Clinical Trial Protocol

An open label, phase II study to investigate DSA rebound in patients with a positive crossmatch, made transplantable with imlifidase

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Phase:	2
Proposed indication:	Kidney transplantation in highly sensitized patients
Principal investigator:	Vasishta Tatapudi
EudraCT Number:	N/A
IND Number:	128074
Name and Address of Sponsor:	Hansa Biopharma AB P.O. Box 785 SE-220 07 Lund Sweden

Signature page

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

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Signature

Signatory Principal Investigator

Vasishta Tatapudi, MD

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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

An open label, phase II study to investigate DSA rebound in patients with a positive crossmatch, made transplantable with imlifidase

Co-ordinating Investigator

Principal Investigator: Dr. Vasishta Tatapudi

Trial Site

One site, NYU Langone Health Transplant Institute

Planned trial period	**Clinical Phase**
First subject first visit (FSFV) Q3 2022 Last subject last visit (LSLV) Q3 2024	2

Background and Scientific Justification for Conducting the Trial

Renal transplantation is the preferred treatment for patients with end-stage renal disease since it increases patient survival and quality of life and results in substantial savings in health care costs compared to dialysis. However, sensitization to anti-human leukocyte antigen is a major and often insurmountable barrier to successful kidney transplantation. Approximately one third of patients in the US waiting for kidney transplantation are sensitized to potential donor tissues, i.e. they have antibodies to human leukocyte antigen (HLA) (Iyer et al. 2013). Preformed donor specific antibodies (DSA) typically arise due to immunization- during earlier pregnancies, blood transfusions, previous transplants or infections (Stites et al. 2015; Thomas et al. 2015). A patient with significant HLA antibodies to a potential donor will show a strong positive crossmatch to that donor and that is a contraindication to transplantation since it will cause immediate damage to the graft. As many as 13% of the US patients on the transplantation waitlist are highly sensitized, i.e. have a calculated panel reactive antibody (cPRA) ≥ 80% of which 7% with a cPRA 98-100% (Hart et al. 2019).

For patients with a wide range of HLA antibodies it can be extremely difficult to find a compatible donor even after the implementation of the new kidney allocation system (KAS) in 2014. The modifications to the KAS have helped broaden access to organ transplantation for highly sensitized patients, however, despite the initial significant improvement in access, there remains a pool of highly sensitized patients with low likelihood of ever receiving an organ offer (Stewart et al. 2016; Schinstock et al. 2016; Stegall 2019; Schinstock et al. 2017). Further, an analysis of the United Network for Organ Sharing (UNOS) data 2010-2016, showed that for patients with cPRA ≥99.5%, the transplant rates decrease with increasing levels of sensitization. Recent data showed that patients with cPRA ≥99.9% constitute the

largest group in the 100% cPRA cohort (99.5-100%) and continue to have prolonged waiting time and the lowest rate of deceased donor (DD) transplantation (Jackson et al. 2019; Schinstock et al. 2019). For these highly sensitized candidates with an incompatible living donor, Kidney Paired Donation (KPD) program can improve the prospects of finding a compatible living donor but the probability of finding a match through KPD programs is insignificant.

The general benefit of transplantation even with an incompatible kidney was investigated in a study comparing patients receiving an incompatible living donor kidney with patients staying on the waiting list with or without later transplantation (Orandi et al. 2016). Prior to transplantation the patients received perioperative desensitization therapy according to a protocol of the site's own choice. The results demonstrated that receipt of a kidney transplant from an incompatible live donor was associated with a significant survival benefit as compared with the matched controls staying on the waiting list throughout the studied period, 8 years.

Data demonstrate that successful desensitization followed by transplantation of patients with DSA is clearly associated with short term and long term survival benefits compared to staying on dialysis (Montgomery et al. 2011; Orandi et al. 2014; Orandi et al. 2016; Vo et al. 2013), despite a higher reported incidence of active antibody mediated rejection (AMR) (20% to 61%) compared to non-sensitized patients where AMR is very rare (Lefaucheur et al. 2008; Gloor et al. 2010; Vo, Wechsler, et al. 2008; Haririan et al. 2009; Marfo et al. 2011; Thielke et al. 2009; Riella et al. 2014). In addition, the patient's quality of life is dramatically improved and there is substantial cost effectiveness associated with desensitization and transplantation compared to dialysis (Vo et al. 2013).

There are no approved treatments for desensitization nor is there a standardized protocol for desensitization in the US. However, a few institutional protocols have been developed and tested in clinical settings (Iyer et al. 2013). All these protocols use techniques to block out antibodies through high-dose intravenous immunoglobulin (IVIg) or remove them by plasmapheresis/ immunoadsorption (IA), often combined with low-dose IVIg (Montgomery et al. 2000; Jordan et al. 2004). Some protocols use anti-CD20 antibodies i.e. rituximab to inhibit the synthesis of IgG (Vo, Lukovsky, et al. 2008). There have been no randomized controlled trials of these protocols. In addition, desensitization protocols are usually combined with induction therapy using steroids and antithymocyteglobulin (ATG) and/or anti-IL2R antibody (e.g. basiliximab) to prevent acute cell mediated rejections in high-risk patients.

