Clinical Trial Protocol

A prospective, observational long-term follow-up trial of kidney transplant patients treated with imlifidase or plasma exchange after an active/chronic active Antibody-Mediated Rejection episode

Clinical Trial Protocol No.:	20-HMedIdeS-18
Protocol version and date:	1.1, 22-NOV-2021
Investigational Medicinal Product:	N/A
Phase:	Long-term prospective follow-up trial
Proposed indication:	Active/chronic active Antibody-Mediated Rejection
Coordinating investigator:	[redacted]
EudraCT No.:	2020-004777-49
IND No.:	128074
Name and Address of Sponsor:	Hansa Biopharma AB P.O. Box 785 SE-220 07 Lund Sweden

Signature page

This protocol version includes Non-Substantial Amendment. No. 01. According to Hansa Biopharma's SOP, only the responsible CRM approves this type of amendments by signing the "Hansa Biopharma AB Approval of Non-Substantial Amendment to Protocol "-form.

It is referred to the previous protocol (version 1.0, 02-OCT-2020) for approvals by Hansa Biopharma's signatories and the signatory coordinating principal investigator.

Investigators and Clinical Trial Administrative Structure

Coordinating	Name and title: Address: Phone E-mail	[redacted] [redacted] [redacted] [redacted]
Sponsor's Senior Medical Director	Name and title: Address: Phone: E-mail:	[redacted] Hansa Biopharma AB, P.O. BOX 785, SE- 220 07, Lund, Sweden [redacted] [redacted]

Contact details for all investigators responsible for conducting the trial, medically qualified physicians responsible for all trial site related medical decisions (if other than the investigators), clinical laboratories, other medical and/or technical departments and/or institutions involved in the trial, monitors, and relevant sponsor representatives are supplied in a trial contact list filed in the investigator site file/trial master file.

Synopsis

Name of Sponsor/Company Hansa Biopharma AB (hereafter referred to as Hansa Biopharma)	
Title of the Trial A prospective, observational long-term follow-up trial of kidney transplant patients treated with imlifidase or plasma exchange after an active/chronic active Antibody-Mediated Rejection (AMR) episode	
Co-ordinating Investigator [redacted]	
Trial Sites All sites, approximately 8-11 sites, in US, Europe and Australia, that have participated in trial 16-HMedIdeS-12 will be asked to participate.	
Planned trial period First subject first visit (FSFV) OCT/2020 Last subject last visit (LSLV) 3 years (+/- 4 months) after last subject's first visit in feeder trial	**Clinical Phase** Long-term prospective follow-up trial
Background and Scientific Justification for Conducting the Trial The aim of this trial is to collect data and provide a better understanding of the long-term outcome of imlifidase treatment on active or chronic active AMR in kidney transplant recipients. This is met by collecting data during extended follow up at 1, 2, and 3 years after treatment with either imlifidase or plasma exchange in trial 16-HMedIdeS-12. Data for parameters such as kidney graft survival, patient survival, kidney function, treatment of rebound of DSA and anti-drug antibodies will be collected.	

Objectives

The primary objective of this trial is to evaluate kidney graft survival in subjects that have been treated with imlifidase or plasma exchange in association with AMR in trial 16-HMedIdeS-12 (referred to as the feeder trial).

Secondary objective(s) are to:

- Evaluate overall graft survival at Year 1 and 2
- Evaluate patient survival at Year 3
- Evaluate kidney function at Year 1, 2 and 3
- Evaluate DSA levels at Year 1, 2 and 3
- Evaluate anti-imlifidase IgG levels at year 1, 2 and 3 after
- Investigate the occurrence of AMR episodes after completed the feeder trial (classified according to Banff 2017 (Haas et al. 2018) or later version)
- Investigate the occurrence of other graft rejection episodes (classified according to Banff 2017 or later version)

Endpoints:

The primary endpoint of this trial is the overall graft survival, evaluated at Year 3.

Secondary endpoints of this trial are:

- Overall graft survival evaluated at Year 1 and 2
- Patient survival, evaluated at 3 years after start of treatment in feeder trial
- Kidney function, as evaluated by eGFR, S/P-creatinine and albumin/creatinine ratio in urine at 1, 2, and 3 years after start of treatment in feeder trial
- Proportions of subjects with presumed or biopsy proven AMR episodes (classified according to Banff 2017 or later version) within 3 years after start of treatment in feeder trial
- Proportion of subjects with presumed or biopsy-proven rejection episodes, (other than AMR episodes) classified according to Banff 2017 or later version) up to 3 years after start of treatment in feeder trial
- DSA levels at 1, 2, and 3 years after start of treatment in feeder trial
- Anti-imlifidase IgG at 1, 2, and 3 years after start of treatment in feeder trial

Methodology

This is an observational 3-year follow up trial. The trial will primarily evaluate kidney graft survival in subjects with active or chronic active AMR treated with imlifidase or plasma exchange. Subjects that have participated in trial 16-HMedIdeS-12 (called the feeder trial) will be asked to participate. The subjects will attend three follow up visits 1, 2, and 3 years after start of treatment in the feeder trial.

Trial Procedures/Assessments

At all visits, graft survival and information about graft rejection episodes will be assessed. Blood samples for graft function (creatinine and eGFR), and analysis of DSA and ADA will be collected as well as a urine sample for albumin/creatinine ratio. Information about patient survival and comorbidity (infections, malignancy, diabetes mellitus, cardiovascular events and comorbidity leading to worsening of kidney function) will be recorded.

Number of subjects

Up to 30 subjects will be included.

Diagnosis and main criteria for inclusion/exclusion

Inclusion criteria:

- Signed Informed Consent obtained before any trial-related procedures
- Willingness and ability to comply with the protocol
- Previous treatment with imlifidase or plasma exchange in trial 16-HMedIdeS-12

Exclusion criteria:

- Inability by the judgement of the investigator to participate in the trial for any other reason

Medicinal Product(s)

Not applicable

Duration of treatment

Each subject will be followed up 1, 2, and 3 years after start of treatment in feeder trial.

