Clinical Study Protocol

including non-substantial Amendment 03

A prospective, observational long-term follow up study of patients treated with imlifidase (IdeS) prior to kidney transplantation

Study No.:	17-HMedIdeS-14
Investigational Medicinal Product:	NA
Phase:	Prospective, follow up study
EudraCT Number:	NA
IND Number:	128074
Name and Address of Sponsor:	Hansa Biopharma.AB. Box 785 220 07 Lund Sweden

Protocol Revision History including Summary of Changes

Version	Date	Overall Rational for Changes
Version 1.0	03 APR 2018	N/A Original Protocol
Version 2.0	20 JUN 2018	• Assessment of Quality of Life Questionnaires were changed, it was decided to use two instead of three questionnaires. • Kidney biopsy data will be recorded directly in CRF intsead of retrieved from the biopsy reports. • Any version of Banff classification can be used for classification of acute rejection episodes. • EudraCT number on first page is removed since the study was not submitted to any European regulatory authority.
Version 3.0	27 SEP 2020	• The method of data collection will be changed from paper CRF to electronic CRF. • A study visit can be performed remotely if a subject is not able to visit the site. • Clarify the wordings “acute rejection episode” and “DSA rebound” by change wordings to “graft rejection episode”. • Clarify that creatinine and proteinuria results from graft rejection episodes will be collected as well as from the time for planned 1- and 2-Years visits if study start was after those visits should have taken place.
Version 4.0	22 NOV 2021	• Updates due to change in CRO responsible for SAE and SUSAR handling.

See Appendix 1 “Protocol Amendment History” for details of Amendment 03.

Synopsis

Name of Sponsor/Company

Hansa Biopharma AB (hereafter referred to as Hansa Biopharma)

Title of the study

A prospective observational, long term follow up study of patients treated with imlifidase prior to kidney transplantation

Signatory Coordinating Investigator (s)

Dr. Bengt von Zür-Muhlen

Study Site(s)

Six sites will be involved; 2 in Sweden, 1 in France and 3 in the US.

Planned study period	**Clinical Phase**
First subject first visit (FSFV) Q2 2018 Last subject last visit (LSLV) Q3 2022	Observational study

Background and Scientific Justification for Conducting the Study

The rationale for the current protocol is to collect data from extended follow up in subjects that have received a kidney transplant following imlifidase dosing to provide a better understanding regarding the long-term outcome for these subjects. Data of parameters such as patient and graft survival, comorbidity, treatment of graft rejection episodes and quality of life as well as anti-drug antibody levels will be collected.

This prospective, observational follow up study of subjects who have received imlifidase prior to kidney transplantation will provide important data to future prescribers and patients of the potential long-term benefits of imlifidase mediated transplantation.

Primary objective:

Evaluation of graft survival in subjects who have undergone kidney transplantation after imlifidase administration.

Secondary Objectives:

- Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of patient survival, kidney function, comorbidity, treatments and quality of life.
- Assessment of safety blood sampling in transplanted subjects treated with imlifidase
- Assessment of donor specific antibodies (DSA) in transplanted subjects treated with imlifidase
- Assessment of immunogenicity (anti-drug antibodies, ADA) in transplanted subjects treated with imlifidase

Endpoints

The primary endpoint of this study is to determine overall graft survival, defined as time from transplantation to graft loss at 1, 2, 3 and 5 years after first dose of imlifidase.

Graft loss is defined as: Permanent return to dialysis for at least 6 weeks, re-transplantation, or nephrectomy.

Secondary Endpoints

The following secondary endpoints will be evaluated at 1, 2, 3 and 5 years from the first dose of imlifidase:

- Overall patient survival (time from transplantation to death for any cause)
- Kidney function as evaluated by eGFR, P-creatinine, proteinuria
- Number of graft rejection episodes (Banff classification)
- Safety laboratory tests
- Treatment of graft rejection episode
- Comorbidity
- DSA levels
- Presence of BK virus
- ADA as evaluated by anti-imlifidase IgG
- Health related quality of life as evaluated by patient questionnaires

Methodology

This is a five year, long-term follow up, observational study. The study will primarily determine the time of graft survival in subjects who have received imlifidase prior to kidney transplantation. Subjects that have participated, or are currently participating, in the imlifidase kidney transplantation studies (called feeder studies) 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06 will be included. The subjects will attend 4 follow up visits, 1, 2, 3 and 5 years after imlifidase administration.

Study Procedures/Assessments

At all visits, graft function (creatinine, eGFR, proteinuria) and time of graft survival will be assessed. Blood samples for analysis of DSAs, ADA and antibodies towards BK virus will be taken as well as total IgG and hematology samples. Information about patient survival, comorbidity (infections, malignancy, diabetes mellitus and cardiovascular events) and treatments of graft rejection episode (dialysis, plasmapheresis, medications) will be recorded. The subjects will be asked to complete QoL questionnaires.

Number of subjects

Up to 46 subjects will be included depending on subjects' willingness to participate in the study.