Imlifidase is an immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* that is highly specific for IgG. The cleavage of IgG generates one F(ab')$_2$- and one homodimeric Fc-fragment and efficiently neutralizes Fc-mediated activities of IgG [redacted] (Vincents et al. 2004; von Pawel-Rammingen et al. 2002; Wenig et al. 2004). Clinical studies with imlifidase have demonstrated that the treatment enables transplantation in patients otherwise highly unlikely to be transplanted, by converting a positive crossmatch to a negative (Jordan et al. 2017; Lorant et al. 2018; Jordan et al. 2020; Lonze 2021; Schinstock 2020). The treatment is highly efficacious as demonstrated by 100% crossmatch conversion

in patients treated. Imlifidase-mediated IgG degradation constitutes a novel therapeutic principle for the treatment of IgG-driven human diseases. A treatment regimen allowing transplantation of highly sensitized patients with deceased or living donor organs, while keeping the occurrence of AMR at a low level, would provide an important improvement in the treatment of these patients.

Preclinical studies in non-human primate models of transplantation in highly sensitized recipients suggest that combining co-stimulation blockade by belatacept with plasma-cell depleting therapy by bortezomib may durably suppress DSA and decrease the risk of AMR (Burghuber et al. 2019). In this trial, treatment with drugs that prevent or suppress DSA rebound by targeting antibody-producing plasma-cells and their B-cell precursors is suggested. Bortezomib is a proteasome inhibitor which has activity against mature plasma cells, the source of DSA. Belatacept is a fusion protein composed of the Fc-fragment of a human IgG_1 linked to the extracellular domain of CTLA-4, which is a molecule crucial in blocking T-cell co-stimulation, and was shown to be effective in reducing *de novo* DSA generation in humans (Sethi et al. 2017; Vincenti et al. 2016). Rituximab, an anti-CD20 monoclonal antibody that targets B-cells and immunomodulatory agent IVIg are commonly used in desensitization regimens and for the treatment of AMR (Montgomery et al. 2011; Orandi et al. 2014; Orandi et al. 2016; Vo et al. 2013).

The trial will investigate whether the suggested treatment regimen can suppress DSA recurrence and the occurrence of AMR in highly sensitized patients with a positive crossmatch towards their living donor. These patients have a high unmet medical need in transplantation today.

Objectives

Primary objective

- To evaluate DSA rebound during the first 3 months after transplantation

Secondary objectives

- To evaluate AMR frequency up to 6 months after transplantation
- To evaluate DSA rebound up to 6 months after transplantation
- To evaluate crossmatch conversion within 24 hours after imlifidase treatment
- To evaluate DSA and complement binding (C1q) DSA MFI levels
- To evaluate graft and patient survival
- To evaluate safety parameters
- To evaluate kidney function
- To evaluate pharmacokinetic (PK) profile of imlifidase
- To evaluate pharmacodynamic (PD) profile of imlifidase

- To evaluate immunogenicity profile of imlifidase (ADA)
- To evaluate health related quality of life (HRQoL) specifically patients' life participation

Exploratory Objective

[redacted]

Endpoints

Primary endpoint

- Proportion of patients with DSA rebound during the first 3 months after transplantation.

Secondary endpoints

- Proportion of patients with kidney biopsy proven AMR (according to Banff 2019) up to 6 months after transplantation (based on for cause biopsies and protocol biopsies)
- Proportion of patient with DSA rebound up to 6 months after transplantation
- Proportion of patients with negative flow crossmatch test within 24 hours after imlifidase treatment
- Levels of DSA and complement binding(C1q) DSA MFI before imlifidase treatment and up to 6 months after transplantation
- Graft survival at 6 months after transplantation
- Patient survival at 6 months after transplantation
- Safety parameters (AEs, clinical laboratory tests, vital signs and ECG) up to 6 months after transplantation
- Kidney function assessed by creatinine, estimated glomerular filtration rate (eGFR), and protein/creatinine ratio in urine up to 6 months after transplantation
- Imlifidase pharmacokinetics up to 14 days after imlifidase
- Imlifidase pharmacodynamics up to 10 days after imlifidase

- Anti-drug antibodies (ADA) levels up to 6 months after imlifidase
- Change in patient-reported life participation, as measured by the PROMIS Social Health domain "Ability to participate in social roles & activities, PROMIS-SF-8a", from baseline to 6 months after transplantation

Exploratory endpoints

[redacted]

Methodology

This is a phase 2, single center, open label, single arm, exploratory trial. The trial will investigate the frequency of DSA rebound and AMR in highly sensitized kidney patients made transplantable with imlifidase. The primary objective is to investigate DSA rebound during the first 3 months after transplantation.

The definition of rebound is the following:

1. When the positive FCXM at screening is due to low titer, non-complement binding DSAs, rebound is measured as:
    a. Immuno-dominant DSA: a post-transplant MFI value that is ≥50% the pre-imlifidase value

    OR

    b. Total DSAs: a post-transplant serum where ≥50% of the DSA prior to imlifidase treatment have an MFI value that is ≥50% of the pre-transplant MFI value AND the sum MFI must be ≥50% of the pre-transplant value

2. When the positive FCXM at screening is due to high titer, complement binding DSAs, rebound is measured as:

    a. Immuno-dominant DSA: a post-transplant MFI value at 1:16 dilution that is ≥8000 MFI

    OR

    b. Total DSAs: a post-transplant 1:16 diluted serum where ≥50% of the DSA prior to imlifidase treatment have an MFI value that is ≥50% of the pre-transplant MFI value AND the sum MFI must be ≥8000

An HLA antibody is considered a DSA when the MFI value is at least 3000 in the serum analyzed prior to imlifidase treatment. Either a or b must be fulfilled for the increase in DSA to be defined as rebound.