Statistical methods

This is a long-term observational trial and for the evaluation and presentation of data descriptive techniques will be used. The data from the clinical assessments will be summarized by time point and treatment group in the feeder trial. Summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables. Counts and, if relevant, percentages will be presented for categorical variables. The primary endpoint, overall graft survival will be evaluated and presented with Kaplan-Meier curves. There will be no formal statistical hypothesis or testing because of the observational nature of the trial. Since this is a long-term follow up trial to the 16-HMedIdeS12 trial, no sample size and associated power calculations has been made.

Protocol Revision History including Summary of Changes

Protocol Version	Date	Including Amendment Type and No.	Overall Rationale for Changes
1.1	22-NOV-2021	Non-substantial amendment No. 01	• Change in CRO responsible for SAE/SUSAR reporting
1.0	02-OCT-2020	N/A	Initially approved protocol

See Appendix 1 “Clinical Study Protocol Amendment” for details of Amendment No. 01.

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List of Abbreviations

ABMR	Antibody-mediated rejection
ADA	Anti-drug antibody
AE	Adverse event
AMR	Antibody-mediated rejection
CKD	Chronic kidney disease
eCRF	Electronic Case report form
CRO	Contract research organisation
CTCAE	Common Terminology Criteria for Adverse Events
DSA	Donor-specific antibodies
EMA	European Medicines Agency
EOT	End of Trial
$F(ab')_2$	Antigen-binding fragments (two) of IgG linked by cysteine-bridge(s)
FDA	The Food and Drug Administration
GCP	Good clinical practice
eGFR	Estimated glomerular filtration rate
HLA	Human leukocyte antigen
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IdeS	Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*
IEC	Independent ethics committee
Ig	Immunoglobulin
Imlifidase	Immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*, previously named HMED-IdeS or IdeS
IMP	Investigational medicinal product
IRB	Institutional review board
MedDRA	The Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
N/A	Not applicable
RA	Regulatory authority
S/P-	Serum/plasma-
SAB-HLA	Single antigen bead assay
SAE	Serious adverse event
SAP	Statistical analysis plan
SDV	Source document verification
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file

1. INTRODUCTION

1.1 Background

Antibody-mediated rejection (AMR) is one of the most challenging adverse events following kidney transplantation and a major cause of graft dysfunction and graft loss. AMR is triggered by donor-specific antibodies (DSA). DSA specifically target Human leukocyte antigen (HLA) molecules expressed by the transplant endothelium and cause complement-mediated damage and microvascular inflammation. Over time, features of chronic injury develop, e.g. transplant glomerulopathy. Transplant glomerulopathy is a known consequence of persistent DSA positivity which results in graft failure and return to dialysis with attendant consequences for the patient 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).

The time duration from the transplantation to the onset of clinical symptoms of AMR varies largely between individuals. The difference in time course of development of clinical symptoms of AMR might partly depend on whether the targeted HLA molecule has been previously encountered by the transplant recipient or not. An early AMR (< 30 days post-transplant) is commonly classified as active AMR and most often triggered by an immunological recall response with pre-existing DSA. A late AMR (> 30 days post-transplant) is classified as either active or chronic active AMR and is caused by either a recall DSA response or newly developing naïve immune response associated with de novo DSA production (Schinstock et al. 2020).

Therapies for AMR are limited (Sellares et al. 2012). Currently used therapies include high dose IVIg +/- rituximab, plasma exchange 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 treat AMR.

Imlifidase is an IgG-degrading enzyme of *Streptococcus pyogenes* that cleaves all four human subclasses of IgG with high efficacy and strict specificity. Cleavage of IgG generates one $F(ab')_2$- and one homodimeric Fc-fragment and efficiently neutralizes Fc-mediated activities of IgG, including complement activation and Fcγ receptor binding. The rapidity of the IgG cleavage by imlifidase is considered a major advantage as compared with plasma exchange, which often requires several rounds over several days to achieve a sufficient DSA reduction. 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. Previous clinical trials supporting the rapid elimination of anti-HLA antibodies by imlifidase are summarized in Table 1.

The short-term efficacy and safety of imlifidase in active and chronic active AMR is currently being investigated in an ongoing randomized, open-label, multi-centre trial, using plasma exchange as active control (16-HMedIdeS-12). A total of 30 subjects will be included, 20 in the imlifidase arm and 10 in the plasma exchange arm. In brief, the primary objective is to investigate the efficacy of imlifidase in removing DSA in patients who are experiencing an

AMR episode after kidney transplantation. Key efficacy outcome measures such as kidney function and graft survival will be followed as secondary endpoints, as will DSA levels, up to 180 days after treatment.

While a rapid removal of DSA by imlifidase might be expected, DSA is likely to rebound unless well-controlled by concomitant immunosuppressive therapy. Therefore, there is a need to also address the long-term benefit of imlifidase in AMR.

Table 1. Summary table of clinical studies with imlifidase showing rapid effect on anti-HLA antibodies/DSA.

Trial No. / EudraCT No./ IND No.	**Phase / Subjects**	**Main objectives**
13-HMedIdeS-02 / 2013-005417-13	II / Patients with CKD N= 8	Efficacy in patients with CKD defined as imlifidase dosing scheme resulting in HLA antibody levels acceptable for transplantation, within 24 h from dosing. Safety in the transplantation setting.
13-HMedIdeS-03 / 2014-000712-34	II / Patients N=10	Safety in the transplantation setting. Efficacy defined as HLA antibody levels acceptable for transplantation.
14-HMedIdeS-04 / EudraCT: NA IND 124301 (Investigator initiated trial)	II / Patients N=17	Safety in combination with Cedars Sinai's "standard protocol" for desensitization of highly sensitized patients. Efficacy in prevention of ABMR.
15-HMedIdeS-06 / 2016-002064-13 IND: 128074	II / Patients N=19	Efficacy in creating a negative crossmatch test. Safety in the transplantation setting.