Diagnosis and main criteria for inclusion/exclusion

Inclusion Criteria:

1) Signed Informed Consent obtained before any study-related procedures
2) Previous dosing with imlifidase followed by kidney transplantation and participation in one of the following clinical studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 or 15-HMedIdeS-06

Exclusion Criteria:

1) Individuals deemed unable to comply with the protocol
2) Inability by the judgment of the investigator to participate in the study for other reasons

Medicinal Product(S)

Not applicable

Statistical methods

This is a long-term non-interventional study and for the evaluation and presentation of data descriptive techniques will be used. The data from the clinical assessments will be summarised by feeder study and time point. 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 will be analysed by the Kaplan-Meier survival method. There will be no formal statistical hypothesis or testing because of the observational nature of the study.

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List of Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
CKD	Chronic Kidney Disease
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DD	Deceased Donor
DSA	Donor Specific Antibodies
eGFR	estimated Glomerular Filtration Rate
EQ-5D-5L	European Quality of Life -5 Levels
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HLA	Human Leukocyte Antigen
HR-QoL	Health Related Quality of Life
ICH	International Conference on Harmonization
IdeS	Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IVIg	Intravenous Immunoglobulin
KDQOL-SF	Kidney Disease Quality of Life-Short Form
KM	Kaplan-Meier
LD	Living Donor
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Florescence Intensity
PE	Plasma Exchange
QA	Quality Assurance
RA	Regulatory Authority
SAB	Single Antigen Bead
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Document Verification
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. INTRODUCTION

The company code initially used in this project was HMED-IdeS (sometimes abbreviated to IdeS) and thus many reports refer to this name. The International Nonproprietary Name (INN) imlifidase was recently assigned for the active substance and going forward this name will be used.

1.1 Background

Renal transplantation is the preferred treatment choice for patients with end stage kidney disease since it increases survival and patient quality of life and results in substantial savings in health care costs compared to dialysis (Montgomery et al. 2005).

Approximately one third of patients waiting for kidney transplantation are sensitized to human leukocyte antigen (HLA) and sensitization hampers the identification of a suitable donor (Iyer et al. 2014). The presence of strong HLA donor specific antibodies (DSAs) is a direct contraindication to transplantation because of the risk of hyper-acute antibody-mediated rejection with acute allograft loss. For transplant candidates who have antibodies, which react against a wide range of HLA, it can be difficult to find a donor against whom they have no antibodies. This is true both for patients waiting for a deceased donor kidney and for those within a paired donation program who have an available live donor against which they have DSAs.

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

Imlifidase is an IgG-degrading enzyme of *Streptococcus pyogenes* that cleaves all four human subclasses of IgG with strict specificity. Cleavage of IgG generates one $F(ab')_2$- and one homodimeric Fc-fragment and efficiently neutralizes Fc-mediated activities of IgG (HMed doc. No. 2012-003) (Wenig et al. 2004; Vincents et al. 2004; von Pawel-Rammingen et al. 2002). Imlifidase-mediated IgG degradation constitutes a novel therapeutic principle for the treatment of IgG-driven human diseases.

Hansa Biopharma AB has performed *in vitro* studies and clearly demonstrated that imlifidase effectively cleaves purified IgG as well as IgG in serum from human and rabbit. Imlifidase is very specific in that no other substrate has been found (HMed Doc. No. 2012-003). In addition, imlifidase treatment rapidly and substantially cleaved anti-HLA IgG in serum from sensitized chronic kidney disease (CKD) grade 5 patients *in vitro* (HMed Doc. No. 2012-005).

The reactivity to individual HLA-antigens was reduced below the critical Mean Florescence Intensity (MFI) acceptable for transplantation and a positive crossmatch test was turned into negative. Imlifidase offers a unique and powerful approach for removing the impenetrable immunology barrier HLA antibodies present and would allow potentially life-saving transplants to highly sensitized patients who are currently not eligible for kidney transplantation.

The clinical studies performed or ongoing with imlifidase within the transplantation program are summarised in Table 1.

Table 1. Summary table of clinical studies with imlifidase in the transplantation program.

Study No / EudraCT No	**Phase / Subjects**	**Doses / Follow up time**	**Main objectives**	**Comments**	**Status / Country / Subject Numbers**
11-HMedIdeS-01 / 2012-000 969-21	I / Healthy subjects	0.010, 0.040, 0.12 and 0.24 mg/kg BW 64 d	Safety	First-in-man, double blind, randomized, single ascending dose, 20 active, 9 placebo. IgG completely cleaved within 1-2 h. Safe and well tolerated.	Completed / SE / N=29
13-HMedIdeS-02 / 2013-005417-13	II / CKD Patients	0.12 and 0.25 mg/kg BW given once or twice within 48 h / 64 d	Efficacy in CKD patients defined as imlifidase dosing scheme resulting in HLA antibody levels acceptable for transplantation, within 24 h from dosing. Safety in the transplantation setting.	Single arm with ascending doses. Primary efficacy endpoint reached. Safe and well tolerated. One patient was transplanted (not part of protocol). Deceased donor.	Completed / SE / N= 8
13-HMedIdeS-03 / 2014-000712-34	II / Patients	0.25 and 0.5 mg/kg / 180 d	Safety in the transplantation setting. Efficacy defined as HLA antibody levels acceptable for transplantation.	Similar design as 13-HMedIdeS-02 but transplantation part of protocol. Deceased and living donors. Safe and well tolerated. All patients desensitized and transplanted	Completed / SE / N=10

