientific Justification for Conducting the Study

Antibody mediated rejection (AMR) is one of the most challenging adverse events after kidney transplantation and despite advances in the understanding of the pathophysiological processes causing this reaction it remains the main cause for graft dysfunction. AMR can occur in patients with preexisting anti-Human Leukocyte Antigen (HLA) Donor-Specific Antibodies (DSA) or in patients without DSA at transplantation but who develop de novo DSA.

Transplant Glomerulopathy (TG) is a known consequence of persistent DSA positivity which rapidly dissipates allograft function resulting in graft failure and return to dialysis with attendant emotional consequences for the patients and financial costs for the health care system.

Currently used therapies include high dose IVIg +/- rituximab, Plasma Exchange (PE) with low dose IVIg +/- rituximab, eculizumab and a minimal experience with bortezomib. However, no therapy is currently approved, and patients are often treated with combination therapies that make analysis of efficacy of any one agent difficult. Thus, there is a large unmet clinical need for new therapies to prevent and treat AMR.

This study is designed to investigate the safety and efficacy of imlifidase removing anti-HLA antibodies in the treatment of active or chronic active AMR after transplantation. The primary objective of this study is to determine if imlifidase is effective in removing DSAs and thus lessen antibody mediated kidney damage in subjects experiencing post-transplant antibody mediated rejection.

Objectives

The primary objective of this study is to:

- Investigate the efficacy of imlifidase compared with PE in removal of DSA in patients who are experiencing an active or chronic active AMR episode after kidney transplantation

Secondary objectives of this study are to:

- Evaluate DSA levels up to 180 days after treatment
- Evaluate HLA-antibodies levels up to 180 days after treatment
- Evaluate the overall kidney function up to 180 days after treatment
- Investigate the occurrence of AMR up to 180 days after treatment
- Investigate the safety and tolerability of imlifidase compared to PE in patients experiencing active or chronic active AMR episodes
- Evaluate the number of PE-sessions needed
- Evaluate the pharmacokinetics, pharmacodynamics and immunogenicity of imlifidase

Endpoints

The primary endpoint of this study is:

- Maximum reduction in mean DSA level at any time point during the 5 days following the start of treatment

Secondary endpoints of this study are:

- DSA levels up to 180 days after treatment
- HLA-antibodies levels up to 180 days after treatment
- Kidney function change from baseline, (at screening), as evaluated by eGFR, P-creatinine and albumin/creatinine ratio in urine up to 180 days after treatment
- Proportion of subjects with graft loss within 180 days of treatment
- Signs of transplant glomerulopathy 180 days post treatment
- Change from baseline (at screening) in histopathology per Banff Criteria at 29 and 180 days
- Change from baseline (at screening) in mRNA levels in kidney biopsies evaluated [redacted] at 29 and 180 days from baseline. If kidney biopsy is performed before screening, mRNA levels will be evaluated on day 29 and day 180 (no baseline will be available)
- Safety parameters (AEs, safety laboratory tests, vital signs and ECG)
- Type, frequency and intensity of adverse events
- Number of sessions with PE
- Total Serum IgG levels over time
- Presence of intact IgG on SDS-page/Western blot until start of IVIg treatment
- DSA functionality determined by C1q or C3d analysis pre- and post-treatment
- PK profile of imlifidase (C_{max}, T_{max}, $t_{½}$, AUC, CL, V)
- Presence of ADA (anti-imlifidase IgG)

Methodology

This is a randomized, open label, multi-centre, active control study. The study will primarily examine the reduction in mean levels of DSA after treatment with imlifidase compared with PE in patients diagnosed with active or chronic active AMR according to Banff 2017 criteria, including presence of DSA(s). Included subjects will be randomized to receive either one dose of imlifidase 0.25 mg/kg or 5-10 sessions of PEs. All subjects will receive pulse methylprednisolone for three days, starting before the first treatment, followed by a tapering schedule with prednisolone/prednisone. Subjects will receive high dose IVIg 3 days after imlifidase treatment and directly after the last PE. A single dose of rituximab will be given 5 days after completed IVIg infusion.

Study Procedures/Assessments

Before inclusion into the study, a biopsy will be collected from all subjects, and assessments of DSA and ADA (IgE), vital signs, ECG as well as laboratory parameters including haematology, clinical chemistry, haemostasis, urinalysis, and PCR test for SARS-CoV-2 will take place. Subjects will be randomised to imlifidase infusion, 0.25 mg/kg over 15 min, or 5-10 PE treatment, and subsequently followed for 180 days after start of treatment. Blood samples for DSA, PK, PD and ADA will be collected at multiple time points during the study. Protocol biopsies will be performed on day 29 and on day 180 and kidney function will be followed by plasma or serum creatinine measurements, eGFR calculations and urine sample for measurement of albumin/creatinine ratio during the full study period.

Safety parameters will be assessed up to day 180. Reporting of adverse events will be done throughout the study.

Number of subjects

A total of 30 subjects will be included in the study distributed as 20 subjects in the imlifidase arm and 10 subjects in the PE arm. The sample size is not based on a formal calculation but with 20+10 subjects the expected width of the 95% CI of the difference in DSA reduction at any timepoint during the 5 days following the start of treatment (primary endpoint) is 8% point. This expected width is considered acceptable for evaluating a possible difference or similarity between the two treatments.

Diagnosis and main criteria for inclusion/exclusion

Main inclusion criteria are:

- Male and/or female donor kidney recipients, age ≥18 years at the time of screening
- Presence of DSA(s)
- Meet the Banff 2017 criteria for active or chronic active AMR
- At least 25% rise in serum creatinine compared to last individual value taken prior to the AMR. Patients with delayed graft function and AMR within 10 days after transplant (confirmed by kidney biopsy) can be included regardless of serum creatinine level

Main exclusion criteria are:

- Previous treatment with imlifidase
- Previous high dose IVIg treatment (2 g/kg) within 28 days prior to inclusion
- Subjects with significantly abnormal general serum screening lab results, judged inappropriate for inclusion in the study by the investigator
- Clinically relevant active infection(s) as judged by the investigator
- Any condition that in the opinion of the investigator could increase the subject's risk by participating in the study such as severe immune deficiency and severe cardiac insufficiency (New York Heart Association (NYHA) Class IV) or severe uncontrolled heart disease

- Known allergy/sensitivity to imlifidase, IVIg and/or rituximab and the respective excipients
- Patient unable to tolerate treatment with plasmapheresis or immunoadsorption, as judged by the investigator
- Positive PCR test for SARS-CoV-2 virus infection
- Current diagnosis or history of thrombotic thrombocytopenic purpura (TTP), or known familial history of TTP

Medicinal Product(s)

Imlifidase is provided as a freeze-dried powder for concentrate for solution for infusion, 11 mg per vial. After reconstitution with sterile water for injection, the concentrate contains 10 mg/mL imlifidase. The concentrate will be added to 50 mL sodium chloride 9 mg/mL (0.9 %) solution for infusion and administered as an infusion.

PE will be prepared and administered according to standard at each site.

Duration of treatment

Subjects randomized to imlifidase treatment will receive one intravenous dose of imlifidase, 0.25 mg/kg, administered over 15 minutes.

Subjects randomized to PE treatment will receive 5-10 sessions of PE, as judged by the investigator.

Statistical methods

This is an open-label study and the statistical evaluation and presentation of data will be descriptive by nature. For the primary endpoint and certain secondary endpoints, the treatment difference will be presented with 95% CI. The continuous efficacy endpoints will be summary tabulated by n, mean, median, standard deviation, minimum and maximum and presented graphically when relevant. Categorical efficacy responses will be presented by counts and percentages. The safety endpoints will be summarised as for the efficacy endpoints.

Protocol Revision History including Summary of Changes

Protocol Version	Date	Including Amendment Type and No.	Overall Rationale for Changes
6.3_US	17Nov2021	Non-substantial amendment no. 03	• Change in CRO responsible for SAE/SUSAR reporting • Extension of study duration by 6 months • Updated number of study sites to approximately 14
6.2_US	06Oct2020	Substantial amendment no. 02	• To ensure that patients with asymptomatic Covid-19 are not included in the trial • Serum sickness no longer classified as a risk • Thrombocytopenic purpura (TTP) is now defined as a contraindication Extension of study duration by 9 months
6.1_US	03Mar2020	Amendment No. 01	• Allow for a kidney biopsy performed within standard of care to be used for inclusion. • Clarify inclusion criteria #5 by adding chronic active AMR. • Clarify that the 3 latest creatinine values prior to the *current* AMR will be collected. • Extension of study duration by 8 months. • Benefit/risk section was updated with new number for infusion reactions according to the latest version of IB.
6.0	22 Mar 2019	N/A	Initial approved protocol

See Appendix 1 “Clinical Study Protocol Amendment” for details of Amendment No 03

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AMR	Antibody Mediated Rejection
AUC	Area Under the Curve
CKD	Chronic Kidney Disease
CL	Clearance
C_{max}	Maximum serum concentration
CRF	Case Report Form
CRO	Contract Research Organis
CSR	Clinical Study Report
DSA	Donor Specific Antibody
DD	Deceased Donor
ECG	Electrocardiogram
EOS	End of Study
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FU	Follow up
GCP	Good Clinical Practice
HLA	Human Leukocyte Antigen
IA	Immunoadsorption
ICH	International Conference on Harmonisation
IdeS	Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IVIg	Intravenous Immunoglobulin
LD	Living Donor
[redacted]	[redacted]
NIMP	Non-Investigational Medicinal Product
PD	Pharmacodynamics
PE	Plasma Exchange
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set

PPS	Per Protocol Analysis Set
PQC	Product Quality Complaint
RA	Regulatory Authority
SAB	Single Antigen Bead
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Document Verification
SOC	Standard of Care
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Thrombotic Thrombocytopenic Purpura
T_{max}	Time to maximum plasma concentration
$t_{1/2}$	Terminal half-life
V	Volume

1. INTRODUCTION

The company code initially used for the active substance in this project was HMED-IdeS (sometimes abbreviated to IdeS) and thus many reports refer to this name.

The International Non-proprietary Name (INN) imlifidase was recently assigned for the active substance and this name will be used throughout this document.

1.1. Background

Patient population and unmet medical need

Antibody Mediated Rejection (AMR) is one of the most challenging adverse events after kidney transplantation and despite advances in the understanding of the pathophysiological processes causing this reaction it remains the main cause for graft dysfunction. AMR can occur in patients with preexisting anti-Human Leukocyte Antigen (HLA) Donor-Specific Antibodies (DSA) or in patients without DSA at transplantation but who develop de novo DSA.

Significant advances have occurred in the ability to predict patients at risk for and to diagnose AMR. The pathophysiology of AMR suggests a prime role for antibodies, B-cells and plasma cells. Recent research has indicated that B-cells and plasma cells produce DSAs that interact with the endothelium, which activates the cellular pathways responsible for the development of microcirculatory changes and tissue injury.