1.2 Scientific Rationale

The aim of this trial is to collect data and provide a better understanding of the long-term outcome of imlifidase treatment on active or chronic active AMR in kidney transplant recipients. This is met by collecting data during extended follow up at 1, 2, and 3 years after start of treatment with either imlifidase or plasma exchange in trial 16-HMedIdeS-12. Data for parameters such as kidney graft survival, patient survival, kidney function, treatment of rebound of DSA and anti-drug antibodies will be collected.

1.3 Benefit/Risk Assessment

The subjects included in this trial have been treated with imlifidase or plasma exchange in the feeder trial. The current trial is performed to collect long-term follow up data on graft function. No IMP will be administered in this trial. Most of the assessments performed under the current protocol are already part of the follow up within standard of care for these subjects and consequently they will not be exposed to any additional risk.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this trial is to evaluate kidney graft survival in subjects that have been treated with imlifidase or plasma exchange in association with AMR in the trial 16-HMedIdeS-12 (referred to as the feeder trial).

2.1.2 Secondary Objectives

The secondary objectives of this trial are to:

- Evaluate overall graft survival at Year 1 and 2
- Evaluate patient survival at Year 3
- Evaluate kidney function at Year 1, 2 and 3
- Evaluate DSA levels at Year 1, 2 and 3
- Evaluate anti-imlifidase IgG levels at Year 1, 2 and 3
- Investigate the occurrence of AMR episodes after completion of the feeder trial (classified according to Banff 2017 (Haas et al. 2018) or later version)
- Investigate the occurrence of other graft rejection episodes (classified according to Banff 2017 or later version)

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of this trial is the overall graft survival, evaluated at Year 3

2.2.2 Secondary Endpoints

Secondary endpoints of this trial are:

- Overall graft survival evaluated at Year 1 and 2
- Patient survival, evaluated at 3 years after start of treatment in feeder trial
- Kidney function, as evaluated by eGFR, S/P-creatinine and albumin/creatinine ratio in urine at 1, 2, and 3 years after start of treatment in feeder trial
- Proportions of subjects with presumed or biopsy proven AMR episodes (classified according to Banff 2017 or later version) within 3 years after start of treatment in feeder trial
- Proportion of subjects with presumed or biopsy-proven rejection episodes, (other than AMR episodes) (classified according to Banff 2017 or later version) up to 3 years after start of treatment in feeder trial
- DSA levels at 1, 2, and 3 years after start of treatment in feeder trial
- Anti-imlifidase IgG at 1, 2, and 3 years after start of treatment in feeder trial

3. INVESTIGATIONAL PLAN

3.1 Overall Trial Design

This is an observational 3-year follow up trial. Trial sites that have participated, or are currently participating, in trial 16-HMedIdeS-12 (the "feeder trial") will be contacted and requested to approach subjects for enrolment in the trial. Up to 30 subjects will be included depending on subjects' willingness to participate in the trial. Subjects who lose their graft during the feeder trial or in the intermediate time before being able to enter this trial will not continue in the trial but information about the graft loss will be collected.

The trial will primarily evaluate graft survival. The subjects will attend 3 follow up visits 1, 2 and 3 years after start of treatment in the feeder trial. Signing of Informed Consent may be performed any time between last visit in the feeder trial and up to first visit in the follow up trial.

Kidney function and patient survival will be assessed. Graft rejection episodes will be determined using classification according to Banff 2017 or later version. Information from kidney biopsies performed within standard of care will be collected. Blood samples for analysis of DSA and ADA will be collected at each visit. Medically relevant comorbidity (infections, malignancy, diabetes mellitus, cardiovascular events and comorbidity leading to worsening of kidney function), will be recorded. Information about treatments of graft rejection episodes will be recorded (e.g. plasma exchange and IVIg) as well as creatinine-level and DSA data conducted within standard of care due to the graft rejection episode.

If a planned visit cannot be performed, subjects may be contacted by phone and assessments described in this protocol may be collected from a local laboratory.

The overall trial outline is summarized in Figure 1.

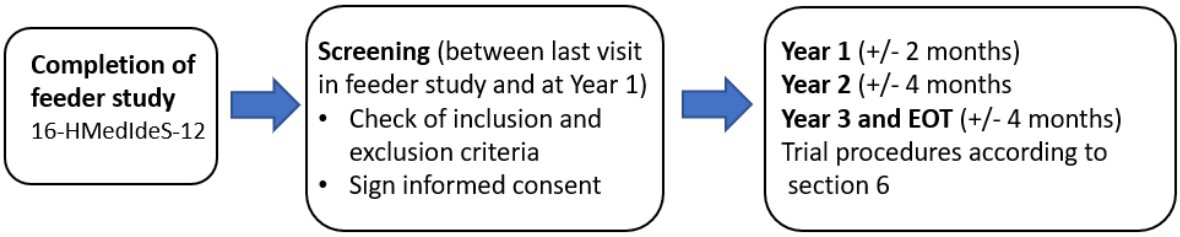

Figure 1. Overall trial design.

3.1.1 Medical monitoring

Medical monitoring will be performed at an interval described in the Medical monitoring plan.

3.1.2 Interim Analysis

No interim analysis is planned but reports may be created if judged needed.

3.2 Trial Schedule

The first subject first visit is planned in October 2020, 1 year after first subject was treated in the feeder trial.

Last subject last visit in this trial will be 3 years (+/- 4 months) after last subject's first visit in the feeder trial.

3.3 Planned Number of Trial Sites and Subjects

All sites included in the feeder trial, approximately 14 sites, in US, Europe and Australia, will be asked to participate, and up to 30 subjects may be included.

3.4 End-of-Trial

The planned End-of-Trial is defined as last subject last visit. Hansa Biopharma will ensure that an End-of-Trial Notification is submitted to the concerned health authority and IEC/IRB according to local requirements.

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

4. TRIAL POPULATION

4.1 Eligibility Criteria

Subjects who have been treated with imlifidase or plasma exchange in the feeder trial may be included. The subjects will be approached, and informed consent will be obtained for participation in the current trial.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Confirmed eligibility or reasons for screening failure will be recorded in the eCRF.