Study No / EudraCT No	Phase / Subjects	Doses / Follow up time	Main objectives	Comments	Status / Country / Subject Numbers
14-HMedIdeS-04 / EudraCT: NA IND 124301	II / Patients	0.24 and 0.5 mg/kg / 180 d	Safety in combination with Cedars Sinai's "standard protocol" for desensitization of highly sensitized patients. Efficacy in prevention of ABMR.	Investigator sponsored IND. Imlifidase combined with rituximab and IVIg. All transplantations successful except one graft loss which occurred due to non-HLA and non-IgG ABMR. Biopsy suggested rejection due to IgM and IgA.	Completed / US / Total N=17 Analysis and reporting ongoing.
15-HMedIdeS-06 / 2016-002064-13 IND: 128074	II / Patients	0.25 and 0.5 mg/kg / Primary endpoint: 24 h Safety: 180 d	Efficacy in creating a negative crossmatch test. Safety in the transplantation setting.	Deceased and living donors. Target population cannot be transplanted with current available methods for desensitization. All transplantations (18) were successful except one graft loss. For one patient, imlifidase dosing was interrupted due to allergic reaction and the patient was not transplanted.	Ongoing / US, FR & SE / Total N=19 Recruitment ended 15 Dec 2017.

BW=body weight, h=hours, d=days

In completed (13-HMedIdeS-02, 13-HMedIdeS-03 and 14-HMedIdeS-04) and ongoing studies (15-HMedIdeS-06), subjects have been treated with imlifidase and transplanted with kidneys from deceased or living donors. The follow up periods were 6 months post transplantation except for 13-HMedIdeS-02 with 2 months follow up. The current protocol aims at collecting key information regarding overall graft function and safety from all subjects that have been treated with imlifidase prior to kidney transplantation.

1.2 Rationale

The rationale for the current protocol is to collect data from extended follow up in subjects that have received a kidney transplant following imlifidase dosing to provide a better understanding regarding the long-term outcome for these subjects. Data of parameters such as patient and graft survival, kidney function, comorbidity, treatment of graft rejection episodes and quality of life as well as anti-drug antibody levels will be collected.

1.3 Benefit / Risk Aspects

The subjects included in this study have received imlifidase prior to kidney transplantation in previous clinical studies. The current study is performed to collect long-term follow up data on graft function and safety. 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 impose any additional risk.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

The primary objective of this study is to evaluate graft survival in subjects who have undergone kidney transplantation after imlifidase administration.

Secondary Objectives

The secondary objectives include:

- Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of patient survival, kidney function, comorbidity, treatments and quality of life.
- Assessment of safety blood sampling in transplanted subjects treated with imlifidase
- Assessment of donor specific antibodies (DSA) in transplanted subjects treated with imlifidase
- Assessment of immunogenicity (anti-drug antibodies, ADA) in transplanted subjects treated with imlifidase

2.2 Endpoints

Primary Endpoint

The primary endpoint of this study is to determine overall graft survival, defined as time from transplantation to graft loss at 1, 2, 3 and 5 years after first dose of imlifidase.

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 (EMA Guideline on clinical investigation of immunosuppressants for solid organ transplantation 2008) .

Secondary Endpoints

The following secondary endpoints will be evaluated after the first dose of imlifidase at the time points 1, 2, 3 and 5 years:

- Overall patient survival defined as time from transplantation to death for any cause

- Kidney function as evaluated by eGFR, P-creatinine, proteinuria
- Number of graft rejection episodes (classified by Banff , (Haas et al. 2018))
- Safety laboratory tests (hematology, total IgG)
- Treatment of graft rejection episodes
- Comorbidity
- DSA levels as evaluated by SAB-HLA analysis
- Presence of BK virus
- ADA as evaluated by anti-imlifidase IgG
- Health related quality of life (HR-QoL) as evaluated by patient questionnaires EQ-5D-5L and KDQOL-SF.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a five year, long-term follow up, observational study. Centers that have participated, or are currently participating, in selected imlifidase kidney transplantation studies (referred to as "feeder studies") will be contacted and requested to approach subjects for enrolment in the study. The following studies will be considered feeder studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06. Up to 46 subjects will be included depending on subjects' willingness to participate in the study.

The study will primarily determine the time of graft survival in subjects who have received imlifidase prior to kidney transplantation. The subjects will attend 4 follow up visits, 1, 2, 3 and 5 years after imlifidase administration. Some subjects will not perform all 4 visits because the study start will be after the subjects' first visit should have taken place.