Satisfying data on the effectiveness of currently available therapies is limited, and post-transplant AMR and chronic AMR remain significant problems (Djamali et al. 2014). Transplant Glomerulopathy (TG) is a known consequence of persistent DSA positivity which rapidly dissipates allograft function resulting in graft failure and return to dialysis with attendant emotional consequences for the patients and financial costs for the health care system (Gloor et al. 2008; Jordan et al. 2010; Lefaucheur et al. 2010; Port et al. 1993; Reinsmoen et al. 2008; OPTN 2012). Therapies for AMR are limited (Sellares et al. 2012). Currently used therapies include high dose IVIg +/- rituximab, plasma exchange (PE) with low dose IVIg +/- rituximab, eculizumab and a minimal experience with bortezomib. However, no therapy is currently approved, and patients are often treated with combination therapies that make analysis of efficacy of any one agent difficult. Thus, there is a large unmet clinical need for new therapies to prevent and treat AMR.

Imlifidase

Imlifidase is an IgG-degrading enzyme of *Streptococcus pyogenes* that cleaves all four human subclasses of IgG with strict specificity. Imlifidase hydrolyzes human IgG below the hinge region thereby generating one $F(ab')_2$ fragment and one Fc-fragment which does not bind to Fcγ-receptors and does not activate complement. Thus, the proteolytic activity of imlifidase on IgG molecules prevents IgG mediated phagocytosis, antibody-dependent cellular cytotoxicity and complement mediated injury (Winstedt et al. 2015; Jarnum et al. 2017). Imlifidase is highly specific towards IgG and other Ig molecules, i.e. IgA, IgD, IgE and IgM, are not cleaved and no other substrates have been identified. Apart from imlifidase restricted target specificity, the speed of the reaction is a major advantage of imlifidase. Within a few hours after dosing, the

entire pool of IgG is fully cleaved into $F(ab')_2$ and Fc fragments thereby creating a window where IgG levels are kept very low for approximately one week.

Repeat dose toxicology studies have been performed in rabbit and dog and the no observed adverse effect level (NOAEL) was set to 2 mg/kg and lowest observed adverse effect level (LOAEL) to 20 mg/kg in both species.

Previous clinical experience with imlifidase

Six studies with imlifidase have been completed:

1. First human study, to assess the safety and tolerability of the IgG cleaving enzyme from the *Streptococcus pyogenes* Immunoglobulin G degrading enzyme of (11-HMedIdeS-01, EudraCT no. 2012-000 969-21).
2. A study to evaluate the safety and efficacy of imlifidase in Chronic Kidney Disease Patients (CKD) (13-HMedIdeS-02, EudraCT no. 2013-005417-13)
3. A phase II study to evaluate the safety, tolerability, efficacy and pharmacokinetics of intravenous ascending doses of imlifidase in kidney transplantation in sensitized patients (13-HMedIdeS-03, EudraCT no. 2014-000712-34)
4. A phase II pilot study to evaluate the safety, tolerability, efficacy, pharmacodynamics and pharmacokinetics of imlifidase in asymptomatic antibody-mediated thrombotic thrombocytopenic purpura (TTP), in patients with low ADAMTS13 (15-HMedIdeS-08, EudraCT no. 2016-000249-30).
5. A phase I/II study to assess safety, tolerability and efficacy of imlifidase given immediately prior to kidney transplantation to reduce DSAs in highly sensitized CKD patients awaiting DD kidney transplantation (14-HMedIdeS-04, FDA IND 124301)
6. A phase II study to evaluate the efficacy of imlifidase to desensitize transplant patients with a positive crossmatch test, the primary endpoint is conversion of a positive crossmatch test to negative in highly sensitized patients (15-HMedIdeS-06, FDA IND 128074, EudraCT no. 2016-002064-13)

Study 11-HMedIdeS-01 was a double blind, randomized, dose escalation study in healthy subjects performed in Sweden. Two clinically effective doses (0.12 and 0.24 mg/kg) were identified and imlifidase was considered safe and well tolerated in the population.

Study 13-HMedIdeS-02 was a Swedish single-centre, single arm, dose finding, Phase II study in sensitized CKD patients with the primary endpoint to find an imlifidase dosing scheme resulting in HLA-antibody levels acceptable for transplantation in the majority of patients. Patients received imlifidase infusions of 0.12 mg/kg twice, 0.25 mg/kg once, or 0.25 mg/kg twice. The study also assessed safety, tolerability, pharmacokinetics, and pharmacodynamics of imlifidase. The study did not include transplantation of the patients. However, patients were not removed from the transplant waitlist during the study and one patient was transplanted following imlifidase treatment. The efficacy objective was reached, and imlifidase was considered safe and well tolerated.

Study 13-HMedIdeS-03 was a Swedish two-centre, single arm, Phase II study to assess safety and efficacy of imlifidase given immediately prior to kidney transplantation to reduce DSAs in sensitized CKD patients awaiting deceased donor (DD) or living donor (LD) transplantation. The primary endpoint was safety. Ten patients (8 DD, 2 LD) were treated with single doses of 0.25 or 0.5 mg/kg imlifidase along with standard immunosuppressive treatment, but no additional desensitizing agents. Imlifidase was well tolerated at both doses, efficiently reduced anti-HLA antibody levels, including DSA, and all 10 patients could be transplanted.

Study 15-HMedIdeS-08 was a Phase II pilot study in UK to evaluate the safety, tolerability, efficacy, pharmacodynamics and pharmacokinetics of imlifidase in asymptomatic antibody-mediated thrombotic thrombocytopenic purpura patients with low ADAMTS13 activity. The study was prematurely terminated due to a non-favorable risk benefit profile in the first two patients, presumably related to the underlying disease. The patients were dosed with 0.25 mg/kg imlifidase.

Study 14-HMedIdeS-04 was an investigator-initiated phase I/II, single arm, exploratory study in the US. Patients received a single dose of 0.24 mg/kg imlifidase in addition to pre-treatment with rituximab and IVIg. Patients were eligible for inclusion if they had a panel reactive antibodies (PRA)> 50% and a positive crossmatch test against their available DD or had DSA(s) before imlifidase treatment. The study enrolled 17 patients all being transplanted.

Study 15-HMedIdeS-06 was a Phase II study in the US and EU. The study enrolled patients with DSAs and a positive crossmatch test to their available LD or DD. A total of 18 patients were enrolled and transplanted with a kidney from a DD (13) or LD (5). Enrolled patients were treated with imlifidase on day 0. In addition to imlifidase, patients were given high dose IVIg (2 g/kg, maximum of 140 g) on day 7 and rituximab on day 9. DSA levels were monitored pre- and at several time points after imlifidase dosing. Safety, including kidney function, was monitored at multiple time points up to 180 days after treatment. Pharmacokinetics (PK), Pharmacodynamics (PD) and Anti-Drug Antibody (ADA) were measured.

Two studies with imlifidase are ongoing:

1. A phase II study to evaluate the efficacy and safety of imlifidase in anti-GBM disease (Glomerular Basement Membrane/Goodpasture's disease) with adverse renal prognosis (15-HMedIdeS-10, EudraCT no. 2016-004082-39)
2. A prospective, observational long-term follow up study of patients treated with imlifidase prior to kidney transplantation (17-HMedIdeS-14, FDA IND 128074)

Study 15-HMedIdeS-10 is an ongoing investigator initiated multi-centre, open-label Phase II study conducted in EU. The study will enroll 15 patients. Imlifidase 0.25 mg/kg is given IV over 30 min to patients with severe anti-GBM disease on background of standard care consisting of pulse methylprednisolone, oral prednisolone/prednisone and intravenous cyclophosphamide combined with PE.

Study 17-HMedIdeS-14 is an ongoing, five year, follow up, observational study. Up to 46 subjects who have participated in previous studies, received imlifidase and been transplanted will be enrolled.

1.2. Study Design and Dose Rationale

Antibodies to HLA antigens have a strong correlation with allograft injury and loss. More than 5000 renal allografts are lost each year in the U.S., approximately 75-80% due to antibody mediated injury (Loupy et al. 2012). Clearly, the most important way to approach antibody mediated allograft injury is through the development of antibody-targeted therapies. This would address all pathogenic mechansisms associated with alloantibodies and allow grafts to continue functioning for much longer periods of time. Successful treatment would improve the length and quality of life of allograft recipients and reduce costs to the health care system.

This is a randomized, open-label, multi-centre study, designed to investigate the safety and efficacy of imlifidase compared with PE, in removing anti-HLA antibodies to treat active or chronic active AMR post-transplant. Imlifidase at 0.25 and 0.50 mg/kg have been demonstrated to be safe and effective in removing IgG antibodies including DSAs in patients awaiting kidney transplantation.

20 subjects will be randomized to receive a single dose of 0.25 mg/kg imlifidase. High dose IVIg will be given on day 4 (this may be given over 2 days) and then a single dose of rituximab 5 days after completion of the IVIg infusion.

10 subjects will be randomized to be treated with PEs. 5-10 sessions of PE will be performed at the discretion of the investigator. Immunoadsorption (IA) may replace PE, at the investigator's discretion. Subjects in the PE arm will be treated with high dose IVIg on the last day of PE (may be given over 2 days as judged by the investigator) followed by a single dose of rituximab given 5 days after completion of the IVIg infusion.

1.3. Benefit/Risk Aspects

Subjects in this study may benefit from being treated with imlifidase to resolve early graft rejection. The potential benefit of imlifidase compared to currently used methods, e.g. PE, is the efficacious and immediate removal of DSAs. It is anticipated that a faster DSA removal will result in less damage to the allograft and thus a better outcome for the patient. If imlifidase fails to remove DSAs to satisfactory levels or if the DSAs rebound, the patient will be treated with PE and/or other standard of care (SOC) treatments, as judged by the investigator. SOC treatment can be initiated at any point for patients in the treatment arm if needed. The decision to initiate other SOC treatments will normally be based on DSA rebound. Since DSA is monitored frequently, signs of antibody rebound will be detected early and appropriate treatment initiated immediately. Thus, it is anticipated that there will be no risk that the patient does not receive the best available treatment.

Since imlifidase effectively removes the IgG pool, there may be an increased risk of infection. To minimize the risk for bacterial infections all subjects included in the study will receive prophylactic antibiotics. Subjects will be closely monitored for infections and instructed to contact the principal investigator immediately if they have any sign of infection. There will be a physician specialized in infectious diseases available for medical advice in case of a patient showing signs of infection. In case of infection in a patient with low IgG plasma levels, intravenous immunoglobulin may be indicated. Subjects will be screened for SARS-CoV-2 and subjects with a positive test will not be included in the study. As SARS-CoV-2-naïve subjects

do not have any IgG antibodies towards the virus, and since imlifidase does not prevent IgG synthesis, administration of imlifidase is not considered to have any impact on patient safety should the subject subsequently become infected with SARS-CoV-2.

Although samples for analysis of ADA will be taken at screening, it is not possible to wait for the sample to be analyzed before inclusion in the study as this would delay the treatment and thus have a serious impact on patient outcome.

As for all biologics, there is a risk of infusion reactions associated with imlifidase treatment. Three non-serious and one serious infusion related reactions regarded as related to treatment have occurred in 114 subjects receiving imlifidase. Signs and symptoms associated with infusion related reactions included, but were not limited to dyspnoea, pharyngeal oedema, sinus tachycardia, chest discomfort and flushing. To mitigate the risk of infusion related reactions, all subjects receive glucocorticoid and antihistamine treatment prior to dosing and are closely monitored during the infusions.