12 patients with a living donor will be included in the trial. All patients will receive high-dose methylprednisolone as induction therapy starting on the day of transplantation and continued for 3 days. It will then be tapered over several days and, when applicable, converted to oral prednisone. Induction therapy with rATG will start [redacted] and be given on at least 3 days. Treatments to prevent rejection will be rituximab administered [redacted] and high dose IVIg administered [redacted] The treatments with belatacept and bortezomib will start about 3 weeks prior to transplantation. Three doses of belatacept will be administered at days -21, -16 and -7 and for bortezomib 4 doses (1 cycle) will be administered. Belatacept administration is continued after transplantation with 6 additional doses starting on day 6 and ending at week 13. Bortezomib administration is continued with 2 more cycles, starting the second cycle on day 2 and the third 3 weeks later. An ECG and echocardiogram will be performed after each bortezomib cycle. Maintenance immunosuppression therapy will be tacrolimus, mycophenolate mofetil (MMF) and prednisone. Tacrolimus and MMF therapies will start once the first dose of bortezomib is administered.

Imlifidase is administered within the 24-hour period prior to transplantation. Prior to imlifidase infusion the patients will be premedicated with methylprednisolone (250 mg IV) and loratadine (10 mg PO) to prevent infusion reactions. The patients will be monitored for 6 months after transplantation. The patients will be hospitalized the first 14 days (may vary between patients) and thereafter return for 9 planned scheduled visits (visits 13-21).

Trial Procedures/Assessments

At screening the following will be collected/assessed/measured; signed informed consent, inclusion/exclusion criteria, demography, medical and surgical history, HLA-typing, height and weight, vital signs (pulse, blood pressure, body temperature), concomitant medication, virology (hepatitis B and C, HIV, CMV, EBV and SARS-CoV-2), chemistry panel (including p-creatinine and eGFR), CBC with differential, coagulation, urine protein/creatinine ratio, crossmatch tests, and DSA. A physical examination, ECG and echocardiogram measurements, peripheral neuropathy assessment, a pregnancy test (women

of childbearing potential) and a HRQoL assessment will be done at screening and at the last trial visit.

Inclusion/exclusion criteria, medical and surgical history and concomitant medication will be checked prior to infusion with imlifidase. Data on donor demographics, kidney condition and HLA-typing will be collected. A pregnancy test will be performed unless the patient has been hospitalized since the screening visit. The following will be assessed/measured; vital signs, weight, chemistry panel (including p-creatinine/eGFR), CBC with differential, coagulation, urine protein/creatinine ratio, DSA, flow crossmatch tests (FCXM and if possible, CDCXM) and anti-imlifidase IgG antibodies. Measurements for imlifidase pharmacokinetic and pharmacodynamic profiles will start.

Imlifidase will be infused IV over 15 minutes. A flow crossmatch test will be performed 1, 2, 4 and 24 hours after the end of the infusion to confirm the conversion from a positive to a negative test. A second dose may be given if the crossmatch test at 4 hours after the initial dose remains positive. In case of a second dose additional crossmatch tests will be performed pre-dose and at 2 hours post dose in addition to remaining tests from the first dose.

After imlifidase infusion the following will be assessed on repeated occasions; pulse and blood pressure, body temperature, chemistry panel (including p-creatinine and eGFR), CBC with differential, coagulation, urine protein/creatinine ration, anti-imlifidase IgG antibodies, DSA and complement binding (C1q) DSA[redacted]. A full pharmacokinetic and pharmacodynamic profile will be calculated. [redacted] ytomegalovirus, Epstein Barr and BK viruses will be monitored throughout the trial period. Adverse events and concomitant medications will be registered throughout the trial.

Number of subjects

12 patients with a living donor will be enrolled in the study.

Diagnosis and main criteria for inclusion/exclusion

Patients with chronic kidney disease who are eligible for transplantation.

Inclusion criteria

1. Signed Informed Consent obtained before any trial-related procedures
2. Male or female age 18 to 70 years at the time of screening
3. Highly sensitized patients registered on the UNOS waiting list for kidney transplantation, with either of the following:
   - cPRA ≥ 99.9%

- cPRA ≥ 98% and have been in kidney paired donation or kidney paired exchange programs for at least 1 year

4. A positive crossmatch towards a living donor
5. Willingness and ability to comply with the protocol

Exclusion criteria

1. Previous treatment with imlifidase
2. Previous high dose IVIg treatment (2 g/kg) within 28 days prior to imlifidase treatment
3. Breast-feeding or pregnancy
4. Women of child-bearing potential not willing or able to practice FDA-approved forms of contraception. Two medically acceptable methods of highly effective contraception must be used for the duration of the study (e.g. oral, transdermal, intravaginal, injectable or implantable contraceptive; intrauterine device; intrauterine hormone-releasing system; vasectomized partner; bilateral tubal occlusion; or double-barrier method). For a woman to be considered postmenopausal this ascertainment must be made according to medical records and clinical history and may be aided by measurement of elevated postmenopausal serum gonadotropin levels (FSH).
5. ABO blood group incompatible transplantations (A2 and A2B kidneys will not be accepted for B recipients)
6. Positive serology for HIV
7. Clinical signs of HBV, HCV, CMV, or EBV infection
8. EBV seronegative or with unknown EBV serostatus
9. Positive SARS-CoV-2 test at any time point from screening to transplantation
10. Active tuberculosis
11. Ongoing serious infections as judged by the investigator
12. Severe other conditions requiring treatment and close monitoring e.g. cardiac failure ≥ grade 4 (New York Heart Association), unstable coronary disease or oxygen dependent respiratory disease
13. A history of proven hypercoagulable condition
14. Current peripheral neuropathy of Grade 2 with pain, or Grade 3 (severe symptoms; limiting self-care activities of daily living) based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0
15. Present, or history of, thrombotic thrombocytopenic purpura (TTP) or known familial history of TTP
16. Intake of investigational drugs (other than imlifidase) within 5 half-lives
17. Contemporaneous participation in a medical device study
18. Known allergy/sensitivity (except local reactions) to imlifidase or to any drug (or the excipients) specified in the protocol

19. Known mental incapacity or language barriers precluding adequate understanding of the Informed Consent information and the trial activities
20. Inability by the judgement of the investigator to participate in the trial for any other reason

Investigational Medicinal Product

Imlifidase, is provided as a freeze-dried powder for concentrate for solution for infusion, 11 mg/vial. After reconstitution with sterile water for injection, the concentrate contains 10 mg/mL imlifidase. The concentrate will be added to 50 mL sodium chloride 9 mg/mL (0.9%) solution for infusion and administered as an infusion. Imlifidase 0.25 mg/kg will be infused intravenously over 15 minutes.