Kidney function (creatinine, eGFR, proteinuria) and graft survival will be assessed. Graft rejection episodes will be determined by Banff classification. Information from kidney biopsies performed within standard of care will be collected. Blood samples for analysis of DSAs, ADA and antibodies towards BK virus will be taken as well as total IgG and safety hematology samples. Medically relevant comorbidity (infections, malignancy, diabetes mellitus and cardiovascular events) will be recorded. Information about treatments of graft rejection episodes will be recorded (dialysis, plasmapheresis, medications). At all visits, the subjects will be asked to complete QoL questionnaires. The overall study outline is summarized in Figure 1.

3.1.1 Overall Study Outline

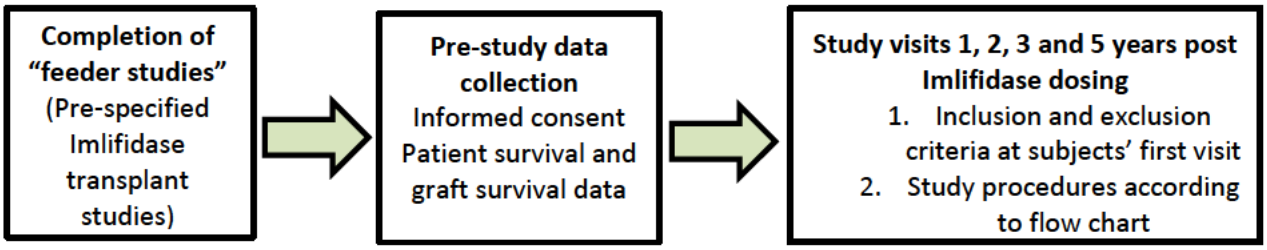

Figure 1.Overall study outline

3.1.2 Follow up Procedures

The study subjects will be followed up according to clinical standard of care during and after study completion.

3.2 Study Schedule

Planned first subject first visit:	Q2 2018
Planned recruitment period:	NA
Planned last subject last visit:	Q4 2022
Planned completion of the Clinical Study Report:	Q4 2023

3.3 Planned number of study sites and subjects

There will be 6 study sites involved in the study; 2 in Sweden, 1 in France and 3 in US. In total, up to 46 male and female subjects will be asked to participate.

3.4 Planned End of Study

The planned End of Study is defined as last subject last visit. Hansa Biopharma will ensure that End of Study notification is submitted to the concerned regulatory authorities and IEC/IRB according to local requirements.

For procedures in case of premature termination or suspension of the study, see Section 12.4.

4. STUDY POPULATION

4.1 General

Subjects who have received imlifidase prior to kidney transplantation in a feeder study will be included. The subjects will be approached, and informed consent will be obtained for participation in the current study. Up to 46 subjects will be included depending on subject willingness to participate.

4.2 Selection Criteria

Subjects must meet all inclusion criteria and no exclusion criteria to be eligible for the study.

4.2.1 Inclusion Criteria

- Signed Informed Consent obtained before any study-related procedures
- Previous dosing with imlifidase followed by kidney transplantation and participation in one of the following clinical studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 or 15-HMedIdeS-06

  Note: The primary objective in this study is overall graft survival after imlifidase treatment therefore the subjects can also be included in the event that the subject did not fully complete the feeder study.

4.2.2 Exclusion Criteria

- Individuals deemed unable to comply with the protocol
- Inability by the judgement of the investigator to participate in the study for other reasons

4.3 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.

If a subject prematurely discontinues participation, the End of Study Form (with date and reason for discontinuation) in the CRF must be completed.

5. STUDY PROCEDURES

5.1 Study Visits

For each subject the duration of the study will not exceed 5 years and 6 months post imlifidase dosing.

All subjects considered for the study must be informed about the study, verbally and in writing, and give their written consent before any study procedure is performed. After informed consent is obtained, pre-study visit data such as information on graft survival and patient survival can be collected and entered in the CRF.

Some subjects will not perform all 4 visits because the study start will be after the subjects' first visit should have taken place.

If a subject is not able to attend a planned visit at the site, the visit can be performed remotely. The blood sampling should be performed at the local laboratory (if possible) and QOL forms

sent to the subject. The following activities and assessments will be performed at **1 year (+/-** 2 months**), 2 years (+/-** 4 months**), 3 years (+/-** 4 months**)** and **5 years** (+/- 6 months**) post imlifidase dosing:**

- Check of inclusion and exclusion criteria will be performed at the first visit for each subject after 1, 2 or 3 years post imlifidase dosing.
- Subjects shall complete QoL questionnaires (EQ-5D-5Land KDQOL-SF)
- Evaluation of graft survival
- Record patient survival (if applicable, date and cause of death)
- Safety laboratory tests (see Table 3)
- P-creatinine, eGFR and U-proteinuria tests
- DSA samples
- ADA sample
- BK virus sample
- Record comorbidity such as infections, malignancy, diabetes mellitus and cardiovascular events
- Record graft rejection episodes (classified by Banff)
- If applicable, record information from standard of care kidney biopsy reports
- Record treatments of graft rejection episodes (PE, IVIg, dialysis, other)
- Record current immunosuppressive medication
- Record and report AEs caused by study procedure or a clinically significant safety lab value

5.2 Flow Chart

Table 2. Study flow chart.