In vitro studies have revealed that imlifidase cleaves biologics originating from rabbit and human IgG including; thymoglobulin, IVIg, basiliximab, alemtuzumab, rituximab, adalimumab, denosumab, belatacept and etanercept. The optimal interval between imlifidase administration and these biologics has not been tested (2018-003R).

The rationale for the 3-day window between imlifidase and IVIg dosing is aimed to prevent cleavage of the IVIg based on the pharmacokinetic and pharmacodynamic profiles of imlifidase. In one of the clinical studies (14-HMedIdeS-04), alemtuzumab was given four days post dosing of imlifidase and in one clinical study (15-HMedIdeS-06), IVIg was given seven days post dosing of imlifidase.

Adverse events after administration of IVIg do occur but are seldom serious. There is a very small risk of anaphylaxis, often in subjects with severe IgA deficiency. Other reported side effects include headache, myalgia, transient hypotension and flushing (all of which can be corrected by slowing the infusion rate), meningism, aseptic meningitis, skin reactions (especially eczema), neutropenia, worsening of renal failure, and thromboembolic events (DVT, MI and stroke) attributable to hyperviscosity (Hughes et al. 2014).

As an extra safety measure for women of child bearing potential, the requirement for highly effective contraception is part of the inclusion criteria for this study. Additionally, a pregnancy test will be performed at the screening visit to ensure the patient is not pregnant.

The principal investigators will make sure that sufficient facilities and procedures are available to handle emergency situations during the study. Study sites have extended experience in phase I/II studies within transplantation and graft rejection treatment as well as handling biological drugs. The sites have adequate procedures in place to handle unexpected adverse reactions.

A guidance for the investigator and Reference Safety Information regarding imlifidase can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to:

- Investigate the efficacy of imlifidase compared with PE in removal of DSA in patients who are experiencing an active or chronic active AMR episode after kidney transplantation

2.1.2. Secondary Objectives

Secondary objectives of this study are to:

- Evaluate DSA levels up to 180 days after treatment
- Evaluate HLA-antibodies levels up to 180 days after treatment
- Evaluate the overall kidney function up to 180 days after treatment
- Investigate the occurrence of AMR up to 180 days after treatment
- Investigate the safety and tolerability of imlifidase compared to PE in patients experiencing active or chronic active AMR episodes
- Evaluate the number of PE-sessions needed
- Evaluate the pharmacokinetics, pharmacodynamics and immunogenicity of imlifidase

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint of this study is:

- Maximum reduction in mean DSA level at any time point during the 5 days following the start of treatment

2.2.2. Secondary Endpoints

Secondary endpoints of this study are:

- DSA levels up to 180 days after treatment
- HLA-antibodies levels up to 180 days after treatment
- Kidney function change from baseline (at screening) as evaluated by eGFR, P-creatinine and albumin/creatinine ratio in urine up to 180 days after treatment
- Proportion of subjects with graft loss within 180 days of treatment
- Signs of transplant glomerulopathy 180 days post treatment
- Change from baseline (at screening) in histopathology per Banff Criteria at 29 and 180 days

- Change from baseline (at screening) in mRNA levels in kidney biopsies evaluated by [redacted] at 29 and 180 days from baseline. If kidney biopsy is performed before screening, mRNA levels will be evaluated on day 29 and day 180 (no baseline will be available)
- Safety parameters (AEs, safety laboratory tests, vital signs and ECG)
- Type, frequency and intensity of adverse events
- Number of sessions with PE
- Total Serum IgG levels over time
- Presence of intact IgG on SDS-page/Western blot until start of IVIg treatment
- DSA functionality determined by C1q or C3d analysis pre- and post-treatment
- PK profile of imlifidase (C_{max}, T_{max}, $t_{½}$, AUC, CL, V)
- Presence of ADA (anti-imlifidase IgG)

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a randomized, open label, multi-centre, study with an active control. The study will primarily examine the reduction in mean levels of DSA after treatment with imlifidase compared to PE in patients diagnosed with active or chronic active AMR according to Banff 2017 criteria (Haas et al. 2018), including presence of DSA(s). A total of 30 male and/or female patients will be included in the study.

The randomization will be 2:1. 20 subjects will receive a single dose of 0.25 mg/kg imlifidase and 10 subjects will be treated with 5-10 sessions of PEs. High dose IVIg followed by a single dose of rituximab will be given after treatments with imlifidase and PE. For doses, see Section 5. Other treatments and/or procedures for AMR can be used as required at the investigator's discretion. SOC treatment can be initiated at any point for patients in the treatment arm if needed as judged by the investigator. The decision to initiate other SOC treatments will normally be based on DSA rebound. Since DSA is monitored frequently, signs of antibody rebound will be detected early and appropriate treatment initiated immediately.

The duration of the hospitalization for subjects in the imlifidase arm will be at least 2 days. In the control arm, the duration of the hospital stay will follow standard of care at each study site.

Presence of DSA will be assessed pre-dose and at multiple times during the study. Protocol biopsies will be performed at screening, and on day 29 and day 180 after first day of treatment to assess changes in allograft histopathology and mRNA levels. . If kidney biopsy is performed within 5 days prior to screening it will not have to be repeated at screening visit and mRNA levels will be measured on day 29 and day 180. In addition, kidney function will be followed by plasma or serum creatinine measurements, eGFR calculations and albumin/creatinine ratio in urine during the full study period.

The study outline is summarized in Figure 1 (imlifidase) and Figure 2 (PE) below.

Figure 1: Overall study outline imlifidase arm

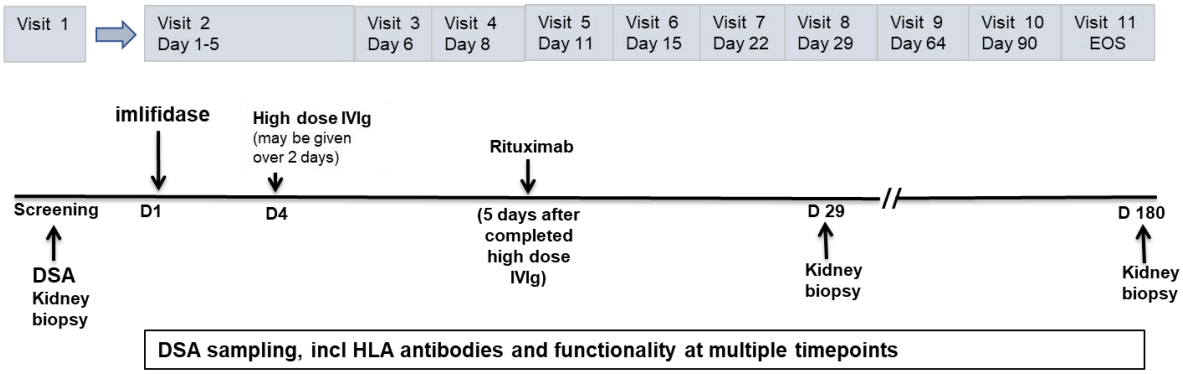
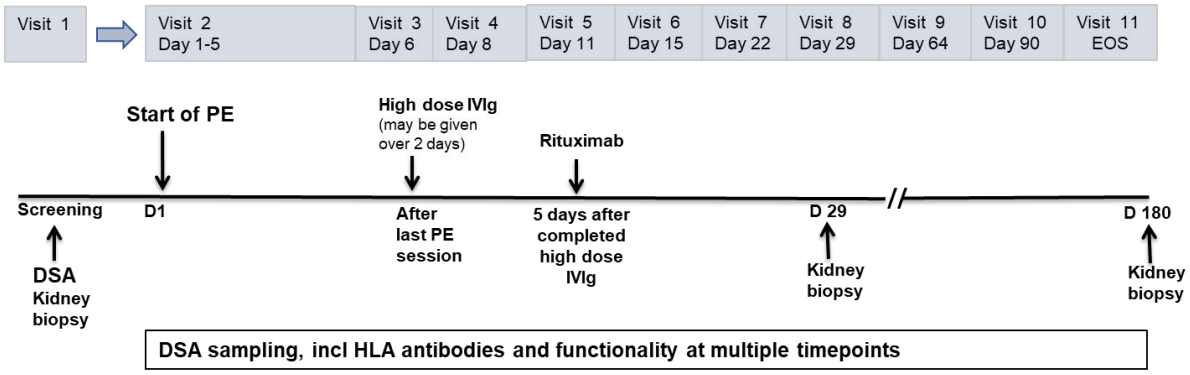


Figure 2: Overall study outline PE arm



Safety parameters (safety laboratory tests, vital signs and ECG) as well as kidney function and AEs will be monitored up to 180 days after start of treatment.

3.1.1. Follow-up Procedures

The subjects will be followed until 180 days after start of treatment. Subjects who lose their graft during the course of the study will remain in the study and be followed according to the study protocol and clinical practice at the site.

After study completion, all study subjects will be followed regularly by the nephrologist or transplant surgeons according to each centre's follow-up routines for transplanted subjects. The frequency of outpatient visits will be adjusted individually to the state of patient health and transplant function.

3.1.2. Safety Review Committee

A Safety Review Committee (SRC) will be established to evaluate safety and tolerability data. The committee will meet 14 days after the first patient has received the first treatment to evaluate available safety and tolerability data. If no clinically significant changes are identified, the second and third subject will be dosed and evaluated following the same schedule. After 6 and 11 imlifidase-treated subjects have completed visit 8 (day 29) the committee will meet again. Evaluation of data will include subjects from both treatment arms (i.e., imlifidase and PE). The SRC will meet on an ad hoc basis if any important safety issue arises anytime during the conduct of the study. The SRC will consist of at least 3 physician members: a drug safety physician, and two consultants, all independent to Hansa Biopharma. Other internal and external experts will be invited to attend the meetings if any issue arises that require additional expertise. A working procedure for the SRC will be described in an SRC charter.

3.2. Study timeline

The expected study start is Q1 2019 with 12 months recruitment and 6 months follow up for included subjects. The recruitment period has been extended to 35 months.

3.3. Planned number of study sites and subjects

This is a multi-centre study. Approximately 14 sites, in US, Europe and Australia, will be included. A total of 30 male and/or female subjects will be enrolled in the study.

3.4. End-of-Study

The planned end-of-study is defined as last subject last visit. Hansa Biopharma will ensure that an end-of-study notification is submitted to the concerned Regulatory Authority (RA) and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) according to local requirements.

For procedures in case of premature termination or suspension of the Study, see Section 13.4.

4. STUDY POPULATION

4.1. Selection Criteria

To be eligible for the study, subjects must meet all inclusion criteria and no exclusion criteria. If a subject has been screened and meets all inclusion and no exclusion criteria but does not receive imlifidase and a new AMR occurs, the subject may be rescreened.