Duration of treatment

Imlifidase will be administered as a single IV infusion over 15 minutes. If the first dose does not have sufficient effect the administration is repeated.

Statistical methods

This is an open-label trial, and the statistical evaluation and presentation of data will be descriptive by nature. Continuous variables will be summarized by number of observations (n), mean, median, standard deviation, minimum and maximum. Categorical variables will be presented by counts and percentages. In addition, the data will be presented graphically when relevant.

No formal sample size calculations have been performed for this exploratory trial. The number of subjects enrolled is considered sufficient to provide adequate information about the general safety and efficacy at this stage of development.

Protocol Revision History including Summary of Changes

Version	Date	Reason for Change	Summary of Major Changes
V. 1.0	4 Feb 2020	Original protocol	NA
V. 2.0	31 Mar 2021	Version 1 of the Clinical Trial Protocol was finalized but never implemented. Version 2 is the first version submitted to the FDA.	NA
V. 3.0	14 Jul 2021	Version 3 is updated after feedback from the FDA.	- Route of administration of bortezomib changed from IV to SQ. - ECG and echocardiogram at screening, after each bortezomib cycle and end of trial added. - Exclusion criteria regarding peripheral neuropathy added. - Peripheral neuropathy assessment added. - Bortezomib treatment specific discontinuation criteria added. - Study level stopping criteria further clarified. - Minor typos corrected, clarifications added and trial timelines updated.
V. 4.0	23 Jun 2022	Version 4 is updated before trial initiation	- Change of Sponsor's Medical Expert - Change of CRO responsible for SAE/SUSAR reporting and clarification of responsibilities in SUSAR reporting - Section on adverse events of special interest (AESI) added - Change of guidance on donor SARS-CoV2 testing - Clarification of biological sampling procedures (handling, storage, and destruction)

			- Additional timepoints for ADA sampling added - Minor typos corrected, clarifications added, and trial timelines updated.

Table of Content

[redacted]

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List of Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ADR	Adverse Drug Reaction
AMR	Antibody Mediated Rejection
ATG	Anti-Thymocyte globulin derived from rabbit
AUC	Area Under the Curve
CD52	Cluster of differentiation 52, or CAMPATH-1antigen
CL	Clearance of drug from plasma/serum
C_{max}	Maximum Concentration
CMR	Cell mediated rejection
CDC	Complement Dependent Cytotoxicity
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
%CV	Percentage Coefficient of Variation
CMV	Cytomegalovirus
cPRA	Calculated PRA
XM	Crossmatch
[redacted]	[redacted]
DSA	Donor Specific Antibodies
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	European Quality of Life -5 Levels
FCXM	Flow Cytometry Crossmatch Test
GCP	Good Clinical Practice
HAR	Hyperacute rejection
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRQoL	Health Related Quality of Life
IA	Immunoadsorption
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL2R	Interleukin-2 receptor

IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous(ly)
IVIg	Intravenous Immunoglobulin
LLQ	Lower Level of Quantification
MedDRA	The Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity
MMDx	Moculecular Microscope® Diagnostic System
MMF	Mycophenolate mofetil
N/A	Not Applicable
NIMP	Non-Investigational Medicinal Product
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PLEX	Plasma Exchange
POD	Post Operative Day
PP	Per Protocol
PQC	Product Quality Complaint
PRA	Panel Reactive Antibody
PROMIS	Patient-Reported Outcomes Measurement Information System
QA	Quality Assurance
RA	Regulatory Authority
SAB	Single Antigen Bead
SAB-C1q	Anti-HLA antibodies with complement binding capacity measured with the SAB assay
SAB-HLA	Anti-HLA antibodies measured with the SAB assay
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ScIgG	Single-cleaved IgG
SDS-PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
SDV	Source Document Verification
SOC	System Organ Class
SQ	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
$T_{1/2}$	Terminal half-life
T_{max}	Time to Maximum concentration
UNOS	United Network for Organ Sharing
V_z	Apparent Volume of distribution
WBC	White Blood Corpuscles

Definition of Terms

Enrolled	When the subjects, or his/her representative, and the investigator have signed the informed consent form

1. INTRODUCTION

1.1 Background

Approximately one third of patients in the US waiting for kidney transplantation are sensitized to potential donor tissues, i.e. they have antibodies to human leukocyte antigen (HLA) (Iyer et al. 2013). Preformed donor specific antibodies (DSA) typically arise due to immunization- during earlier pregnancies, blood transfusions, previous transplants or infections (Stites et al. 2015; Thomas et al. 2015). A patient with significant HLA antibodies to a potential donor will show a strong positive crossmatch to that donor and that is a contraindication to transplantation since it will cause immediate damage to the graft. At worst, DSA can result in hyperacute rejection (HAR) beginning immediately after perfusion, inevitably resulting in graft loss (Kissmeyer-Nielsen et al. 1966; Patel et al. 1969). As many as 13% of the US patients on the transplantation waitlist are highly sensitized, i.e. a calculated panel reactive assay (cPRA) ≥ 80% of which 7% with a cPRA 98-100% (Hart et al. 2019).