4.2 Inclusion Criteria

- Signed Informed Consent obtained before any trial-related procedures
- Willingness and ability to comply with the protocol
- Previous treatment with imlifidase or plasma exchange in the trial 16-HMedIdeS-12

  Note: The primary objective of this trial is overall graft survival after treatment with imlifidase or plasma exchange. Therefore, subjects can also be included even if the subject did not fully complete the feeder trial follow up but was dosed with imlifidase or plasma exchange in the trial 16-HMedIdeS-12.

4.3 Exclusion Criteria

- Inability by the judgement of the investigator to participate in the trial for any other reason

4.4 Restrictions

4.4.1 Prohibited Therapy

Subjects will continue with their prescribed therapies (drugs or procedures) during the trial.

4.5 Discontinuation of Subjects

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

A subject that prematurely discontinues participation will, if possible, be called in for an End-of-Trial Visit (as defined in Visit Procedures, Section 6.1.2). Even if the subject is not able to attend, the End-of-Trial Form must be completed.

5. TRIAL TREATMENT

No IMP will be administered in this trial.

5.1 Concomitant Medications and Therapies

Only immunosuppressive medications will be recorded in the concomitant medication module in the eCRF throughout the trial, beginning from screening to end of trial. Medication and therapies to treat recurrent AMR episodes will be recorded in the eCRF.

Recorded information will include indication, name of drug, route of administration and start and stop date.

6. TRIAL PROCEDURES

6.1 Trial Visits

The flow chart of all trial visits, including applicable visit windows, is provided in Section 6.2. A list of scheduled activities/assessments for each visit is provided in Sections 6.1.1 to 6.1.2 and further details of how each activity/assessment is to be performed is given in the subsections to Section 7.

All subjects considered for the trial must be informed about the trial, verbally and in writing, and give their written consent before any trial procedure is performed.

Informed consent may be signed at the last visit in the feeder trial. For each subject, the duration of the trial, including the time from signing informed consent to end of trial will not exceed 3 years and 10 months. This includes 6 months if informed consent is signed at the end of trial in feeder trial and the visit window of 4 months at Year 3 visit.

If a subject is not able to attend a planned visit, the subject may be contacted by phone and assessments described in this protocol may be collected from a local laboratory.

6.1.1 Screening

Screening may be conducted at the earliest at the last visit in feeder trial and at the latest at Year 1 (one year after start of treatment in feeder trial +/- the visit window of 2 months).

The following assessments and activities will be performed:

- Check inclusion and exclusion criteria
- Sign informed consent, see section 15.5
- Assessment of graft survival. For subjects with graft loss after last visit in the feeder trial, date, reason for graft loss, medical history, and root cause will be recorded.
- Record patient survival (if applicable, date and cause of death)

6.1.2 Year 1, Year 2, and Year 3 (End-of-Trial)

The following visit windows applies:
Year 1: (+/- 2 months)
Year 2 and Year 3 (End-of-Trial): (+/- 4 months)

The following activities and assessments will be performed:

- Assessment of graft survival. For subjects with graft loss since last visit in the feeder trial or screening (if screening is done at a separate visit), date, reason for graft loss, medical history, and root cause will be recorded.
- Record patient survival (if applicable, date and cause of death)
- Collect information about graft rejection episodes, (classified by Banff 2017 or later). For-cause biopsies together with contemporaneous local DSA analyses, kidney function parameters (P-creatinine, U-albumin/creatinine ratio) and treatments (e.g. plasma exchange and IVIg) will be collected to assess the rejection episodes.
- Record information from standard of care biopsies, if available
- Sample for S/P-creatinine will be drawn (eGFR will be calculated by the Sponsor)
- Collect urine sample for measurement of albumin/creatinine ratio
- Sample for HLA antibodies, including DSA, and ADA will be drawn
- Record comorbidity such as infections, malignancy, diabetes mellitus, cardiovascular events and comorbidity leading to worsening of kidney function, that occurred after end of trial in feeder trial
- Record current immunosuppressive medications
- Record treatment with dialysis
- AEs related to trial procedure or IMP in feeder trial will be recorded, see section 9

6.2 Flow Chart

Table 2. Flow chart.

Visit (post treatment in feeder trial)	**Screening**	**Year 1**	**Year 2**	**Year 3 (EOT)**
Visit window	**EOT feeder trial to Year 1**	**+/- 2 months**	**+/- 4 months**	**+/- 4 months**
Assessment				
Informed consent	x[1]			
Inclusion and exclusion criteria	x[1]			
Enrolment and allocation of subject no	x[1]			
Graft survival status	x	x	x	x
Patient survival status	x	x	x	x
Graft rejection episodes[2]		x	x	x
Kidney graft biopsy reports[3]		x	x	x
S/P-creatinine, eGFR calculation (performed by Sponsor)		x	x	x
U-Albumin/creatinine ratio		x	x	x
Sample for HLA antibodies, including DSA, and ADA *central lab*		x	x	x
Comorbidity[4]		x	x	x
Current immunosuppressive medication		x	x	x
Treatment with dialysis		x	x	x
Adverse events related to trial procedure or IMP in feeder trial[5]		x	x	x

Footnote

1) Signing of Informed consent and check of inclusion and exclusion criteria can be done any time between end of the feeder trial and at Year 1.
2) Record graft rejection episodes (classified by the Banff 2017 or later version), creatinine and DSAs taken in standard of care due to the episode and treatments (e.g. plasma exchange and IVIg).
3) If standard of care kidney biopsies are collected for any reason, at any time-point, e.g. suspected graft rejections, record information in the eCRF.
4) Record comorbidity that are medically relevant and registered in the subject`s medical record. Medically relevant comorbidity are infections, malignancy, diabetes mellitus, cardiovascular events and comorbidity leading to worsening of kidney function
5) Only Adverse events caused by a procedure in the protocol (e.g. blood sampling) or related to IMP in feeder trial will be recorded.