4.2. Inclusion Criteria

1. Signed Informed Consent obtained before any study-related procedures
2. Willingness and ability to comply with the protocol
3. Male and/or female donor kidney recipients age ≥18 years at the time of screening
4. Presence of DSA(s)
5. Meet the Banff 2017 criteria for active or chronic active AMR
6. At least 25% rise in serum creatinine compared to last individual value taken prior to the AMR. Patients with delayed graft function and AMR within 10 days after transplant (confirmed by kidney biopsy) can be included regardless of serum creatinine level
7. Women of child-bearing potential willing or able to use at least one highly effective contraceptive method throughout the study. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
        - oral
        - intravaginal
        - transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation
        - oral
        - injectable
        - implantable
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomised partner
    - true abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
8. Men willing to use double-barrier contraception from the first day of treatment until at least 2 months after the dose of imlifidase, if not abstinent

4.3. Exclusion Criteria

1. Previous treatment with imlifidase
2. Previous high dose IVIg treatment (2 g/kg) within 28 days prior to inclusion
3. Lactating or pregnant females
4. Significantly abnormal general serum screening lab results judged inappropriate for inclusion in the study by the investigator
5. Intake of other investigational drugs within 5 half-lives (or similar) of the product prior to inclusion
6. Clinically relevant active infection(s) as judged by the investigator
7. Any condition that in the opinion of the investigator could increase the subject's risk by participating in the study such as severe immune deficiency and severe cardiac insufficiency (New York Heart Association (NYHA) Class IV) or severe uncontrolled heart disease
8. Known allergy/sensitivity to imlifidase, IVIg and/or rituximab and the respective excipients
9. Patient unable to tolerate treatment with plasmapheresis or immunoadsorption, as judged by the investigator
10. Unsuitable to participate in the study for any other reason as judged by the investigator
11. Positive PCR test for SARS-CoV-2 virus infection.
12. Current diagnosis or history of thrombotic thrombocytopenic purpura (TTP), or known familial history of TTP

4.4. Method of Assigning Subjects to Treatment Groups

At the screening visit, study subjects will be identified by a site-specific screening identification number. The lowest available site-specific subject number will be allocated, when the subject has fulfilled the eligibility criteria. The subjects will be randomized to imlifidase or PE treatment in a 2:1 ratio according to a computer-generated randomisation list created by the CRO. Block randomisation will be used.

4.5. Discontinuation of Subjects

The subjects have the right to withdraw from the study at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible. The investigator also has the right to withdraw subjects. In either event, the investigator must notify monitor.

A subject that prematurely discontinues participation must, if possible, be called in for a last visit and undergo the assessments and procedures scheduled for the end of study follow up visit. Even if the subject is not able to attend, the End of Trial Form in the eCRF must be completed. Subjects who, for a medical reason, cannot comply with the protocol procedures will be followed by best procedure to retrieve safety and efficacy data.

Minor infusion-related reactions have been observed in some patients receiving imlifidase for other indications. These are usually mild and include chest discomfort, flushing, pharyngeal oedema and dyspnea. More severe reactions can occur.

If a minor infusion-related reaction (CTCAE grade 1 or 2) is suspected the infusion should be temporarily stopped and the patient should be observed for clinical signs of allergic reactions. If a significant infusion-related reaction or anaphylactic reaction occurs (CTCAE grade 3 or higher) then the imlifidase therapy should be discontinued immediately.

The patient should be treated by the investigator according to local practice for an allergic reaction or a severe allergic reaction/anaphylaxis, respectively. If the symptoms resolve, the infusion can be resumed. If the symptoms persist or worsen then the drug infusion should not be restarted.

5. STUDY TREATMENTS

5.1. Investigational Medicinal Product

Imlifidase is provided as a freeze-dried powder for concentrate for solution for infusion, 11 mg per vial. After reconstitution with sterile water for injection, the concentrate contains 10 mg/mL imlifidase. The concentrate will be added to 50 mL sodium chloride 9 mg/mL (0.9 %) solution for infusion and administered as an infusion.

The excipients are: mannitol, polysorbate 80, Tris (tris(hydroxymethyl)aminomethane) buffer and EDTA. The excipients are all of pharmacopoeial quality.

Imlifidase for infusion will be prepared by the pharmacist or study nurse and the administration will be performed by the study nurse or physician at site. Details on preparation, labelling, administration and accountability of imlifidase are described in the pharmacy manual that will be provided to the site and pharmacy prior to inclusion of the first subject.

One intravenous dose of imlifidase, 0.25 mg/kg, administered over 15 minutes, will be given to subjects randomized to receive imlifidase.

5.1.1. Conditions for Storage and Use

Vials with imlifidase should be stored in a refrigerator at +2°C to +8°C.

The solution for infusion should be stored at +2°C to +8°C, protected from light. The solution should be used within 12 hours. The solution should be placed in room temperature approximately 30 minutes before administration.

The investigator will ensure that the Investigational Medicinal Product (IMP) always will be stored in appropriate conditions in a secure location. The storage compartment will be monitored regularly, and the temperature documented.

5.1.2. Packaging and labelling

Packaging and labelling of the IMP will be performed in accordance with Good Manufacturing Practice (GMP) and national regulatory requirements.

5.2. Control treatment

The control treatment in this study is PE which is a treatment with no active substance and thus not an IMP. PE will be prepared and performed according to the standard of care at each site. 5-10 sessions of PE will be performed.

5.3. Non-Investigational Medicinal Product(s)

Non-Investigational Medicinal Products (NIMPs) will be sourced from the investigational site pharmacy supply. Essential information about the NIMPs is to be found in the latest versions of respective Summary of Product Characteristics.

The subjects will be treated with the following NIMPs (other treatments may be used as required at the investigator's discretion):

Prophylactic antibiotic (all subjects):

All subjects will receive a standard regimen of antibiotics according to local clinical practice, starting before the first treatment and continuing until IgG levels return to acceptable values, as judged by the investigator.

Premedication (imlifidase arm):

All subjects in the imlifidase arm, will be given antihistamine (orally) as pretreatment before imlifidase infusion.

Treatment schedule for steroid dosing (all subjects):

Day 1: Methylprednisolone 500 mg as premedication before treatment

Day 2-3: Methylprednisolone 500 mg daily

Day 4: Prednisolone/prednisone 60 mg

Day 5: Prednisolone/prednisone 50 mg

Day 6: Prednisolone/prednisone 40 mg

Day 7: Prednisolone/prednisone 30 mg

Day 8: Prednisolone/prednisone 20 mg will continue daily for 1 week, followed by 10 mg daily for 1 week and thereafter 5 mg daily throughout the study

Treatment with IVIg (all subjects)

Imlifidase arm: subjects will be given a high dose of IVIg (2 g/kg BW, maximum of 140 g), on day 4 (may be given over 2 days, as judged by the investigator). If a subject in this arm has to be treated with PE for medical reasons, IVIg will be given after the last session of PE.

PE arm: a high dose of IVIg (2 g/kg BW, maximum of 140 g) will be given after the last session of PE (may be given over 2 days, as judged by the investigator).

Treatment with Rituximab (all subjects)

A single dose of rituximab, 375 mg/m^2, will be given to all subjects 5 days after completion of the IVIg infusion.

Rituximab requires use of contraception for 12 months after treatment. Women of childbearing potential will be encouraged to continue using highly effective contraceptive method for at least 6 months after end of study.

5.3.1. Conditions for Storage and Use

The investigator will ensure that the NIMPs will be stored in appropriate conditions, according to labels, in a secure location with controlled access. The storage compartment shall be monitored regularly, and the temperature shall be documented.

5.4. Blinding

This is an open-label study. Due to the nature of the control treatment, blinding of the control treatment is not feasible.

5.5. Compliance, Accountability and Destruction of IMP(s) and NIMP(s)

5.5.1. Compliance

The administration of all medication (including investigational products) will be done by trained study personnel and must be recorded in the appropriate sections of the eCRF. All investigational treatments must also be documented in the accountability logs. 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.

5.5.2. Accountability and Destruction of IMP(s) and NIMP(s)

It is the principal investigator's/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. All IMP and NIMPs are handled and stored safely and properly

4. The IMP 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. The study pharmacist will maintain and keep the total accountability records. At the end of the study, the pharmacist will return all unused IMPs to Hansa Biopharma for destruction after it has been checked by monitor. The used IMP vials will be accounted for and destructed at site, after control by monitor.

5.6. Product Quality Complaints

A PQC is a reported defect related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution and/or usage. The defect can be related to the product itself or to the product's label, delivery system, or packaging. Examples of PQCs include but are not limited to contamination, label errors, and delivery system failures.

Hansa Biopharma must be made aware of any PQCs as soon as possible on the day of detection. Hansa Biopharma will assess the impact of the reported defect and take any necessary precautions to ensure the safety of the study subjects and the credibility of the study results. PQCs should be reported using the IMP Issue form to ensure that all relevant information is captured.

5.7. Concomitant Medication(s) and Therapy

Maintenance immunosuppression such as tacrolimus, mycophenolate mofetil, cyclosporine A, prednisolone and others are prescribed at the discretion of the treating physician or investigator according to SOC. These drugs can be used the same day as the infusion of imlifidase and be continued during the treatment of AMR. No specific maintenance immunosuppressive treatment in addition to what the patient already has is needed within the study.

Other concomitant medication and/or other therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. All concomitant medication and other therapy, including i.e., premedication, prophylactic antibiotics, steroids and PE, must be recorded on the concomitant medication page in the CRF throughout the study, beginning from screening to end of study. Recorded information will include indication, name of drug or therapy, dose (if available), route of administration and start and stop date.

6. STUDY PROCEDURES

6.1. Study Visits

For each subject, the duration of the study, including the screening period and the follow-up visit will not exceed 7 months.

AEs and concomitant medication and treatment will be collected throughout the study and are not specified for each visit.

PE-arm: high dose IVIg will be given after the last session of PE. Since the number of sessions with PE may be different between subjects and thus not given at a specific visit and will not be described below. Samples for DSA and PD will be taken 24 hours after the last session of PE. A PD sample will be taken prior to and after (may be the day after) completion of high dose IVIg. If there are scheduled PD samples at these time points, no extra samples are needed. Rituximab will be given 5 days after completion of the IVIg infusion.

6.1.1. Visit 1 (screening)

Subjects will be informed about the study, the anticipated benefits and theoretical risks, in writing and verbally and sign the inform consent form.

The screening visit will include to the following:

- Signing of informed consent form by subject
- Demographics (age, sex and race)
- Number of pregnancies (if applicable)
- Medical/surgical history, including transplantation and previous AMR(s)
- The 3 latest creatinine values prior to the current AMR will be collected. The latest value will be used as baseline value for inclusion
- Physical examination
- Height and weight
- Vital signs (blood pressure, pulse rate, respiratory frequency, and body temperature)
- PCR test for SARS-CoV-2 virus
- Pregnancy test (serum)
- ECG
- Safety laboratory tests (Table 5)
- Urine sample for measurement of albumin/creatinine ratio
- DSA sample will be collected

- Kidney biopsy will be performed. Kidney biopsy performed within standard of care and 5 days prior to screening can be used for inclusion and does not need to be repeated at screening.
- Sample for ADA (IgE) (no need to wait for result before start of treatment)
- Check of inclusion and exclusion criteria
- Randomisation to treatment arm

6.1.2. Visit 2 (treatment), Day 1-5

The following activities and assessments will be performed on day 1, prior to start of treatment with imlifidase or PE:

- Blood pressure, pulse rate and respiratory frequency, and body temperature
- Baseline samples for DSA, PK, PD, and ADA (IgG) will be collected prior to start of treatment
- P-creatinine
- Urine sample for measurement of albumin/creatinine ratio

Imlifidase arm: Methylprednisolone, antihistamine and antibiotic prophylaxis will be administered before the imlifidase infusion.