For patients with a wide range of HLA antibodies it can be extremely difficult to find a compatible donor even after implementation of the new kidney allocation system (KAS) in 2014. The modifications to the KAS have helped broaden organ access to transplantation for highly sensitized patients. However, despite the initial significant improvement in access, there remains a pool of highly sensitized patients with low likelihood of ever receiving an organ offer (Stewart et al. 2016; Schinstock et al. 2016; Stegall 2019; Schinstock et al. 2017). Further, an analysis of the United Network for Organ Sharing (UNOS) data 2010-2016, showed that for patients with cPRA of ≥99.5%, the transplant rates decrease with increasing levels of sensitization. Recent data showed that patients with cPRA ≥99.9% constitute the largest group in the 100% cPRA cohort (99.5-100%) and continue to have prolonged waiting time and the lowest rate of deceased donor (DD) transplantation (Jackson et al. 2019; Schinstock et al. 2019). For these highly sensitized candidates with an incompatible living donor, Kidney Paired Donation (KPD) program can improve the prospects of finding a compatible living donor but the probability of finding a match through KPD programs is insignificant.

The general benefit of transplantation even with an incompatible kidney was investigated in a study comparing patients receiving an incompatible living donor kidney with patients staying on the waiting list with or without later transplantation (Orandi et al. 2016). Prior to transplantation the patients received perioperative desensitization therapy according to a protocol of the site's own choice. The results demonstrated that receipt of a kidney transplant from an incompatible live donor was associated with a significant survival benefit as compared with the matched controls staying on the waiting list throughout the studied period, 8 years.

Data demonstrate that successful desensitization followed by transplantation of patients with DSA is clearly associated with short term and long term survival benefits compared to staying on dialysis (Montgomery et al. 2011; Orandi et al. 2014; Orandi et al. 2016; Vo et al. 2013), despite a higher reported incidence of active antibody mediated rejection (AMR)

(20% to 61%) compared to non-sensitized patients where AMR is very rare (Lefaucheur et al. 2008; Gloor et al. 2010; Vo, Wechsler, et al. 2008; Haririan et al. 2009; Marfo et al. 2011; Thielke et al. 2009; Riella et al. 2014). In addition, the patient's quality of life is dramatically improved and there is substantial cost effectiveness associated with desensitization and transplantation compared to dialysis (Vo et al. 2013).

There are no approved treatments for desensitization nor is there a standardized protocol for desensitization in the US. However, a few institutional protocols have been developed and tested in clinical settings (Iyer et al. 2013). All of these protocols use techniques to block out antibodies through high-dose intravenous immunoglobulin (IVIg) or remove them by plasmapheresis/ immunoadsorption (IA), often combined with low-dose IVIg (Montgomery et al. 2000; Jordan et al. 2004). Some protocols use anti-CD20 antibodies i.e. rituximab to inhibit the synthesis of IgG (Vo, Lukovsky, et al. 2008). There have been no randomized controlled trials of these protocols. In addition, desensitization protocols are usually combined with induction therapy using steroids and antithymocyteglobulin (ATG) and/or anti-IL2R antibody (e.g. basiliximab) to prevent acute cell mediated rejections in high-risk patients.

Imlifidase is an immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* that is highly specific for IgG. The cleavage of IgG generates one F(ab')$_2$- and one homodimeric Fc-fragment and efficiently neutralizes Fc-mediated activities of IgG [redacted] (Vincents et al. 2004; von Pawel-Rammingen et al. 2002; Wenig et al. 2004). Clinical studies with imlifidase have demonstrated that the treatment enables transplantation in patients otherwise highly unlikely to be transplanted, by converting a positive crossmatch to a negative (Jordan et al. 2017; Lorant et al. 2018; Jordan et al. 2020; Lonze 2021; Schinstock 2020). The treatment is highly efficacious as demonstrated by 100% crossmatch conversion in patients treated. Imlifidase (Idefirix®) has a conditional approval in Europe for desensitization of highly sensitized patients prior to transplantation against a positive XM with a deceased donor kidney.

However, as with other desensitization methods, DSA tend to reappear within weeks of imlifidase treatment and transplantation, which may cause AMR and increased risk of graft loss. The incidence of AMR in highly sensitized patients is 20-61%, compared with approximately 5% in non-sensitized patients. Imlifidase-mediated IgG degradation constitutes a novel therapeutic principle for the treatment of IgG-driven human diseases. A treatment regimen allowing transplantation of highly sensitized patients with deceased or living donor organs, while keeping the occurrence of AMR at a low level, would provide an important improvement in the treatment of these patients.

Clinical studies

Patients in transplantation studies were treated with imlifidase and all patients who received a clinically relevant dose were transplanted. In studies including immunologically difficult patients (cPRA >95%), it was shown that treatment with 1 or 2 doses of 0.25 mg/kg imlifidase before transplantation converted positive crossmatches into negative and was effective in reducing or eliminating DSAs, allowing transplantation of all treated patients. However, DSA rebound started after about one week in most patients leading to AMR episodes at an

incidence of 31%, similar to what has been reported previously with desensitized patients (Jordan et al. 2017; Lorant et al. 2018; Jordan et al. 2020). A treatment regimen which prevents or suppresses DSA rebound is likely to decrease the AMR frequency in highly sensitized patients with HLA antibodies.