Visit post imlifidase dosing	1 year[1]	2 years	3 years	5 years
Visit window	(+/- 2 months)	(+/- 4 months)	(+/- 4 months)	(+/- 6 months)
Informed consent	x[2]			
Eligibility	x[2]			
Enrollment and allocation of patient number	x[2]			
QoL questionnaires (EQ-5D-5L, KDQOL-SF)	x	x	x	x
Patient survival status	x[3]	x	x	x
Graft survival status	x[3]	x	x	x
Graft rejection episodes[4]	x	x	x	x
Kidney biopsy reports [5]	x	x	x	x
P-creatinine, eGFR calculation (performed by Sponsor)	x	x	x	x
Proteinuria (dipstick)	x	x	x	x
Hematology (Hemoglobin, Diff of leukocytes, Thrombocytes)	x	x	x	x
Total IgG	x	x	x	x
BK test	x	x	x	x
DSA (HLA antibody, Luminex) *central lab*	x	x	x	x
DSA (HLA antibody, Luminex)) *local lab*	x	x	x	x
ADA (Anti-imlifidase IgG) *central lab*	x	x	x	x
Comorbidity[6]	x	x	x	x
Current immunosuppressive medication	x	x	x	x
Treatment of graft rejection episode (PE, IVIg, dialysis, other)	x	x	x	x
Adverse events[7]	x	x	x	x

[1] Some subjects will not perform all 4 visits because the study start will be after the subject`s first visit should have taken place. If applicable, record creatinine and proteinuria results from planned time for 1- and 2 Years visits. End of Study (EOS) will occur 5 years (+/- 6M) after transplantation or earlier in the case of death, withdrawal of consent or lost to follow up.

[2] These activities shall be performed at subject`s first visit that can take place 1, 2, or 3 years post imlifidase dose depending on when the subject was transplanted in the feeder study.

[3] After informed consent is obtained, pre-study visit data such as information on graft survival and patient survival can be collected and entered in the CRF. If applicable, record cause and date of death.

[4] Record biopsy proven graft rejection episodes (classified by the Banff classification) and creatinine and proteinuria results from the episode.

[5] If standard of care kidney biopsies are performed for any reason, at any time-point, e.g. suspected rejections, record information in the CRF.

[6] Record comorbidities that are medically relevant and registered in the subject`s medical record. Medically relevant comorbidity are infections, malignancy, diabetes mellitus and cardiovascular events.

[7] Adverse events caused by a procedure in the protocol (blood sampling) or a clinically significant safety lab value are the only AEs that will be captured and reported. If the lab value is attributable to worsening renal function, graft rejection or natural progression of disease, it will not be reported as AE

6. STUDY ASSESSMENTS

6.1 Assessments related to Primary Endpoint

The time points for all study assessments are shown in the study flow chart (Table 2). Laboratory sampling, shipment, and analysis will be described in detail in the laboratory manual.

6.1.1 Graft Survival

The primary endpoint of this study is to determine overall graft survival, defined as time from transplantation to graft loss. 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.

6.2 Assessments related to Secondary Endpoints

6.2.1 Patient survival

Overall patient survival is defined as time from transplantation to death for any cause. If applicable, information on time and cause of death will be recorded.

6.2.2 Kidney function

Kidney function will be evaluated by P-creatinine and calculation of estimated filtration rate (eGFR) by MDRD/CKD-EPI formula (performed by Sponsor). Proteinuria will be measured by dipstick. The samples will be taken at the time points presented in the study flow chart. Creatinine and proteinuria results from graft rejection episodes will be collected as well as from the time for planned 1- and 2-years visit if study start was after those visits should have taken place.

6.2.3 Kidney biopsy

If standard of care kidney biopsies are performed for any reason, at any time-point, e.g. suspected rejections, information will be collected and recorded in the CRF.

6.2.4 Graft rejection episodes

Information about the occurrence of graft rejection episodes will be collected, following Banff classification.

6.2.5 Treatment of graft rejection episodes

Information about treatments of graft rejection episodes will be recorded (e.g dialysis, plasmapheresis and medications).

6.2.6 Comorbidity

Information about comorbidities that are medically relevant and registered in the subjects' medical record will be collected. Medically relevant comorbidity are e.g. infections, malignancy, diabetes mellitus and cardiovascular events.

6.2.7 Donor Specific Antibodies (DSA)

Samples for determination of DSAs will be analysed in LABScreen single antigen HLA class I and class II assays. The assays allow determination of the mean fluorescence intensity (MFI) of antibodies in patient serum reacting to an array of individual HLA immobilized to beads. Analyses of DSAs will be performed centrally, at Hansa Biopharma , Lund. The date and time of collection of each sample will be recorded on the sample log and in the CRF.

Samples for DSA will also be analysed by the hospital laboratory and the results will be evaluated by the Investigator and recorded in the CRF.

6.2.8 Immunogenicity by Anti-Drug Antibodies (ADA)

Samples for the determination of anti-drug antibody (ADA) levels in serum will be analysed for anti-imlifidase IgG using a customized imlifidase ImmunoCAP test. The analysis will be performed at the central laboratory, Thermofisher Scientific, Immuno Diagnostics, Service Laboratory, Alleröd, Denmark. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report. The ADA samples will be taken at the times presented in the study flow chart. The date and time of collection of each sample will be recorded on the laboratory requisition form and in the CRF.