PE arm: Methylprednisolone and antibiotic prophylaxis will be administered before the first treatment.

Treatment with antibiotics will continue until IgG levels return to acceptable values as judged by the investigator. Methylprednisolone will be administered according to treatment schedule, see Section 5.3.

The following activities will be performed after the start of treatment:

- Blood pressure and pulse rate will be monitored at 2, 6, 24, 48, 72, and 96 hours
- Respiratory frequency and body temperature will be monitored at 24, 48, 72, and 96 hours
- Safety laboratory tests (Table 5) will be collected at 24, 48, 72, and 96 hours
- Urine sample for measurement of albumin/creatinine ratio at 24, 48, 72, and 96 hours.
- Imlifidase arm: Samples for PK will be collected at 30 minutes and 1 hour
- Samples for DSA, PK and PD will be collected at 2 and 6 hours
- Samples for DSA, PK, PD and ADA (IgG) will be collected 24 hours after treatment.
- Samples for DSA, PK and PD will be collected at 48, 72, and 96 hours. The 72-hour sample must be taken prior to high dose IVIg is given in the imlifidase arm

Imlifidase arm: High dose IVIg will be given on day 4 (at least 72 hours after the imlifidase infusion). Dose may be given over 2 days as judged by the investigator.

6.1.3. Visit 3, Day 6

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- Samples for DSA, PK and PD will be collected
- Urine sample for measurement of albumin/creatinine ratio

6.1.4. Visit 4, Day 8

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- Urine sample for measurement of albumin/creatinine ratio
- Samples for DSA, PK, PD and ADA (IgG) will be collected

6.1.5. Visit 5, Day 11 (+/- 2 days)

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- Urine sample for measurement of albumin/creatinine ratio
- Samples for DSA, PK, PD and ADA (IgG) will be collected

Imlifidase arm: Rituximab will be given 5 days after the completion of the IVIg infusion

6.1.6. Visit 6, Day 15 (+/- 2 days)

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- Urine sample for measurement of albumin/creatinine ratio
- Samples for DSA, PK, PD and ADA (IgG) will be collected

6.1.7. Visit 7, Day 22 (+/- 3 days)

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected

- Urine sample for measurement of albumin/creatinine ratio
- Samples for DSA, PD and ADA (IgG) will be collected

6.1.8. Visit 8, day 29 (+/- 3 days)

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- Urine sample for measurement of albumin/creatinine ratio
- Kidney biopsy will be performed
- Samples for DSA, PD and ADA (IgG) will be collected
- Austria only, pregnancy test (serum)

6.1.9. Visit 9, Day 64 (+/- 7 days) and Visit 10, Day 90 (+/- 7 days)

The following activities and assessments will be performed:

- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- Urine sample for measurement of albumin/creatinine ratio
- Samples for DSA, PD and ADA (IgG) will be collected
- Austria only, pregnancy test (serum)

6.1.10. Visit 11 (follow up, end of study), day 180 (+/- 14 days)

The following activities and assessments will be performed:

- Physical examination
- Blood pressure, pulse rate and body temperature will be monitored
- Safety laboratory tests (Table 5) will be collected
- ECG
- Pregnancy test (serum)
- Urine sample for measurement of albumin/creatinine ratio
- Kidney biopsy will be performed
- Samples for DSA, PD and ADA (IgG) will be collected

6.2. Flow Chart imlifidase arm

Table 1: Study flow chart imlifidase arm, Screening to End of Study

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Type of visit	**Screening**	**Treat-ment**	**Assessments**								**FU/End of study**
Day		**1-5**	**6**	**8**	**11**	**15**	**22**	**29**	**64**	**90**	**180**
Assessment /Time window			0	0	±2d	±2d	±3d	±3d	±7d	±7d	±14d
Informed Consent	X	See table 2									
Demographics	X										
Medical/surgical history, incl transplantation and previous AMRs	X										
Record historical creatinine values	X										
Record number of pregnancies *(if applicable)*	X										
Inclusion/exclusion criteria	X										
Randomization	X										
Physical examination	X										X
Height and weight	X										
Blood pressure and pulse rate	X		X	X	X	X	X	X	X	X	X
Respiratory frequency	X										
Body temperature	X		X	X	X	X	X	X	X	X	X
PCR test for SARS-CoV-2 virus	X										
ECG	X										X
Pregnancy test *(serum)*	X										X
Pregnancy test *(serum)* Austria	X							X	X	X	X
Safety laboratory tests *(incl creatinine for eGFR)*	X		X	X	X	X	X	X	X	X	X
Urine sample for measurement of albumin/creatinine ratio	X		X	X	X	X	X	X	X	X	X
ADA (IgE)	X[a]										
DSA, incl HLA antibodies and functionality	X[b]		X	X	X	X	X	X	X	X	X
PK sampling			X	X	X	X					

Table 1: Study flow chart imlifidase arm, Screening to End of Study

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Type of visit	**Screening**	**Treat-ment**	**Assessments**								**FU/End of study**
Day		**1-5**	**6**	**8**	**11**	**15**	**22**	**29**	**64**	**90**	**180**
Assessment /Time window			0	0	±2d	±2d	±3d	±3d	±7d	±7d	±14d
PD sampling			X	X	X	X	X	X	X	X	X
ADA(IgG)				X	X	X	X	X	X	X	X
Kidney biopsy	X[c]							X[c]			X[c]
Methylprednisolone /Prednisolone			Will be given according to treatment schedule (section 5.3) and continue as long as prescribed by investigator								
Antibiotic prophylaxis			Treatment will continue until IgG levels return to acceptable values, as judged by the investigator								
Rituximab					X[d]						
Concomitant medication and other treatment	Throughout the study										
Adverse events	Throughout the study										

[a] Sample will be taken pre-dose but no need to wait for result before start of treatment

[b] One DSA sample will be sent to local lab for evaluation for inclusion and one DSA sample will be collected for analysis at Hansa Biopharma

[c] One piece of tissue will be sent to local pathology lab and one piece of tissue will be sent for analysis at [redacted]. If kidney biopsy is performed prior to screening, a piece of tissue cannot be sent for [redacted] unless site stores tissue in mRNA later as standard of care. Then the tissue may be sent for [redacted] analysis after informed consent is signed.

[d] Rituximab will be given 5 days after completed high dose of IVIg

Table 2: Study flow chart imlifidase arm, visit 2, treatment

Visit Number	**2**									
Time	**Pre-dose**	**Treat-ment**	**30 min**	**1 h**	**2 h**	**6 h**	**24 h**	**48 h**	**72 h**	**96 h**
Assessment /Time window			±10 min	±10 min	±15 min	±30 min	±2h	±2h	±6h	±6h
Blood pressure and pulse rate	X				X	X	X	X	X	X
Respiratory frequency	X						X	X	X	X
Body temperature	X						X	X	X	X
Safety laboratory tests (incl creatinine)							X	X	X	X
Methylprednisolone/ prednisolone[a]	X						X	X	X	X
Antihistamine	X									
Antibiotic prophylaxis	X		Treatment will continue until IgG levels return to acceptable values, as judged by the investigator							
DSA, incl HLA antibodies and functionality	X				X	X	X	X	X[b]	X
PK sampling	X		X	X	X	X	X	X	X[b]	X
PD sampling	X				X	X	X	X	X[b]	X
ADA (IgG)	X						X			
P-creatinine (for calculation of eGFR)	X									
Urine sample for measurement of albumin/creatinine ratio	X						X	X	X	X
Imlifidase infusion		X								
High dose IVIg									X[c]	
Concomitant medication and other treatment	Throughout the visit									
Adverse events	Throughout the visit									

[a] Methylprednisolone/prednisolone will be given according to the treatment schedule in section 5.3
[b] Samples should be taken prior to start of high dose IVIg is given
[c] May be given over two days

6.3. Flow Chart PE arm

Table 3: Study flow chart PE arm, Screening to End of Study

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Type of visit	**Screening**	**Treat-ment**	**Assessments**								**FU/End of study**
Day		**1-5**	**6**	**8**	**11**	**15**	**22**	**29**	**64**	**90**	**180**
Assessment /Time window			0	0	±2d	±2 d	±3 d	±3 d	±7d	±7d	±14d
Informed Consent	X	See table 4									
Demographics	X										
Medical/surgical history, incl transplantation and previous AMRs	X										
Record historical creatinine values	X										
Record number of pregnancies *(if applicable)*	X										
Inclusion/exclusion criteria	X										
Randomization	X										
Physical examination	X										X
Height and weight	X										
Blood pressure and pulse rate	X		X	X	X	X	X	X	X	X	X
Respiratory frequency	X										
Body temperature	X		X	X	X	X	X	X	X	X	X
PCR test for SARS-CoV-2 virus	X										
ECG	X										X
Pregnancy test (serum)	X										X
Pregnancy test *(serum)* Austria	X							X	X	X	X
Safety laboratory tests (incl creatinine for eGFR)	X		X	X	X	X	X	X	X	X	X
Urine sample for measurement of albumin/creatinine ratio	X		X	X	X	X	X	X	X	X	X
ADA (IgE)	X[a]										
DSA, incl HLA antibodies and functionality (*if applicable, taken before PE)*	X[b]		X	X	X	X	X	X	X	X	X

Table 3: Study flow chart PE arm, Screening to End of Study

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Type of visit	**Screening**	**Treat-ment**	**Assessments**								**FU/End of study**
Day		**1-5**	**6**	**8**	**11**	**15**	**22**	**29**	**64**	**90**	**180**
Assessment /Time window			0	0	±2d	±2 d	±3 d	±3 d	±7d	±7d	±14d
PK sampling			X	X	X	X					
PD sampling (*if applicable, taken before PE)*			X[d]	X[d,e]	X[d,e]	X	X	X	X	X	X
ADA(IgG)				X	X	X	X	X	X	X	X
Kidney biopsy	X[c]							X[c]			X[c]
Methylprednisolone /Prednisolone			Will be given according to treatment schedule (section 5.3) and continue as long as prescribed by investigator								
Antibiotic prophylaxis			Treatment will continue until IgG levels return to acceptable values, as judged by the investigator								
High dose IVIg			High dose IVIg will be given after last PE session. Dose may be given over two days								
Rituximab				Will be given 5 days after completed high dose IVIg							
Concomitant medication and other treatment	Throughout the study										
Adverse events	Throughout the study										

a) Sample will be taken pre-dose but no need to wait for result before start of treatment

b) One DSA sample will be sent to local lab for evaluation of inclusion and one DSA sample will be collected for analysis at Hansa Biopharma

c) One piece of tissue will be sent to local pathology lab and one piece of tissue will be sent for analysis at [redacted]

If kidney biopsy is performed prior to screening, a piece of tissue cannot be sent for [redacted] analysis unless site stores tissue in mRNA later as standard of care. Then the tissue may be sent for [redacted] analysis after informed consent is signed.