1.2 Scientific Rationale

This is a phase 2, single center, open label, single arm, exploratory trial. The trial will investigate the DSA rebound and frequency of AMR in highly sensitized patients made transplantable with imlifidase. The primary objective is to investigate the DSA rebound during a period of 3 months from transplantation. The trial will include 12 highly sensitized patients on the kidney transplant list who have a positive crossmatch test towards a living donor and either a cPRA≥ 99.9% or have been in kidney paired donation or kidney paired exchange programs for at least 1 year with a cPRA ≥ 98%. These patients have a high unmet medical need in transplantation today and current data show that imlifidase has the potential to inactivate DSAs and thereby convert a positive crossmatch test into negative, allowing these highly sensitized patients to be transplanted.

Preclinical studies in non-human primate models of transplantation in highly sensitized recipients suggest that combining co-stimulation blockade by belatacept with plasma-cell depleting therapy by bortezomib may durably suppress DSA and decrease the risk of AMR (Burghuber et al. 2019). In this trial treatment with drugs that prevent or suppress DSA rebound by targeting antibody-producing plasma-cells and their B-cell precursors is suggested. Bortezomib is a proteasome inhibitor which has activity against mature plasma cells, the source of DSA. Belatacept is a fusion protein composed of the Fc-fragment of a human IgG_1 linked to the extracellular domain of CTLA-4, which is a molecule crucial in blocking T-cell co-stimulation, and was shown to be effective in reducing *de novo* DSA generation in humans (Sethi et al. 2017; Vincenti et al. 2016). Rituximab, an anti-CD20 monoclonal antibody that targets B-cells and immunomodulatory agent IVIg are commonly used in desensitization regimens and for the treatment of AMR (Montgomery et al. 2011; Orandi et al. 2014; Orandi et al. 2016; Vo et al. 2013).

This trial will investigate whether the suggested treatment regimen can suppress DSA recurrence and the occurrence of AMR in highly sensitized patients.

To assess response to bortezomib and belatacept therapies, the immunological status of the transplant recipients will be evaluated both quantitatively and qualitatively in bone marrow and lymph nodes.

1.3 Benefit/Risk Aspects

Patients in this trial are highly sensitized and may benefit from being treated with imlifidase to enable kidney transplantation. The potential benefit of imlifidase over currently used methods for antibody removal include the extremely efficient inactivation of DSAs which enable desensitization even for patients that are very highly sensitized and with high antibody titers. The administration of the proteasome inhibitor, bortezomib, and the T-cell blocking monoclonal antibody, belatacept, along with the anti-CD20 monoclonal antibody rituximab,

and IVIg will potentially suppress DSA rebound and decrease the number of AMR episodes in the highly sensitized transplanted patients participating in the study.

Since imlifidase effectively removes the IgG pool, there may be an increased risk of infection. Patients in this trial will receive antibiotics in connection with imlifidase treatment and transplantation and high dose IVIg [redacted] which will minimize the risk for bacterial infections. In addition, patients will be closely monitored for infections and instructed to contact the principal investigator immediately if they have any sign of infection. There will be a physician specialized in infectious diseases available for medical advice if a patient shows signs of infection. In case of infection in a patient with low IgG plasma levels, intravenous immunoglobulin may be indicated.

As for all biologics, there is a risk of infusion reactions associated with imlifidase treatment. Three non-serious and one serious infusion related reactions regarded as related to treatment have occurred in 83 subjects receiving imlifidase and 1 non-serious infusion reaction in a subject receiving placebo. To mitigate the risk of infusion related reactions, all subjects receive glucocorticoid and antihistamine treatment prior to dosing and are closely monitored during the infusions.

To date, a total of 46 patients in clinical studies have been transplanted after treatment with imlifidase. Imlifidase was well-tolerated, with only few related adverse events (AEs) reported and no clinically relevant safety findings.

In vitro studies have revealed that imlifidase cleaves biologics originating from rabbit and human IgG, including: thymoglobulin, IVIg, basiliximab, alemtuzumab, rituximab, adalimumab, denosumab, belatacept and etanercept. The suggested intervals between imlifidase administration and these biologics are presented in the Investigator's Brochure (IB) for imlifidase. [redacted]

Both IVIg and rituximab are commercially available agents that have been well studied for use in transplantation for treatment of AMR (Sethi et al. 2017). These agents are typically well tolerated but may potentially cause infusion reactions necessitating pre-medications prior to infusion (Vo, Lukovsky, et al. 2008).

Belatacept is approved for prevention of rejection in renal transplant patients (Sethi et al. 2017). A trial with 666 renal transplant patients published 2016 reveals that serious infections were the most common side effect in kidney transplant patients with urinary tract infections (UTI) dominating (Vincenti et al. 2016). Measures will be in place for early detection and management of UTI in trial patients.

Bortezomib is approved for treatment of multiple myeloma and mantle cell lymphoma and have been studied in renal transplant patients both as a desensitization agent and for treatment of AMR. Recent clinical studies have suggested that bortezomib has the capability to downregulate circulating antibodies and treat AMR episodes (Requiao-Moura et al. 2017).

Most commonly reported AEs include diarrhea, thrombocytopenia and peripheral neuropathy. It should be noted that diarrhea is a commonly observed side effect of immunosuppressive drugs and that the events of thrombocytopenia and peripheral neuropathy were both responsive to treatment (Requiao-Moura et al. 2017).

The effect of bortezomib and belatacept on a cellular level will be investigated through tissue sampling from the bone marrow and iliac lymph nodes. The biopsies, including kidney biopsies, are generally safe procedures and complications are rare but may include bleedings, infections and discomfort from the biopsy site.