6.2.9 Health Related Quality of Life Questionnaire (HR-QoL)

At all visits, two patient questionnaires will be used to assess health related quality of life. European Quality of Life-5 levels (EQ-5D-5L) and Kidney Disease Quality of Life Questionnaire-short form (KDQOL-SF). The individual guidelines for the questionnaires will be followed when administering the forms.

6.3 Safety and other Laboratory Samples

The investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are clinically or non-clinically significant. The local hospital laboratory will be used for the analyses and updated laboratory certificate and reference ranges will be collected. The samples will be taken at the times presented in the study flow chart (Table 2). The safety hematology and clinical chemistry tests will be the following:

Table 3. Safety hematology and clinical chemistry laboratory tests

Hematology[1)]
B-Hemoglobin
B-Differential analysis of leucocytes
B-Thrombocytes
Clinical Chemistry
P-IgG

[1)] May be taken as serum samples if that is standard procedure at local lab

Virology test for BK will also be taken at the local hospital laboratory.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Handling, Storage and Destruction of Biological Samples

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.

ADA and DSA samples may be stored for maximum 2 years after completion of the study report according to local regulations.

Analyses cannot be used or re-used for purposes different from the ones stated in the protocol. Analyses not described in this protocol can only be performed after obtaining the required approvals and new written informed consent.

7.2 Chain of Custody of Biological Samples

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

The principal investigator keeps full traceability of collected biological samples from the patients while in storage at the 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.

7.3 Withdrawal of Informed Consent for Donated Biological Samples

If a subject withdraws consent to the use of biological samples donated 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 Medical
- 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 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 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.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 Definitions

8.1.1 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, whether or not considered causally related to the product. Relationship to the study drug will be deemed as not related, unlikely, possible or probable. An undesirable medical condition can be symptoms (e.g., nausea and chest pain), signs (e.g., tachycardia and enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings and electrocardiograms).

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

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

8.1.2 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.

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.

8.2 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 according to the information in section 8.3.

8.2.1 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 Adverse Events grading (CTCAE v.4.03) whether the AE is serious or not, causality rating, action taken, and outcome.

8.2.1.1 Causality assessment

For each reported AE the investigator will assess the relationship of the event to study procedures 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 (e.g. if a lab abnormality is unrelated to the study procedure the investigator would tick the 'unrelated' box, and then specify as to what they consider the lab abnormality was related to).
- **Related:** applicable to AEs where there is a connection with study procedures.

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

8.2.2 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, rales and dyspnea. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom not part of the diagnosis will be recorded separately, for example: congestive heart failure and conjunctivitis.

8.2.3 Adverse Events Based on Examinations and Tests

If safety lab values are judged as clinically significant, they will be captured as AEs and if SAE criteria is 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).

8.2.4 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, stabilizes, or returns to baseline.

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.

8.2.5 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 Adverse Event 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 Regulatory Authorities (RA) in accordance with International Conference on Harmonisation), Good Clinical Practice (GCP)) and local regulations.

As soon as the Investigator is aware of a potential SAE he/she should contact Primevigilance by e-mail 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:	**Primevigilance**
e-mail:	[redacted]

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

8.2.6 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 investigational product caused the adverse event. 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 the 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 Independent Ethics Committee (IEC) and other appropriate institutional regulatory bodies of all SUSARs received involving risk to human subjects as per their applicable requirements

8.3 Adverse Events of Special Interest

Adverse events caused by a procedure in the protocol (such as blood sampling) or a clinically significant safety lab value are the only AEs that will be captured and reported in the study. If the lab value is attributable to worsening renal function, rejection, or natural progression of disease, it will not be reported as AE.

8.4 Pregnancy and Pregnancy Outcome

Pregnancy was an exclusion criterion in the feeder studies and a pregnancy test was performed at the screening visit in each study. No pregnancies were reported during the clinical studies.

If a subject becomes pregnant during the current 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 HansaBiopharma (or designee).

9. STUDY MANAGEMENT

9.1 Pre-study Activities

Before the first subject is entered 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:

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).

9.2 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.

- Perform Source Data Verification (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 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 CRO will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.3 Source data verification

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

9.4 Audit and Inspection

The investigator will make all the study-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 study.

The main purposes of an audit or inspection are to assess compliance with the study 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 Regulatory Authorities 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 number will appear on these copies.

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

9.5 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.

10. DATA MANAGEMENT

10.1 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 study database is declared clean and released to the statistician, a final copy of the database will be stored at HansaBiopharma. 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.

10.2 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.

10.3 Coding

For medical coding, e.g. AEs, medical 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.

10.4 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.

11. STATISTICAL METHODS

All analyses will be detailed in a separate Statistical Analysis Plan (SAP). As this is a long-term non-interventional study, it is anticipated that the first analysis of the data will occur six months after the first patient first visit. Thereafter, yearly summary analysis of the data will be performed. Summary analysis can also be done ad hoc during the study.