d) If high dose IVIG is given, the PD sample must be taken prior to IVIg

e) If high dose IVIg is completed and there is no scheduled PD sample at the latest the following day, an additional PD sample will be taken

Table 4: Study flow chart PE arm, visit 2, treatment

Visit Number	**2**									
Time	**Pre-dose**	**Treat-ment**	**30 min**	**1 h**	**2 h**	**6 h**	**24 h**	**48 h**	**72 h**	**96 h**
Assessment /Time window			±10 min	±10 min	±15 min	±30 min	±2h	±2h	±6h	±6h
Blood pressure and pulse rate	X				X	X	X	X	X	X
Respiratory frequency	X						X	X	X	X
Body temperature	X						X	X	X	X
Safety laboratory tests (incl creatinine)							X	X	X	X
Methylprednisolone/ prednisolone[a]	X						X	X	X	X
Antibiotic prophylaxis	X		Treatment will continue until IgG levels return to acceptable values, as judged by the investigator							
DSA, incl HLA antibodies and functionality (*if applicable, taken before PE)*	X				X	X	X	X	X	X
PK sampling	X				X	X	X	X	X	X
PD sampling functionality (*if applicable, taken before PE)*	X				X	X	X	X	X	X
ADA (IgG)	X						X			
P-creatinine *(for calculation of eGFR)*	X									
Urine sample for measurement of albumin/creatinine ratio	X						X	X	X	X
PE		X								
Concomitant medication and other treatment	Throughout the visit									
Adverse events	Throughout the visit									

[a] Methylprednisolone/prednisolone will be given according to the treatment schedule in Section 5.3

7. STUDY ASSESSMENTS

When different assessments are scheduled at the same time according to the flow chart, samples for DSA, PK and PD should be prioritized to be taken at the exact time point. Exact time points must be entered into the eCRF. All sampling, shipping and analysing of laboratory samples will be detailed in the laboratory manual.

7.1. Assessments related to endpoints

Samples for DSAs and pharmacodynamics (PD) will be collected at multiple time points as indicated in the study flowcharts (Table 1, Table 2, Table 3 and Table 4). DSAs will be identified by each site using HLA profile data from the donor and the patient together with Single Antigen Bead (SAB) analysis data obtained at baseline.

7.1.1. Determination of donor specific antibodies

Samples for determination of DSAs and HLA-antibodies will be analyzed in a single antigen bead assay (HLA-SAB) as well as in functional assay e.g. C1q or C3d assay. These assays allow determination of the mean fluorescence intensity (MFI) of antibodies in subject serum reacting to an array of individual HLA immobilized to beads. Analyses of HLA antibodies, including DSA, will be performed centrally. The date and actual time of collection of each sample will be recorded in the eCRF. DSAs for each patient will be identified by respective site. DSAs collected in standard of care at other timepoints will also be recorded in the eCRF

DSA taken at screening will also be analysed at the local lab at each site, in addition to centrally, for determination of presence of DSA(s) for inclusion.

7.1.2. Pharmacodynamics

Samples for the determination of IgG levels in serum (PD) qualitative analysis of IgG-fragments will be taken at the times presented in the study flow chart (Table 1, Table 2, Table 3 and Table 4). The date and actual time of collection of each sample will be recorded in the eCRF. Samples for determination of IgG levels in serum will be analysed with a validated electrochemiluminescence based immunoassays using the MSD (Meso Scale Diagnostic) technology. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report. IgG-fragments will be analysed by SDS-PAGE and Western blot, using antibodies directed to human IgG fragments.

7.1.3. Kidney function as evaluated by eGFR, P-creatinine and albumin/creatinine ratio in urine

Evaluation of kidney function based on P-creatinine analysis and calculation of filtration rate (eGFR) using MDRD GFR Equation. Calculation of eGFR will be done directly in the eCRF. Albumin/creatinine ratio in urine will be performed at the time points indicated in the study flowcharts (Table 1, Table 2, Table 3 and Table 4). Creatinine values collected in standard of care at other timepoints will also be recorded in the eCRF.

7.1.4. Kidney biopsy

Kidney biopsies collected at screening or within 5 days prior to screening, on day 29 and day 180 will be assessed according to the Banff 2017 (Haas et al. 2018) criteria, by a local pathologist. In addition, a piece of tissue from the kidney biopsy will be evaluated on the basis of microarray mRNA measurement using the [redacted] a central diagnostic system. If the initial kidney biopsy is performed prior to screening and signed informed consent, mRNA levels will be evaluated on day 29 and day 180. If kidney biopsies are performed at any other time points, if judged necessary by the PI, reports from those will be collected and documented in the eCRF.

7.1.5. Pharmacokinetics

Samples for determination of concentrations of imlifidase in serum will be taken at the times presented in the study flow charts (Table 1, Table 2, Table 3 and Table 4). The actual date and time of collection of each sample will be recorded in the eCRF. Samples will be analyzed by a validated electrochemiluminescence based immunoassay using the MSD technology. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report.

7.1.6. Immunogenicity

Samples for the determination of ADA IgE and ADA IgG levels in serum will be taken at the times presented in the study flow charts (Table 1, Table 2, Table 3 and Table 4). The date and time of collection of each sample will be recorded in the eCRF. Samples will be analysed for anti-imlifidase IgE and IgG, using a customized validated imlifidase ImmunoCAP test. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report.

7.2. Safety Assessments related to Endpoints

7.2.1. Safety Laboratory

The following blood samples will be taken at screening and time points specified in flow charts, Table 1, Table 2, Table 3 and Table 4. Other samples may be taken at the investigator's discretion.

Table 5: Safety laboratory tests

Clinical chemistry*	Hematology	Coagulation
P-IgG	B-Hemoglobin	PT (INR)
P-Alkaline phosphatase (ALP)	B-Differential analysis of leucocytes	P-APTT
P-Alanine aminotransferase (ALT)	B-Thrombocytes	
P-Aspartate aminotransferase (AST)		
P-Bilirubin, total		
P-Glucose		

Table 5: Safety laboratory tests

Clinical chemistry*	Hematology	Coagulation
P-Sodium		
P-CRP		
P-Albumin		
P-Urea		
P-Triglycerides		
P-Creatinine		
P-Creatinine phosphokinase		

* May be taken as serum samples if that is standard procedure at the local lab

7.2.2. Physical Examination

A complete physical examination will be performed at time points indicated in the study flow charts (Table 1 and Table 3) and include an assessment of the following: general appearance, head and neck, lymph nodes, abdomen, musculo-skeletal, cardiovascular, respiratory and gross neurological examination. The physical examination shall be performed by an investigator.

7.2.3. Vital Signs

Blood pressure, pulse rate, respiratory frequency and body temperature will be measured at time points indicated in the study flowchart (Table 1, Table 2, Table 3 and Table 4).

Systolic and diastolic blood pressure will be measured after the subject has been in supine position for at least 5 minutes. All recordings will be performed using validated standard equipment. Clinically significant abnormal findings will be reported as AEs.

7.2.4. ECG

ECG, according to standard procedure at the clinic, will be taken after 10 minutes'-rest at time points indicated in the study flowchart (Table 1 and Table 3). Additional ECGs may be performed by the Investigator for safety reasons.

The Investigator or designee will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. Clinically significant abnormal findings will be reported as AEs.

7.2.5. Adverse Events

AEs will be recorded during the study period, from obtaining the informed consent to the end of study. For further information on definitions and reporting of AEs, see Section 9.

7.3. Other Assessments

7.3.1. Demographics and Baseline Data

Information about gender, race, age at inclusion, weight and height will be collected at the screening visit for each subject. Measurements should be taken without shoes. Medical history will be recorded at screening.

7.3.2. Pregnancy Test

Serum β-hCG will be determined for all female subjects at screening, and at the end of study visit, using validated standard methods.

ONLY FOR AUSTRIA; in accordance with Austrian Medicinal Products Act, women of childbearing potential must perform a pregnancy test monthly during the study. At timepoints with no scheduled study visit, a pregnancy test in urine may be performed at home and result checked at the following visit.

7.3.3. Concomitant medication and other treatments

Concomitant medication and other treatments (including PE) will be recorded throughout the study.

7.3.4. Analysis of SARS-CoV-2 virus

PCR testing for SARS-CoV-2 virus will be performed at screening.

8. BIOLOGICAL SAMPLING PROCEDURES

8.1. Handling, Storage and Destruction of Biological Samples

Safety samples will be disposed after analyses according to local laboratory practice.

Biological blood samples collected for central analysis may be stored by the sponsor for a maximum of 5 years after completion of the study report.

Details on handling of biological samples are described in the laboratory manual that will be provided to the site prior to inclusion of the first subject.

8.2. Chain of Custody of Biological Samples

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

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

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

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

8.3. Withdrawal of Informed Consent for Biological Samples

If a subject withdraws consent to the use of biological samples, the samples will be disposed/destructed, if not already analysed and documented.

The principal investigator:

- Will ensure that subject withdrawal of informed consent is notified immediately to Hansa Biopharma.
- Will ensure that biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented.
- Will ensure the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed, and the action documented returned to the study site.

Hansa Biopharma ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed, and the action documented returned to the study site.

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

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse event

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

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

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

9.1.2. Serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

Hospitalisation: Admittance to an emergency room for observation without being admitted to the hospital may be considered to be an AE but is not considered as an SAE. However, complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious.

9.2. Collection and Recording of Adverse Events

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

AEs will therefore be collected on the AE CRF from the time of signing of the informed consent and throughout the study including the follow-up period.

AEs can be collected by:

- The subject's response to questions about his/her health (a standard non-leading question such as "Have you had any health problems since you were last asked/your last visit?")
- Symptoms spontaneously reported by the subject
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities
- Other information relating to the subject's health becoming known to the investigator (e.g. hospitalisation)

9.2.1. Variables

The following variables will be recorded in the CRF for each AE; description of the AE, the date and time (if applicable) when the AE started and stopped, severity based on Common Terminology Criteria for AEs grading (CTCAE v.4.03) whether the AE is serious or not, causality assessment, action taken and outcome.

9.2.1.1. Causality Assessment

For each reported AE, the investigator will make an assessment of the relationship of the event to study procedures and/or IMP using the following criteria.

- **Unrelated:** applicable to an AE that occurs when the subject was not exposed to study treatment or another cause is obvious.
- **Unlikely to be related:** applicable to an AE that meets the following criteria
    - Does not follow a reasonable temporal sequence from study drug dosing
    - May readily have been produced by the subject's clinical state, environmental, or toxic factors, or other therapy administered to the subject
- **Possibly related:** applicable to AEs where connection with dosing of study drug appears unlikely but cannot be ruled out. Applicable to AEs where:

- It follows a reasonable temporal sequence dosing with study drug
- It follows a known pattern of response to study drug dosing (based on animal studies)

- **Probably related**: applicable to AEs that are considered, with a high degree of certainty, to be related to the study drug. Applicable to AEs where
  - It follows a reasonable temporal sequence study drug dosing
  - It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy
  - It follows a known pattern of response to study drug dosing (based on animal studies).
- For SAEs, causal relationship will also be assessed for any study procedure.

9.2.2. Adverse Events Based on Signs and Symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms, for example: congestive heart failure rather than low ejection fraction. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom not part of the diagnosis will be recorded separately, for example: congestive heart failure and conjunctivitis.