The principal investigator will ensure that sufficient facilities and procedures are available to handle emergency situations during the trial. The trial site has extensive experience in phase I/II studies within transplantation and graft rejection treatment as well as handling biological drugs. The site has adequate procedures in place to handle unexpected adverse reactions.

A guidance for the investigator and Reference Safety Information can be found in the current version of the Investigator's Brochure for imlifidase and in the United States Prescribing Information for belatacept, bortezomib, thymoglobulin, rituximab, and IVIg. The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To evaluate DSA rebound during the first 3 months after transplantation

2.1.2 Secondary Objectives

- To evaluate AMR frequency up to 6 months after transplantation
- To evaluate DSA rebound up to 6 months after transplantation
- To evaluate crossmatch conversion within 24 hours after imlifidase treatment
- To evaluate DSA and complement binding (C1q) DSA MFI levels
- To evaluate graft and patient survival
- To evaluate safety parameters
- To evaluate kidney function
- To evaluate pharmacokinetic (PK) profile of imlifidase
- To evaluate pharmacodynamic (PD) profile of imlifidase
- To evaluate immunogenicity profile of imlifidase (ADA)
- To evaluate health related quality of life (HRQoL) specifically patients' life participation

2.1.3 Exploratory Objectives

[redacted]

2.2 Endpoints

2.2.1 Primary endpoint

- Proportion of patients with DSA rebound during the first 3 months after transplantation

2.2.2 Secondary endpoints

- Proportion of patients with kidney biopsy proven AMR (according to Banff 2019) up to 6 months after transplantation (based on for cause biopsies and protocol biopsies)
- Proportion of patient with DSA rebound up to 6 months after transplantation
- Proportion of patients with negative flow crossmatch test within 24 hours after imlifidase treatment
- Levels of DSA and complement binding (C1q) DSA MFI levels before imlifidase treatment and up to 6 months after transplantation
- Graft survival at 6 months after transplantation
- Patient survival at 6 months after transplantation
- Safety parameters (AEs, clinical laboratory tests, vital signs and ECG) up to 6 months after transplantation
- Kidney function assessed by creatinine, estimated glomerular filtration rate (eGFR), and protein/creatinine ratio in urine up to 6 months after transplantation
- Imlifidase pharmacokinetics up to 14 days after imlifidase
- Imlifidase pharmacodynamics up to 10 days after imlifidase
- Anti-drug antibodies (ADA) levels up to 6 months after imlifidase
- Change in patient-reported life participation, as measured by the PROMIS Social Health domain “Ability to participate in social roles & activities, PROMIS-SF-8a”, from baseline to 6 months after transplantation

2.2.3 Exploratory endpoints

3. INVESTIGATIONAL PLAN

3.1 Overall Trial Design

This is a phase 2, single center, open label, single arm, exploratory trial. The trial will investigate the frequency of DSA rebound and AMR in highly sensitized kidney patients made transplantable with imlifidase. The primary objective is to investigate DSA rebound during a period of 3 months from transplantation.

12 patients with a living donor will be included in the trial. Imlifidase is administered preferably within the 24-hour period prior to transplantation. Prior to imlifidase infusion the patients will be premedicated with methylprednisolone (250 mg IV) and loratadine (10 mg PO) or an equipotent antihistamine. Should a second dose of imlifidase be necessary, premedication will be repeated. The administration of imlifidase is identified as [redacted].

There will be [redacted] scheduled visits prior to imlifidase infusion and transplantation, including the screening visit that will take place during the interval day [redacted]. The patients will be hospitalized for the first 14 days after imlifidase treatment and transplantation (may vary between patients) and after that, a further [redacted] planned clinic visits are planned [redacted]. The follow-up after transplantation will be 6 months for all patients.

The treatments with belatacept and bortezomib will start about 3 weeks prior to imlifidase infusion and transplantation. Three doses of belatacept will be administered with about 5 and 9 days between the doses, and for bortezomib 4 doses (1 cycle) will be administered. Belatacept administration is continued post-transplantation with 6 additional doses starting on day 6 and ending at week 13. Bortezomib administration is continued with 2 more cycles, starting the second cycle on day 3 and the third 3 weeks later. ECG and echocardiogram will be performed after each bortezomib cycle.

All patients will receive high-dose methylprednisolone starting on the day of transplantation, in the operating room, and continued for 3 days. It will then be tapered over several days and, when applicable, converted to oral prednisone. rATG treatment will start [redacted] and be given on at least 3 days, rituximab will be administered [redacted] and intravenous immunoglobulin [redacted]. Maintenance immunosuppression therapy will be tacrolimus, mycophenolate mofetil (MMF) and prednisone. Tacrolimus and MMF therapies will start once the first dose of bortezomib is administered. All therapies are presented in Section 5.

3.1.1 Follow-up Procedures

Following trial termination approximately 6 months post-transplant, all trial patients will be followed up regularly and interdisciplinary by nephrologists and transplant surgeons according to the center's follow-up routines for transplanted patients.

3.1.2 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will monitor participant safety data and evaluate the progress of the trial. The constitution, activities and reports of the DSMB shall be governed by the FDA's "Guidance for Clinical Study Sponsors; Establishment and Operation of Clinical Study Data Monitoring Committees". A trial specific DSMB charter will be available detailing the purpose of the DSMB, scope, timing of meetings, the composition,

roles, responsibilities, procedures and deliverables. The DSMB will be an external group of experts, independent of the sponsor and consist of at least three physicians of which one will be the DSMB chairman. This committee will convene after the first two transplants, then quarterly for the remainder of the trial.