11.1.1 Full Analysis Set (FAS)

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

11.2 Descriptive Statistics

The data from the clinical assessments, including demographics and other baseline characteristics, will be summarised by feeder study and 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.

11.3 Subject disposition

The number of subjects in FAS will be summarized by feeder study. Furthermore, the number of subjects who withdraw from the study will be summarised overall, by withdrawal time, by reason for withdrawal and by feeder study.

11.3.1 Demographics and Other Baseline Characteristics

The subject's demographics and other baseline characteristics will be summarised by feeder study.

11.3.2 Concomitant Medication

Current immunosuppressive medication will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name for each feeder study.

11.3.3 Exposure and Compliance

Since this is a non-interventional follow-up study exposure and compliance will not be calculated.

11.4 Statistical analysis of Primary Endpoint

11.5 Primary endpoint – graft survival

The primary endpoint, overall graft survival, is defined as time from transplantation to graft loss evaluated at 1, 2, 3 and 5 years after first dose of imlifidase. 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. The primary

analysis will be based on intervals of 1 year, but the first annual summary analyses may be based on shorter intervals which will be defined in the SAP. The following events will be censored at the time of occurrence: withdrawal from the study without graft loss, death not caused by graft loss, evaluation time point (the yearly evaluations) and end of study without graft loss. The KM analysis is in this study not comparative because of the non-interventional nature of the study. Hence, there will be no formal statistical hypothesis or testing.

The reason for graft loss will be tabulated by time.

Explorative analyses assessing the influence of age and other baseline characteristics may be defined in the SAP.

11.6 Statistical analysis of Secondary Endpoints

11.6.1 Graft loss not censored for death

This endpoint is defined as the primary endpoint except that death for any cause also counts as a graft loss and therefore this event will not be censored. The endpoint will be analysed and presented as the primary endpoint.

11.6.2 Patient survival

Overall patient survival is defined as time from transplantation to death for any cause evaluated at 1, 2, 3 and 5 years. The analysis will be as for the primary endpoint. The following events will be censored: withdrawal from the study, evaluation time point (the yearly evaluations) and end of study.

11.6.3 Kidney function

The kidney function will be evaluated by eGFR, P-creatinine and proteinuria at 1, 2, 3 and 5 years. The calculation of eGFR will be described in the SAP. The three parameters will be summary tabulated.

11.6.4 Kidney biopsy

If standard of care kidney biopsies are performed for any reason, at any time-point, e.g. suspected rejections, information from the kidney biopsy report will be collected. Data will be summary tabulated.

11.6.5 Number of graft rejection episodes

The number of graft rejection episodes will be tabulated at 1, 2, 3 and 5 years following Banff classification.

11.6.6 Treatment of graft rejection episodes

The treatment of graft rejection episodes will be summary tabulated by 1, 2, 3 and 5 years and by treatment type. Examples of treatment types are dialysis episodes, plasmapheresis and medication.

11.6.7 Comorbidity

Medically relevant comorbidities are e.g. infections, malignancy, diabetes mellitus and cardiovascular events. These events will be tabulated at 1, 2, 3 and 5 years by comorbidity type.

11.6.8 DSA levels

DSA levels will be evaluated by SAB-HLA at 1, 2, 3 and 5 years. The DSA levels will be summary tabulated and presented graphically.

11.6.9 BK virus

Presence of BK virus will be tabulated at 1, 2, 3 and 5 years.

11.6.10 ADA

ADA will be evaluated by anti-imlifidase IgG at 1, 2, 3 and 5 years. Data will be summary tabulated.

11.6.11 Health related quality of life

HR-QoL will be evaluated by patient questionnaires EQ-5D-5L and KDQOL at 1, 2, 3 and 5 years. The individual guidelines for the questionnaires will be followed to create the summary tabulations, the details of which will be given in the SAP.

11.7 Safety Endpoints

11.7.1 Analysis of Adverse Events

Only adverse events related to study procedures or a clinically significant safety lab value will be collected. If the lab value is attributable to worsening renal function, rejection, or natural progression of disease, it will not be reported as an AE.

If such events occur, they will be listed.

11.7.2 Analysis of Safety Variables

All clinical safety laboratory tests will be tabulated at 1, 2, 3 and 5 years.

11.8 Determination of Sample Size

As this is a non-interventional follow up study, no power calculations for sample size estimation were performed. All patients enrolled in the selected previous or ongoing imlifidase kidney transplant studies will be considered for inclusion in this study. It is anticipated that

approximately 46 patients could be included, although the exact number will depend on enrolment and patients' discontinuation figures in ongoing and/or selected clinical studies

12. CHANGES IN STUDY CONDUCT OR PLANNED ANALYSES

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

12.1 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 Regulatory Authorities, 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.

12.2 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 trial master file.

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

Planned protocol deviations are not permitted.

12.3 Changes to the Statistical Analysis Plan

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

12.4 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 and provide them with a detailed written explanation of the termination or suspension.

If the RA or IEC terminates or suspends its approval/favorable 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.