9.2.3. Adverse Events Based on Examinations and Tests

If lab values are judged as clinically significant and/or a treatment has been given, they will be captured as AEs and if SAE criteria are fulfilled they will also be SAEs.

If vital signs are judged as clinically significant and/or require a treatment, then they will be captured as AEs and if SAE criteria are fulfilled they will also be SAEs.

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

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

9.2.4. Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator until stabilization, for as long as medically indicated or the overall clinical outcome of the subject is known, unless the subject is documented as "lost to follow-up". All SAEs and AEs leading to discontinuation should be followed until the event resolves or stabilizes.

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

9.2.5. Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered related to the investigational product, or to the study procedure(s), on a separate SAE form. In the AE form, it will be added that the AE is considered serious. SAEs will be recorded from the time of informed consent.

An assigned contract research organisation (Primevigilance) will be responsible for reporting all SAEs to RAs in accordance with ICH GCP and local regulations. Hansa Biopharma or the study monitor will be responsible for reporting to IECs/IRBs.

As soon as the investigator is aware of a potential SAE he/she should contact Primevigilance by e-mail and 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, subject number, birth date, description of the SAE and a preliminary assessment of causality.

Contact Information to Primevigilance:

[redacted]

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Hansa Biopharma, the monitor, and Primevigilance 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 Hansa Biopharma 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 Hansa Biopharma and Primevigilance.

9.2.6. Reporting of Suspected Unexpected Serious Adverse Reactions

SUSARs must be reported to RAs. A suspected serious adverse reaction is any SAE for which there is a reasonable possibility that the investigational product caused the AE. A serious adverse reaction is considered "unexpected" if it is not listed in the reference safety information section of the investigator brochure or is not listed at the specificity or severity that has been observed.

SUSARs with an outcome of death or which are life threatening must be reported to the relevant RAs 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 an agreement between Hansa Biopharma and Primevigilance. Hansa Biopharma will notify the appropriate RA(s) and all participating study investigators of any SUSARs on an expedited basis and in accordance with applicable regulations. In addition, Hansa Biopharma is

responsible for informing all investigators in all other ongoing studies involving imlifidase about all SUSARs.

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

9.3. Pregnancy and Pregnancy Outcome

Pregnancy is an exclusion criterion and a pregnancy test is performed at the screening visit and at the last study visit.

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

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

10. STUDY MANAGEMENT

10.1. Pre-study Activities

Before the first subject is enrolled into the study, it may be necessary for a representative of Hansa Biopharma to visit the investigational study site for a pre-study visit to:

- Determine the adequacy of the facilities to give Hansa Biopharma information about whether the study centre has knowledge, enough time, a sufficient subject pool, and sufficient training to manage the study in a good way in terms of subject inclusion, subject handling, data and overall study management.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of Hansa Biopharma or its representatives.

Before the first subject is entered into the study, a Hansa Biopharma representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilized at a site initiation visit.

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

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

10.2. Monitoring of the Study

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, ICH GCP, data are being accurately and timely recorded in the CRFs, and IMP accountability checks are being performed.
- Perform SDV (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects.
- If a subject withdraws informed consent to the use of their biological samples; ensure this is reported to Hansa Biopharma and biological samples are identified, disposed/destructed accordingly, and the action is documented, and reported to the subject.

Hansa Biopharma and its representatives will be available between visits if the investigator(s) or other staff at the centre need information and advice about the study conduct. Details about monitoring are specified in a study specific monitoring plan.

10.3. Source Data

Source data is defined in ICH GCP. Except for SAEs, which must always be source data verified, the extent to which SDV will be carried out must be decided, specified and detailed in the Monitoring Plan. For all data recorded, the source document must be defined in a source document agreement at each study site. There must only be one source defined at any time for any data elements. Source data for randomization will be located in the eCRF.

10.4. Audit and Inspection

The investigator will make all the study-related source data and records available at any time to Quality Assurance auditor(s) mandated by Hansa Biopharma, or to domestic/foreign regulatory inspectors or representatives from IECs/IRBs who may audit/inspect the study.

The main purposes of an audit or inspection are to assess compliance with the study protocol and the principles of ICH GCP and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Documents that authorised Hansa Biopharma representatives and representatives from RAs and IECs/IRBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomisation number will appear on these copies.

The investigator should notify Hansa Biopharma without any delay of any inspection by a RA or IEC/IRB.

10.5. Study Agreements

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

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

11. DATA MANAGEMENT

11.1. Case Report Form

An eCRF system provided by a CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Hansa Biopharma and vendor procedures, in accordance with regulatory and system requirements.

After the study database is declared clean and released to the statistician, a final copy of the database will be stored at Hansa Biopharma. The investigator will also receive a copy of the study site's final and locked data (including audit trail, meta-data and queries) as write-protected PDF-files produced by the CRO. The PDF-files will be stored on a CD/DVD and will be provided to the investigator before access to the eCRF is revoked.

11.2. Provider of Data Management

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

11.3. Coding

For medical coding of AEs, medical/surgical history, including transplantation history, and concomitant medication the most recent versions of the Medical Dictionary for Regulatory Activities (MedDRA) and WHO Drug will be used at study closure (unless decided otherwise by Hansa Biopharma).

The coding will be outsourced to a CRO. All coding performed will be approved by Hansa Biopharma prior to study closure/database lock.

11.4. Handling of External Data

Handling of external data received by Hansa Biopharma from vendors will be performed in a secure environment and according to a pre-defined Data Transfer Specification.

12. STATISTICAL METHODS

The statistical analyses will be outsourced to a CRO. Prior to clean file, a Statistical Analysis Plan (SAP) with details on statistical analysis and data presentation will be established. No formal statistical hypothesis testing will be performed in this study.

Summary tables will in general be presented by treatment and total unless this is not appropriate for specific tables. Mean figures will similarly be presented by treatment.

Summary statistics for continuous variables will in general be presented as n, arithmetic mean, standard deviation, median, minimum and maximum. When continuous data are recorded at different time points absolute values at each time point and, if relevant, changes from baseline may be presented.

For categorical data frequencies and percentages will be presented.

Due to the exploratory nature of the study, missing data will remain missing and no adjustment will be implemented.

12.1. Analysis Sets

All enrolled and treated subjects will qualify for the Full Analysis Set (FAS), the Per Protocol Analysis Set (PPS), the Safety Analysis Set and the Pharmacokinetic Analysis Set (PKS). The decision to exclude subjects from any of the analysis sets will be taken by the clinical study team before database lock and documented in the database lock minutes. Further details will be specified in the SAP.

12.1.1. Full Analysis Set

The FAS will include all treated subjects for whom relevant post baseline efficacy and safety data have been collected.

12.1.2. Per Protocol Analysis Set

The PPS will include all subjects in the FAS who are not excluded because of important non-compliance that will affect the efficacy data such as admission criteria, protocol deviations or other non-compliance.

12.1.3. Safety Analysis Set

The safety analysis set comprises all treated subjects.

12.1.4. Pharmacokinetic Analysis Set

The PKS will be defined by the PK analyst taking admission criteria, protocol deviations and other non-compliance into consideration.

12.2. Subject characteristics

The demographics and other baseline characteristics will be summarised and listed using descriptive techniques.

12.2.1. Subject disposition

The subject disposition will present number of subjects as enrolled, completed, withdrawn overall and by reason for withdrawal and finally by each of the analysis set.

12.2.2. Demographics and Other Baseline Characteristics

The subject's demographics and other baseline characteristics will be summarised and listed.

12.2.3. Recent and Concomitant Medication

Recent and concomitant medication will be summarised by anatomical therapeutic chemical (ATC) code. In addition, listings with ATC code and generic drug name will be prepared.

12.2.4. Exposure and Compliance

Exposure will be tabulated and listed.

12.3. Statistical Analysis of Endpoints

12.3.1. Primary efficacy endpoint

The primary endpoint is the maximum reduction in DSA (MFI sum for relevant DSAs) at any time point during the 5 days following the start of treatment. A subject will have at least one DSA and a DSA is considered relevant if it is at least 1000 MFI pre-dose. The reduction is derived as follows:

1) Calculate the reduction (%) in sum of DSAs as $100*(DSA_0 – DSA_t)/DSA_0$ for each subject and time point. Only DSAs with a pre-dose MFI of 1000 or more will be included in the calculations
2) Find the time point with maximum reduction within 5 days for each subject
3) The maximum reduction per subject will give a single value as the primary endpoint for the subject

Where DSA_t is the analysis result in total MFI for relevant DSAs at time t.

Due to the exploratory nature of this study, no formal hypothesis will be tested. The difference in reduction between the two treatments will be presented with 95% CI. Each subject will be given equal weight in the calculation of the treatment difference irrespective of number of DSAs for the subjects.

A summary table showing the proportion of reduction of DSAs calculated per subject will also be presented.

12.3.2. Reduction of total serum IgG

The total serum IgG is measured by the PD assay. A binary endpoint is defined as 'Yes' if the subject minimum IgG value at any timepoint during the 5 days following the start of treatment is less than 5% of baseline. The proportion of subjects with a positive reduction will be summarized in a table. The difference in proportion between treatments will be presented with a 95% CI.

12.3.3. Detectable intact IgG on a Western blot

An endpoint is defined as reached for a subject if no detectable intact IgG is found by the SDS-PAGE/Western blot assay at any time point over 180 days following treatment. The proportion of subjects who reached the endpoint will be summarized in a table. The difference in proportion between treatments will be presented with a 95% CI.

12.3.4. Donor specific antibodies (DSA)

DSAs will be measured using HLA-SAB assay and a functional assay e.g. C1q or C3d assay. MFI levels will be listed per subject and time point. Spaghetti plots will show the DSA level versus time for each subject. A mean plot by treatment and time point will be presented.

Finally, a listing with all DSA by subject and time point will be prepared.

In addition, subject listings of MFI values for all HLA will be presented.

12.3.5. Kidney function

The kidney function will be evaluated by the parameters eGFR, P-creatinine and albumin/creatinine ratio in urine and biopsies. The laboratory parameters will be summarised as part of the safety data tabulation. Derivation of eGFR will be detailed in the SAP.

Kidney biopsies will be assessed according to the Banff (2017) criteria pre-dose and at day 29 and 180. The biopsy data will be summarised by treatment and listed. In addition, [redacted] will be summarised.

12.3.6. Signs of transplant glomerulopathy 180 days post treatment

Possible transplant glomerulopathy 180 days post treatment will be tabulated by treatment and presented by listings.

12.3.7. Number of sessions with PE for 180 days

The number of PE sessions for 180 days will be summarized by treatment and listed.

12.3.8. Number of patients with resolution of AMR at day 180

The number of patients with resolution of AMR at day 180 will be tabulated by treatment and listed.

12.3.9. The number of patients with graft failure at day 180

The number of patients with graft failure at day 180 will be summarized by treatment and listed.

12.3.10. Patient survival at day 180

The patient survival on day 180 will be tabulated and listed.

12.3.11. Pharmacokinetic

Imlifidase concentrations will be summarised by time point for the imlifidase treatment group and presented as spaghetti plots and mean plots.