7. TRIAL ASSESSMENTS

7.1 Assessments related to Primary Endpoint

The primary endpoint of this trial is to determine the overall graft survival, defined as time from start of treatment (imlifidase or plasma exchange) of active or chronic active AMR in feeder trial to graft loss, evaluated at year 3. Graft loss is defined as permanent return to dialysis for at least 6 weeks, re-transplantation, or nephrectomy. The date of graft loss will be recorded. If dialysis is used to define graft loss, the date of graft loss is the first day of the dialysis period defining the graft loss.

7.2 Assessments related to Secondary Endpoints

7.2.1 Overall graft survival at Years 1 and 2

Graft survival at Year 3 is the primary endpoint but graft survival will be evaluated at Years 1 and 2.

7.2.2 Patient survival

Overall patient survival is defined as time from start of treatment (imlifidase or plasma exchange) of active or chronic active AMR in the feeder trial to death for any cause, evaluated at Year 3. The date and cause of death will be recorded.

7.2.3 Kidney function

Evaluation of kidney function will be based on S/P-creatinine analysis and calculation of filtration rate (eGFR) using the MDRD GFR equation. Calculation of eGFR will be done directly in the eCRF. Albumin/creatinine ratio in urine will be collected.

7.2.4 AMR rejection episodes and Graft rejection episodes (other than AMR episodes)

Information about rejection episodes will be collected, according to Banff 2017 or later classification. For-cause biopsies together with contemporaneous local DSA analyses, kidney function parameters (creatinine, albumin/creatinine ratio in urine) and treatments (e.g. plasma exchange and IVIg) will be collected to assess the rejection episodes.

7.2.5 Donor-specific antibody (DSA) levels

Samples for determination of DSA will be analyzed in a single antigen bead assay (SAB-HLA). 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 DSA, will be performed centrally at Hansa Biopharma, Lund, Sweden, for samples taken at the visits. The date and actual time of collection of each sample will be recorded in the eCRF.

DSA analysed as standard of care and associated with a graft rejection episode will be recorded in the eCRF. DSAs for each patient will be identified by the respective site.

7.2.6 Immunogenicity by Anti-Drug Antibodies (ADA)

Samples for the determination of ADA levels in serum will be analysed for [redacted]. The analysis will be performed at the central laboratory, [redacted]. Full details of the analytical method used, and the analysis results will be described in a separate bioanalytical report. The ADA sample will be collected at all visits. The date and time of collection will be recorded on the laboratory requisition form and in the eCRF.

7.2.7 Comorbidity

Information about comorbidities that are medically relevant and registered in the subjects' medical record will be collected. Medically relevant comorbidity are infections, malignancy, diabetes mellitus, cardiovascular events and comorbidities leading to worsening of kidney function.

7.2.8 Demographics

Information about gender, race and age (year) will be collected.

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of Blood

The total blood volume obtained will be about 60 mL over 3 years.

8.2 Handling, Storage and Destruction of Biological Samples

Samples analysed at the local laboratory will be disposed according to local practice.

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

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

8.3 Chain of Custody of Biological Samples

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

The principal investigator keeps full traceability of collected biological samples from the patients while in storage at the 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 trial sites and auditing of external laboratory providers.

8.4 Withdrawal of Informed Consent for Biological Samples

If a subject withdraws consent to the use of biological samples, the samples will be disposed/destroyed, 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 trial 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 trial 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 trial 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 adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product or trial procedure.

No IMP will be administered in this trial and only AEs that the investigator judges as related to IMP administered in the feeder trial, and adverse events caused by a procedure in the protocol (such as blood sampling) will be captured and reported in this trial.

9.1.2 Serious Adverse Event

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

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

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 trials, an AE/SAE can occur at any time after signing of the informed consent until the end of the trial.

AEs will therefore be collected in the eCRF from the time of signing of the informed consent and throughout the trial.

Adverse events caused by a procedure in the protocol (such as blood sampling) or judged as related to the IMP administered in the feeder trial are the only AEs that will be captured and reported in the trial.

9.2.1 Variables

The following variables will be recorded in the eCRF 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 Adverse Events grading (CTCAE, version current at trial start, same version throughout the trial duration) whether the AE is serious or not, causality assessment, action taken (including actions taken with concomitant therapies), and outcome.

9.2.1.1 Causality Assessment

The investigator will make an assessment of the relationship for any AE caused by a procedure in the protocol (such as blood sampling) or judged as related to the IMP administered in the feeder trial using the following criteria:

Related: a relationship to a trial procedure, or IMP administered in the feeder trial, cannot be excluded. Applicable to AEs where:

- It follows a reasonable temporal sequence dosing with trial procedure or IMP administered in the feeder trial
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy

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 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the trial 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 trial, if judged necessary.

9.2.4 Reporting of Serious Adverse Events

SAEs will be recorded from the time of informed consent. Only SAEs caused by trial procedure or related to IMP in the feeder trial will be reported. SAEs will be reported on a separate SAE form.

An assigned contract research organisation (CRO), [redacted] will be responsible for the SAEs handling in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations.

As soon as the investigator is aware of a potential SAE, he/she should contact [redacted] and, in any case no later than 24 hours after the knowledge of such a case. At the time of initial reporting the investigator must provide as a minimum requirement, subject number, birth date, description of the SAE and a preliminary assessment of causality.

Contact Information:	
CRO:	[redacted]
e-mail:	[redacted]

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform the [redacted] about 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. [redacted] will advise the investigator/trial site personnel how to proceed.

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

9.2.5 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

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 IMP 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.

[redacted] will be responsible for ensuring reporting all SUSARs to RAs in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. [redacted] is also responsible for informing all participating trial investigators of any SUSARs on an expedited basis and in accordance with applicable regulations.

The SUSAR reporting procedures are detailed in the trial Safety Management Plan. This plan is an agreement between the Hansa Biopharma, and [redacted]. In addition, Hansa Biopharma is responsible for informing all investigators in all other ongoing studies involving imlifidase about all SUSARs.

Hansa Biopharma or the trial monitor will be responsible for ensuring reporting SUSARs to independent ethics committees (IEC) in EU.