13. REPORTING AND PUBLICATION

13.1 Clinical Study Report

The results from this study will be reported in a clinical study report (CSR) within one year after end of study (section 3.4). This will be prepared by Hansa Biopharma and submitted for comments and signature to the signatory investigator(s).

13.2 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.

13.3 Publications

13.4 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.

13.5 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/or EU Clinical Trials Register if the study is conducted in Europe.

14. ETHICAL AND REGULATORY ASPECTS

14.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, Brazil 2013 in compliance with the approved protocol and applicable regulatory requirements.

The responsibilities of Hansa Biopharma, the monitor and the investigator are defined in the ICH-GCP consolidated guideline (E6 R2) and applicable regulatory requirements in the country where the study takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators.

14.2 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.

14.3 Independent Ethics Committee(s) and Institutional Review Boards (IRB)

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 (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 medical will keep an updated list of submission and approval dates of all documents submitted to IEC(s).

14.4 Regulatory Authority(ies)

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

14.5 Subject Information and Informed Consent

Before any Study-related activities and in agreement with applicable regulatory requirements, 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 Regulatory Authorities, if required). The study subjects will be informed about this new information and re-consent will be obtained.

14.6 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and Hansa Biopharmaand 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). The clinical study site will permit access to such records.

15. ARCHIVING

15.1 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 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 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 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.

15.2 Trial Master File

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

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17. APPENDIX 1

Protocol revision history including Summary of Changes

Protocol Version	Date	Including Amendment Type and No.	Overall Rationale for Changes
1.0	03 Apr 2018		N/A Initial approved protocol
2.0	20 Jun 2018	Non-substantial 01	• Assessment of Quality of Life Questionnaires were changed, it was decided to use two instead of three questionnaires. • Kidney biopsy data will be recorded directly in CRF instead of retrieved from the biopsy reports. • Any version of Banff classification can be used for classification of acute rejection episodes. • EudraCT number on first page is removed since the study was not submitted to any European regulatory authority.
3.0	27 Sep 2020	Non - substantial 02	• The method of data collection will be changed from paper CRF to electronic CRF. • A study visit can be performed remotely if a subject is not able to visit the site. • Clarify the wordings “acute rejection episode” and “DSA rebound” by change wordings to “graft rejection episode”. • Clarify that creatinine and proteinuria results from graft rejection episodes will be collected as well as from the time for planned 1- and 2-Years visits if study start was after those visits should have taken place.
4.0	22 NOV 2021	Non-substantial 03	• Updates due to change in CRO responsible for SAE and SUSAR handling.

Protocol AMENDMENT NUMBER 03 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 protocol is amended in response to a change in the CRO responsible for the SAE and SUSAR handling.

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*. The sections refer to the study protocol Final Version 3.0 including Amendment 02, dated 27 SEP 2020.

1 CHANGE OF CRO RESPONSIBLE FOR SAE/SUSAR REPORTING

Rationale

The CRO handling the SAE and SUSAR reporting have been replaced.

1.1 Amended Section

Section 8.2.5, Reporting of Serious Adverse Events

Changed from

An assigned contract research organisation (Drug Safety Navigator, DSN) will be responsible for reporting all SAEs to Regulatory Authorities (RA) in accordance with International Conference on Harmonisation, Good Clinical Practice (GCP) and local regulations.

As soon as the Investigator is aware of a potential SAE he/she should contact DSN by e-mail 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:	**Drug Safety Navigator (DSN)**
e-mail:	[redacted]

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

Changed to

An assigned contract research organisation (~~Drug Safety Navigator, DSN~~ *Primevigilance*) will be responsible for reporting all SAEs to Regulatory Authorities (RA) in accordance with International Conference on Harmonisation, Good Clinical Practice (GCP) and local regulations.

As soon as the Investigator is aware of a potential SAE he/she should contact ~~DSN~~ *Primevigilance* by e-mail 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:	~~**Drug Safety Navigator (DSN)**~~ ***Primevigilance***
e-mail:	[redacted]

For fatal or life-threatening adverse events where important or relevant information is missing, active follow up is undertaken immediately. Investigators or other site personnel inform Hansa Biopharma and monitor of any follow up information on a previously reported SAE immediately but no later than within 24 hours of when he or she becomes aware of it. The monitor or 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 the Hansa Biopharma, and ~~DSN~~ *Primevigilance*.

1.2 Amended Section

Section 8.2.6, Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Changed from

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 the Hansa Biopharma, and Drug Safety Navigator. 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.

Changed to

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 the Hansa Biopharma, and ~~Drug Safety Navigator~~ *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.

1.3 Amended Section

Section 8.4, Pregnancy and Pregnancy Outcome

Changed from

If a subject becomes pregnant during the current 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 Drug Safety Navigator 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. Drug Safety Navigator will follow up on pregnancy outcome 4 weeks after the projected due date.

Changed to

If a subject becomes pregnant during the current 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 ~~Drug Safety Navigator~~ *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. ~~Drug Safety Navigator~~ *Primevigilance* will follow up on pregnancy outcome 4 weeks after the projected due date.