PK variables (C_{max}, T_{max}, $t_{½}$, AUC, CL, and V) are calculated and will be summarized using n, arithmetic and geometric mean, standard deviation, coefficient of variation (CV), minimum, median, and maximum. For the terminal half life, the harmonic mean will also be presented.

12.3.12. Pharmacodynamics

Pharmacodynamics data (total serum IgG) will be summarized by time point. In addition, data on total serum IgG will be presented by mean and spaghetti plots. Finally, data will be listed. SDS PAGE and Western blot results will be presented by time point.

12.3.13. Analysis of Adverse Events

AEs will be coded according to the latest version of the MedDRA. All data will be listed by patient. Only treatment emergent AEs will be presented in summary tables. Separate data listing will be provided for AEs that are defined as pre-treatment or post-treatment emergent.

12.3.13.1. Pre-treatment Adverse Events

An AE that starts after the subject signed the Informed Consent Form and prior to the first dose of IMP.

12.3.13.2. Treatment Emergent Adverse Events

A treatment emergent adverse event is any adverse event occurring after the administration of the IMP and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after administration of the IMP and within the time of residual drug effect.

The time of residual drug effect is the estimated period after the administration of the IMP, where the effect of the product is still considered to be present based on pharmacokinetic, pharmacodynamic or other substance characteristics. The residual drug effect is generally accepted to be 5 times the terminal half-life. The terminal half-life of imlifidase is expected to be within the range of approx. 100 hours, i.e. in this study the residual drug effect is likely to be well within the 29 Day assessments. All AEs occurring up to Day 29 are regarded as treatment emergent.

12.3.13.3. Post-treatment Emergent Adverse Events

A post-treatment emergent adverse event is any adverse event occurring after the time of residual drug effect of the IMP, i.e. between the end of the treatment period, visit 8, and the follow-up visit 11.

12.3.14. Analysis of Other Safety Variables

The clinical safety laboratory tests, vital signs, and ECG parameters will be summarised for both absolute values and changes from baseline. Values outside the reference ranges will be flagged in listings.

12.3.15. Immunogenicity

Anti-imlifidase antibody data will be summarized by time point and presented using listings.

12.4. Determination of Sample Size

Due to the exploratory nature of the study, there is no formal statistical hypothesis. The difference between treatments for the reduction of DSA will however be presented with 95% confidence interval. A sample size of 20 imlifidase and 10 PE subjects is proposed.

In two previous imlifidase studies, 14-HMedIdeS-04 and 15-HMedIdeS-06, the IgG reduction for 5 days was 90% and 93% respectively. The corresponding standard deviations are 6% and 4% respectively. Assuming a similar variability in the PE treatment arm, the expected width of the 95% CI for the difference in DSA reduction will be around 8% point. This supports that 20+10 patients are appropriate. Also, the sample size is in line with experience from previous similar Phase II studies with other compounds to obtain adequate safety, tolerability and PK data to achieve the objectives of the study.

13. CHANGES IN STUDY CONDUCT OR PLANNED ANALYSES

Any changes and deviations to plans described in the protocol and in the SAP must be documented.

13.1. Protocol Amendment(s)

Any change to this protocol will be documented in a protocol amendment, issued by Hansa Biopharma, and agreed upon by the investigator and Hansa Biopharma prior to its implementation. Protocol Amendments and documents updated as a result of the Protocol Amendment must not be implemented until all approvals (IEC/IRB and RAs, if applicable) have been obtained.

Changes to the protocol to eliminate immediate hazard(s) to study subjects may be implemented prior to IEC(s)/IRB(s) and RA approval.

13.2. Protocol Deviations

Under working conditions, deviations from the protocol may occur. If deviations from the protocol occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed, discussed and documented on the Protocol Deviation Form. Deviation reports and supporting documentation will be kept in the investigator site file and the study master file.

13.3. Statistical Analysis Plan

Any changes to the SAP will be described in the Clinical Study Report and/or in the Statistical Report.

13.4. Premature Termination or Suspension of the Study

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the subjects and should assure appropriate therapy and follow-up.

If the investigator terminates or suspends a study without prior agreement of Hansa Biopharma, the investigator should inform the Institution where applicable. The investigator/institution should promptly inform Hansa Biopharma and should provide Hansa Biopharma with a detailed written explanation of the termination or suspension. If Hansa Biopharma terminates or suspends a Study, the investigator should promptly inform the Institution where applicable. In both cases Hansa Biopharma will promptly inform the RA and IEC/IRB and provide them with a detailed written explanation of the termination or suspension.

If the RA or IEC/IRB terminates or suspends its approval/favourable opinion of a study, Hansa Biopharma should inform the investigators and institutions (where applicable) and provide them with a detailed written explanation of the termination or suspension.

14. REPORTING AND PUBLICATION

14.1. Clinical Study Report

The results from this study will be reported in a clinical study report (CSR) within one year after end of study (see section 4.6). This will be prepared by Hansa Biopharma and submitted for comments and signature to the coordinating (signatory) investigator(s).

14.2. Confidentiality and Data Ownership

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

14.3. Publications

14.3.1. Publication Policy

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

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

14.4. Public disclosure

The study will be registered in a public clinical trials registry i.e. the U.S. National Institutes of Health register ClinicalTrials.gov and EU Clinical Trials Register if the study is conducted in Europe.

15. ETHICAL AND REGULATORY ASPECTS

15.1. Ethical Conduct of the Study

This study will be conducted in accordance with ICH GCP, the approved protocol and applicable regulatory requirements.

The responsibilities of Hansa Biopharma, the monitor and the investigator are defined in the ICH GCP guideline and applicable regulatory requirements in the country where the study takes place.

15.2. Liabilities and Insurance

Hansa Biopharma is, as sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a study subject for injury arising from the subject's participation in the study.

15.3. Independent Ethics Committee(s) and Institutional Review Boards

All ethical and regulatory approvals must be available before a subject is exposed to any study-related procedure, including screening tests for eligibility.

According to applicable regulatory requirements Hansa Biopharma will:

- obtain approval from or notify the relevant IEC(s)/IRB(s) of the protocol, any amendments, the Subject Information Sheet/Informed Consent Form and any advertisements etc.
- send periodic updates to the IEC(s)/IRB(s) if applicable
- provide investigator(s) with an accurate and complete record of all submissions to the local IEC/IRB. The copies should be filed in the investigator file.

Hansa Biopharma will keep an updated list of submission and approval dates of all documents submitted to IEC(s)/IRB(s).

15.4. Regulatory Authority(ies)

According to applicable regulatory requirements Hansa Biopharma will send required documents to the RAs. Hansa Biopharma will keep an updated list of submission and approval dates of all documents submitted to RAs.

Before initiating the clinical study, the Sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the study. Any notification/submission should be dated and contain sufficient information to identify the protocol.

15.5. Subject Information and Informed Consent

Before any study-related activities and in agreement with applicable regulatory requirements, the investigator must give the subject oral and written information about the study in a form that the subject can understand. Investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts and expected benefits of the Study. Before consenting, the subject must be left with ample time to consider and to pose questions.

It must be emphasised that participation is voluntary and that the subject has the right to withdraw from the Study at any time without prejudice.

The original, signed Informed Consent Forms must be kept in the Investigator File.

The subject will receive a copy of the Subject Information and his/her signed Informed Consent Form.

If new information becomes available that may be relevant to the study subject's willingness to continue participation in the study, a new Subject Information and Informed Consent Form will be forwarded to the IEC(s)/IRB(s) (and RAs, if required). The study subjects will be informed about this new information and re-consent will be obtained.

15.6. Subject Participation Card

The subject will be provided with a subject participation card bearing the following information:

- That he/she is participating in a clinical study (incl. study code)
- That he/she has been treated with the study drug
- The name and phone number of the investigator

The subject will be asked to keep the subject participation card in their possession at all times during the study and to return it at the last study visit, if applicable.

Include statement whether each subject's primary care physician will be notified of their participation in the study by the investigator, if the subject agrees.

15.7. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and Hansa Biopharma and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of Hansa Biopharma.

The study monitor or other authorized representatives of Hansa Biopharma may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

16. ARCHIVING

16.1. Retention of Clinical Study Site Documentation

The investigator is responsible for maintaining all the records, which enable the conduct of the study at the site to be fully understood, in compliance with ICH GCP. The study documentation including all the relevant correspondence should be kept by the investigator for at least 25 years *[or longer if so required by local law]* after the completion or discontinuation of the study, if no further instructions are given by Hansa Biopharma.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous CRF/eCRF data for Hansa Biopharma. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 25 years *[or longer if so required by local law]* after the completion or discontinuation of the study.

No study site document may be destroyed without prior written agreement between the investigator and Hansa Biopharma. Should the investigator elect to assign the study documents to another party, or move them to another location, Hansa Biopharma must be notified. If the investigator retires and the documents can no longer be archived by the site, Hansa Biopharma can arrange having the Investigator File archived at an external archive.

16.2. Study Master File

Hansa Biopharma will archive the Study Master File in accordance with ICH GCP and applicable regulatory requirements.

17. REFERENCES

Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M. Diagnosis and management of antibody-mediated rejection: current status and novel approaches. Am J Transplant. 2014;14:255-71.

Gloor J, Cosio F, Lager DJ, Stegall MD. The spectrum of antibody-mediated renal allograft injury: implications for treatment. Am J Transplant. 2008;8:1367-73.

Haas M, Loupy A, Lefaucheur C, Roufosse C, Glotz D, Seron D, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant. 2018;18:293-307.

Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev. 2014:CD002063.

Jarnum S, Runstrom A, Bockermann R, Winstedt L, Crispin M, Kjellman C. Enzymatic Inactivation of Endogenous IgG by IdeS Enhances Therapeutic Antibody Efficacy. Mol Cancer Ther. 2017;16:1887-97.

Jordan SC, Reinsmoen N, Peng A, Lai CH, Cao K, Villicana R, et al. Advances in diagnosing and managing antibody-mediated rejection. Pediatr Nephrol. 2010;25:2035-45.

Lefaucheur C, Loupy A, Hill GS, Andrade J, Nochy D, Antoine C, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. J Am Soc Nephrol. 2010;21:1398-406.

Loupy A, Hill GS, Jordan SC. The impact of donor-specific anti-HLA antibodies on late kidney allograft failure. Nat Rev Nephrol. 2012;8:348-57.

OPTN. Organ Procurement and Transplantation Network. Scientific Registry of Transplant Recipients. 2012 Annual Data Report. (OPTN). optn.transplant.hrsa.gov/ 2012.

Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA. 1993;270:1339-43.

Reinsmoen NL, Lai CH, Vo A, Cao K, Ong G, Naim M, et al. Acceptable donor-specific antibody levels allowing for successful deceased and living donor kidney transplantation after desensitization therapy. Transplantation. 2008;86:820-5.

Sellares J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012;12:388-99.

Winstedt L, Jarnum S, Nordahl EA, Olsson A, Runstrom A, Bockermann R, et al. Complete removal of extracellular IgG antibodies in a randomized dose-escalation Phase I study with the bacterial enzyme IdeS - a novel therapeutic opportunity. PLoS One. 2015;10:e0132011.

18. APPENDIX 1

18.1. Protocol Amendment 03