In US, it is the responsibility of the site investigator to promptly notify the Institutional Review Board (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 in the feeder trial and pregnancy tests are performed at the screening visit and end of trial visit.

If a subject becomes pregnant during the trial, the subject will continue in the trial according to the trial protocol, if possible. A Pregnancy Report Form must be sent by the investigator to [redacted] 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 trial. [redacted] will follow up on the 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-trial pregnancy and considered reasonably related to the trial drug by the investigator will be reported to Hansa Biopharma (or designee).

10. TRIAL MANAGEMENT

10.1 Pre-Trial Activities

All sites that are asked to participate in this trial must have participated in the feeder trial.

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

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

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

10.2 Monitoring of the Trial

During the trial, a Hansa Biopharma representative will have regular contacts with the trial 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 eCRFs.
- Perform Source Data Verification (SDV) (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the trial) including verification of informed consent of participating patients.
- 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 the monitor will be available between visits if the investigator(s) or other staff at the centre need information and advice about the trial conduct. Details about monitoring are specified in a trial specific monitoring plan.

10.3 Source Data

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 trial site. There must only be one source defined at any time for any data elements.

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

10.4 Audit and Inspection

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki 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 Trial Agreements

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

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

11. DATA MANAGEMENT

11.1 Case Report Form

An electronic case report form (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 trial 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 trial site's final and locked data (including audit trail, electronic signature, 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, comorbidity, and concomitant medication the most recent versions of the Medical Dictionary for Regulatory Activities (MedDRA) and WHO Drug Dictionary will be used at trial 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 trial closure/database lock.

11.4 Handling of External Data

If central laboratories or other external data transfers from vendors to Hansa Biopharma will be transmitted, it will be performed in a secure environment according to a Data Transfer Specification.

12. STATISTICAL METHODS

All analyses will be detailed in a separate Statistical Analysis Plan (SAP).

12.1 Analysis Sets

12.1.1 Full Analysis Set (FAS)

The Full Analysis Set will be defined as all patients enrolled. Because of the observational nature of this trial no other analysis set will be defined and all data presentations and analyses will be based on the FAS.

12.2 Subject Characteristics

The data from the clinical assessments will be summarised or listed by treatment group and each time point using descriptive techniques. Summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables (absolute values at each time point and, if relevant, changes from baseline) and counts and, if relevant, percentages will be presented for categorical variables. Where appropriate, the presentation of results will include confidence intervals of estimated treatment differences and plots.

12.2.1 Subject Disposition

All subjects screened will be accounted for. The number of subjects in the analysis sets and the number of subjects who complete the trial will be summarized by treatment group. Furthermore, the number of subjects who withdraw from the trial will be summarised overall and by treatment group and reason for withdrawal. Subjects screened but not found eligible will be listed with reason for screening failure.

12.2.2 Demographics and Other Baseline Characteristics

The subject's demographics and other baseline characteristics will be summarised by treatment group.

12.2.3 Recent and Concomitant Medication

Recent and concomitant immunosuppression medication will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name for each treatment group.

12.3 Statistical Analysis of Primary Endpoints

No formal statistical hypothesis testing will be performed in the trial. Data will be presented by treatment group.

12.3.1 Primary efficacy analysis

Overall graft survival at Year 3. Graft survival is defined as time from start of treatment (imlifidase or plasma exchange) of active or chronic active AMR in feeder trial to graft loss, evaluated at year 3. Graft loss is defined as permanent return to dialysis for at least 6 weeks, re-transplantation, or nephrectomy. If dialysis is used to define graft loss, the date of graft loss will be the first day of the last ongoing dialysis period reported.

The primary endpoint will be analysed by the Kaplan-Meier survival method. The overall graft survival will be tabulated and presented graphically with 95% confidence limits by treatment.

The following events will be censored at the time of occurrence: withdrawal from the trial without graft loss, evaluation time point and end of trial without graft loss.

The reason for graft loss will be tabulated by time.

12.4 Statistical Analysis of Secondary Endpoints

12.4.1 Graft survival at Year 1 and 2

Graft survival at Year 1 and Year 2 will be evaluated as described under 12.3.1.

12.4.2 Patient survival

Patient survival, defined as time from start of treatment in feeder trial to death, evaluated at Year 3 will be listed by patient and summarized by treatment.

12.4.3 Kidney function

Kidney function, as evaluated by eGFR, S/P-creatinine and albumin/creatinine ratio in urine at 1, 2, and 3 years after start of treatment in feeder trial. Variables will be listed by patient and summarized by treatment at Year 1, 2, and 3 after start of treatment in feeder trial. Derivation of eGFR will be detailed in the SAP.

12.4.4 Proportion of subjects with rejection episodes

Proportion of subjects with presumed or biopsy-proven AMR episodes (classified according to Banff 2017 or later) and proportion of subjects with biopsy-proven rejection episodes, (other than AMR episodes) within 3 years after start of treatment in feeder trial will be listed and summarised by treatment group.

12.4.5 DSA level at 1, 2, and 3 years after start of treatment in feeder trial

DSA levels (measured using SAB-HLA assay) 1, 2 and 3 years after start of treatment in feeder trial will be summarized, listed, and presented graphically.

12.4.6 Immunogenicity

Anti-imlifidase antibody 1, 2, and 3 years after start of treatment in feeder trial, will be listed and summarised.

12.5 Analysis of Adverse Events

Only adverse events related to trial procedure or related to IMP administered in feeder trial will be collected and listed.

12.6 Determination of Sample Size

As this is an observational follow up trial, no power calculations for sample size estimation were performed. All patients enrolled in the feeder trial (16-HMedIdeS-12) will be considered for inclusion in this trial. It is anticipated that approximately 30 patients, 20 from the imlifidase arm and 10 from the plasma exchange arm, may be included.

13. CHANGES IN TRIAL 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 trial 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. Deviation reports and supporting documentation will be kept in the investigator site file and the trial master file.

Hansa Biopharma will review all protocol deviations continuously during the trial and assess whether there is a need to update the protocol through an amendment to avoid future deviations.

Planned protocol deviations are not permitted.

13.3 Statistical Analysis Plan

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

13.4 Premature Termination or Suspension of the Trial

If the trial 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 trial 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 Trial, the investigator should promptly inform the Institution where applicable. In both cases Hansa Biopharma will promptly inform the RA and IEC and provide them with a detailed written explanation of the termination or suspension.

If the RA or IEC terminates or suspends its approval/favourable opinion of a trial, 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 Trial Report

The results from this trial will be reported in a clinical trial report (CTR) within one year after end-of-trial. 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 trial, including any data and results from the trial will be the exclusive property of Hansa Biopharma. The investigator and any other persons involved in the trial 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 trial, 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 trial has no publication rights regarding the trial.

14.4 Public Disclosure

The trial will be registered in a public clinical trials registry i.e. the U.S. National Institutes of Health register ClinicalTrials.gov.

15. ETHICAL AND REGULATORY ASPECTS

15.1 Ethical Conduct of the Trial

This trial will be conducted in compliance with the approved protocol (including any approved amendments), the ICH E6 (R2) Good Clinical Practice (GCP), the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association, applicable regulatory requirements, and local legislations. US sites will accordingly be under a US IND while European and other non-US sites will conduct the trial in compliance with respective country's local legislation.

The responsibilities of Hansa Biopharma, the monitor and the investigator are defined in the ICH GCP E6 (R2) consolidated guideline and applicable regulatory requirements in the country where the trial takes place. The investigator is responsible for adhering to the responsibilities of investigators defined in ICH GCP E6 (R2). For studies conducted in the USA, the investigator will additionally ensure adherence to the basic principles of GCP as outlined in the current version of 21 CFR, part 312, subpart D: "Responsibilities of Sponsors and Investigators", part 50: "Protection of Human Subjects", and part 56: "Institutional Review Boards."

15.2 Liabilities and Insurance

Hansa Biopharma is, as the 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 trial subject for injury arising from the subject's participation in the trial.

15.3 Independent Ethics Committee(s) and Institutional Review Board(s)

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

According to applicable regulatory requirements Hansa Biopharma will:

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

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.

15.5 Subject Information and Informed Consent

Before any trial-related activities and in agreement with applicable regulatory requirements, the investigator must give the subject oral and written information about the trial in a form that the subject can understand. The Investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts and expected benefits of the Trial. 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 Trial 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 trial subject's willingness to continue participation in the trial, a new Subject Information and Informed Consent Form will be forwarded to the IEC(s)/IRB(s) (and RAs, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

15.6 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 trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorized third party.

The trial 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 trial. The clinical trial site will permit access to such records.

16. ARCHIVING

16.1 Retention of Clinical Trial Site Documentation

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 25 years after the completion or discontinuation of the trial 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 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 after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Hansa Biopharma. Should the investigator elect to assign the trial 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 Trial Master File

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

17. REFERENCES

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.

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.

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.

Schinstock CA, Mannon RB, Budde K, Chong AS, Haas M, Knechtle S, et al. Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group. Transplantation. 2020;104:911-22.

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.

18. APPENDIX 1

18.1 Protocol Amendment 01

Protocol Amendment Number 01 Summary

AMENDMENT TYPE:

This amendment is considered to be Non-Substantial because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the trial.

RATIONALE FOR THE AMENDMENT:

The overall rationale for the changes implemented in the protocol is the change of the CRO responsible for SAE/SUSAR reporting. In addition, a few editorial updates have been made.

AMENDED SECTIONS IN THE PROTOCOL:

Details of the changes to the protocol are shown below. Changes to the text are shown in ~~strike-through~~ text and new text in *underlined italics*.

OTHER DOCUMENTS AND SYSTEM IMPACTED BY THE AMENDMENT

All study documents related to SAE/SUSAR reporting will be updated as required.

1 Change in CRO responsible for SAE/SUSAR reporting

Hansa Biopharma has changed the CRO responsible for SAE/SUSAR reporting and the protocol has been updated with the new contact details.

1.1 Section 9.2.4 Reporting of Serious Adverse Events (2nd paragraph to 5th paragraph)

Changed from:

An assigned contract research organisation (CRO), [redacted] will be responsible for the SAEs handling in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations.

As soon as the investigator is aware of a potential SAE, he/she should contact [redacted] and, in any case no later than 24 hours after the knowledge of such a case. At the time of initial reporting the investigator must provide as a minimum requirement, subject number, birth date, description of the SAE and a preliminary assessment of causality.

Contact Information:	
CRO:	[redacted]
e-mail:	[redacted]

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

[redacted] about 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 [redacted] will advise the investigator/trial site personnel how to proceed.

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

Changed to:

An assigned contract research organisation (CRO), [redacted] will be responsible for the SAEs handling in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations.

As soon as the investigator is aware of a potential SAE, he/she should contact [redacted] and, in any case no later than 24 hours after the knowledge of such a case. At the time of initial reporting the investigator must provide as a minimum requirement, subject number, birth date, description of the SAE and a preliminary assessment of causality.

Contact Information:	
CRO:	[redacted]
e-mail:	[redacted]

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform the [redacted] about 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. [redacted] will advise the investigator/trial site personnel how to proceed.

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

1.2 Section 9.2.5 Reporting of Suspected Unexpected Serious Adverse Reactions (3rd and 4th paragraph)

Changed from:

[redacted] will be responsible for ensuring reporting all SUSARs to RAs in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. [redacted] is also responsible for informing all participating trial investigators of any SUSARs on an expedited basis and in accordance with applicable regulations.

The SUSAR reporting procedures are detailed in the trial Safety Management Plan. This plan is an agreement between the Hansa Biopharma, and [redacted]. In addition, Hansa Biopharma is responsible for informing all investigators in all other ongoing studies involving imlifidase about all SUSARs.

Changed to:

[redacted] will be responsible for ensuring reporting all SUSARs to RAs in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. [redacted] is also responsible for informing all participating trial investigators of any SUSARs on an expedited basis and in accordance with applicable regulations.

The SUSAR reporting procedures are detailed in the trial Safety Management Plan. This plan is an agreement between the Hansa Biopharma, and [redacted]. In addition, Hansa Biopharma is responsible for informing all investigators in all other ongoing studies involving imlifidase about all SUSARs.

1.3 Section 9.3 Pregnancy and Pregnancy Outcome (2nd paragraph)

Changed from:

…. A Pregnancy Report Form must be sent by the investigator to [redacted] 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 trial. [redacted] will follow up …

Changed to:

… A Pregnancy Report Form must be sent by the investigator to [redacted] 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 trial. [redacted] will follow up ...

2 Editorial changes

A few minor editorial changes were made without any implications on the study protocol and procedures.

2.1 Title page

Changed from:

Clinical Trial 1.0

Protocol version and date:	1.0, 02 OCT-2020
Revision history:	N/A

Changed to:

Clinical Trial ~~1.0~~*Protocol*

Protocol version and date: 1.~~0~~*1*, ~~02 OCT 2020~~*22-NOV-2021*

~~Revision history:~~ ~~N/A~~

2.2 Signature page (Sponsor's signature)

Changed from:

This clinical trial protocol, identified by the version and date above, is approved by:

Chief Operating Officer / Chief Scientific Officer

[redacted]

Signature Date

Vice President R&D / Senior Medical Director, Hansa Biopharma AB

[redacted]

Signature Date

Signatory Coordinating Principal Investigator

[redacted]

Signature Date

Changed to:

This protocol version includes Non-Substantial Amendment No.01. According to Hansa Biopharma's SOP, only the responsible CRM approves this type of amendments by signing the "Hansa Biopharma AB Approval of Non-Substantial Amendment to Protocol "-form.

It is referred to the previous protocol (version 1.0, 02-OCT-2020) for approvals by Hansa Biopharma's signatories and the signatory coordinating principal investigator.

~~This clinical trial protocol, identified by the version and date above, is approved by:~~

~~**Chief Operating Officer / Chief Scientific Officer**~~

[redacted]

~~Signature~~ ~~Date~~

~~**Vice President R&D / Senior Medical Director, Hansa Biopharma AB**~~

[redacted]

~~Signature~~ ~~Date~~

~~**Signatory Coordinating Principal Investigator**~~

[redacted]

~~Signature~~ ~~Date~~

2.3 Investigators and Clinical Administration Structure (2nd row in table)

Changed from:

Sponsor's Medical Expert	Name and title: [redacted] Address: [redacted] Phone: [redacted] E-mail:

Changed to:

Sponsor's ~~Medical Expert~~*Senior Medical Director*	Name and title: [redacted] Address: [redacted] Phone: [redacted] E-mail: [redacted]

2.4 New Section – Protocol Revision History Summary of Changes

Changed from:

-

Changed to:

Protocol Revision History including Summary of Changes

Protocol Version	***Date***	***Including Amendment Type and No.***	***Overall Rationale for Changes***
1.1	*22-NOV-2021*	*Non-substantial amendment No. 01*	• *Change in CRO responsible for SAE/SUSAR reporting* • *Updated number of participating sites to approximately 14*
1.0	*02-OCT-2020*	*N/A*	*Initially approved protocol*

See Appendix 1 "Clinical Study Protocol Amendment" for details of Amendment No. 01.

2.5 Section 1.1 Background (Table 1, 1st row)

Changed from:

Trial No / EudraCT No	**Phase / Subjects**	**Main objectives**

Changed to:

Trial No. / EudraCT No./ *IND No.*	**Phase / Subjects**	**Main objectives**

2.6 Section 3.3 Planned Number of Trial Sites and Subjects

Changed from:

All sites included in the feeder trial, approximately 8-11 sites, in US,…..

Changed to:

All sites included in the feeder trial, approximately ~~8-11~~*14* sites, in US,…..

2.7 Section 6.1.1 Screening (Header and 1st paragraph)

Changed from:

6.1.1 Screening (may be conducted at the earliest at the last visit in feeder trial and at the latest at Year 1 (one year after start of treatment in feeder trial +/- the visit window of 2 months)

Changed to:

6.1.1 Screening ~~(may be conducted at the earliest at the last visit in feeder trial and at the latest at Year 1 (one year after start of treatment in feeder trial +/- the visit window of 2 months)~~

*Screening may be conducted at the earliest at the last visit in feeder trial and at the latest at Year 1 (one year after start of treatment in feeder trial +/- the visit window of 2 months)***.**

The following assessments and activities will be performed:

2.8 Section 6.1.2 Year 1, Year 2, and Year 3 (End-of-Trial) (Header and 1st paragraph)

Changed from:

6.1.2 The following activities and assessments will be performed at Year 1(+/-2 months)**, Year 2** (+/-4 months)**, Year 3 ((+/-4 months)and End-of-Trial)**

Changed to:

6.1.1 ~~The following activities and assessments will be performed at Year 1~~(~~+/- 2 months~~)**~~, Year 2~~** (~~+/- 4 months~~)**~~, Year 3 ((+/- 4 months)and End-of-Trial)~~*Year 1, Year 2, and Year 3 (End-of-Trial)***

The following visit windows applies:

Year 1: (+/- 2 months)

Year 2 and Year 3 (End-of-Trial): (+/- 4 months)

The following activities and assessments will be performed:

2.9 Section 6.2. Flow Chart (1st and 2nd row)

Changed from:

Visit (post treatment in feeder trial)	Screening	Year 1	Year 2	Year 3 EOT
Visit window	EOT feeder trial to year 1	+/- 2 months	+/- 4 months	+/- 4 months

Changed to:

Visit (post treatment in feeder trial)	Screening	Year 1	Year 2	Year 3 (EOT)
Visit window	EOT feeder trial to ~~-~~Year 1	+/- 2 months	+/- 4 months	+/- 4 months

2.10 New Section 18. Appendix 1

Changed from:

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Changed to:

18. APPENDIX 1

18.1 Protocol Amendment 01