3.1.3 Trial Stopping Criteria

The trial may be stopped prematurely if:

1. DSMB assessments of safety findings, such as death related to treatment, graft loss, or any other safety concerns, justifying termination of the trial.
2. Findings that, at the discretion of Principal Investigator and/or sponsor, indicate that further dosing should be stopped.

3.1.4 Bortezomib-Associated Discontinuation Criteria

A subject must be discontinued immediately from bortezomib treatment if she/he experiences any of the following:

1. Bortezomib-associated peripheral neuropathy of Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care activities of daily living) based on CTCAE v5.0, that by the Investigator's clinical judgement prevent further treatment.
2. Bortezomib-associated peripheral neuropathy of Grade 4 (life-threatening consequences; urgent intervention indicated) based on CTCAE v5.0.
3. Acute development or exacerbation of congestive heart failure and new onset of significantly decreased left ventricular ejection fraction (>15%) after bortezomib administration.
4. Hematological toxicities consisting of platelet count $<30\times10^9$/L or ANC $<0.75\times10^9$/L, which does not resolve to Grade 1 or baseline after withholding bortezomib.

If the patient experiences any of the above bortezomib associated discontinuation criteria prior to imlifidase treatment and transplantation, she/he will be withdrawn from the trial.

3.1.5 Interim Analysis

Not applicable.

3.2 Trial Schedule

The first patient first visit (FPFV) is planned to Q3 2022 and the trial will run for about 2 years with a clinical report available about 1 year later.

3.3 Planned number of trial sites and patients

This is a single center trial performed at NYU Langone Health Transplant Institute. It is estimated that about 17 patients need to be screened to enroll 12 patients.

3.4 End-of-Trial

The planned End-of-Trial is defined as the last patient last visit. Hansa Biopharma will submit to 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 Selection Criteria

If a patient has been screened and meets all inclusion criteria and no exclusion criteria but does not start treatments with belatacept and bortezomib according to trial schedule the patient may be re-screened. Patients are not allowed to be re-screened if they have received imlifidase, but transplantation has not been performed or if they have been discontinued/withdrawn due to AE(s). The re-screening procedure will be the same as the previous screening visit with the exception for the virology tests which do not have to be repeated if not more than 6 months old. Medical and surgical history and concomitant medication will be updated if applicable. If a patient is re-screened a new screening number will be issued.

To be eligible for the trial, patients must meet all inclusion criteria and no exclusion criteria.

4.2 Inclusion Criteria

1. Signed Informed Consent obtained before any trial-related procedures
2. Male or female age 18 to 70 years at the time of screening
3. Highly sensitized patients registered on the UNOS waiting list for kidney transplantation, with either of the following:
   - cPRA ≥ 99.9%
   - cPRA ≥ 98% and have been in kidney paired donation or kidney paired exchange programs for at least 1 year
4. A positive crossmatch towards a living donor
5. Willingness and ability to comply with the protocol

4.3 Exclusion Criteria

1. Previous treatment with imlifidase
2. Previous high dose IVIg treatment (2 g/kg) within 28 days prior to imlifidase treatment
3. Breast-feeding or pregnancy
4. Women of child-bearing potential not willing or able to practice FDA-approved forms of contraception. Two medically acceptable methods of highly effective contraception must be used for the duration of the study (e.g. oral, transdermal, intravaginal, injectable or implantable contraceptive; intrauterine device; intrauterine hormone-releasing system; vasectomized partner; bilateral tubal occlusion; or double-barrier method). For a woman to be considered postmenopausal this ascertainment must be made according to medical records and clinical history and may be aided by measurement of elevated postmenopausal serum gonadotropin levels (FSH).
5. ABO blood group incompatible transplantations (A2 and A2B kidneys will not be accepted for B recipients)
6. Positive serology for HIV

7. Clinical signs of HBV, HCV, CMV, or EBV infection
8. EBV seronegative or with unknown EBV serostatus
9. Positive SARS-CoV-2 tests at any time point from screening to transplantation
10. Active tuberculosis
11. Ongoing serious infections as judged by the investigator
12. Severe other conditions requiring treatment and close monitoring e.g. cardiac failure ≥ grade 4 (New York Heart Association), unstable coronary disease or oxygen dependent respiratory disease
13. A history of a proven hypercoagulable condition
14. Current peripheral neuropathy of Grade 2 with pain, or Grade 3 (severe symptoms; limiting self-care activities of daily living) based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0
15. Present, or history of, thrombotic thrombocytopenic purpura (TTP) or known familial history of TTP
16. Intake of investigational drugs (other than imlifidase) within 5 half-lives
17. Contemporaneous participation in a medical device study
18. Known allergy/sensitivity (except local reactions) to imlifidase or to any drug (or the excipients) specified in the protocol
19. Known mental incapacity or language barriers precluding adequate understanding of the Informed Consent information and the trial activities
20. Inability by the judgement of the investigator to participate in the trial for any other reason

4.4 Restrictions

4.4.1 Prohibited Therapy

High dose IVIg treatment (2 g/kg) must not be administered within 28 days prior to imlifidase treatment (exclusion criterion No. 2).

Investigational drugs (other than imlifidase) must not be taken within 5 half-lives of the given drug (exclusion criterion No. 16).

4.5 Method of Assigning Patients to Treatment Groups

After the patient's eligibility has been confirmed (fulfilled the inclusion criteria and no exclusion criteria) at the screening visit, the patient will be allocated a patient identification number (screening number). The screening number is set automatically by the electronic case report form (eCRF) when the patient is added to the database. When a patient is screened, he/she will always be assigned the lowest available screening number.

4.6 Discontinuation of Patients

Patients may be discontinued from trial treatment and assessments at any time. The patients are free to discontinue the participation in the trial at any time and for any reason, without prejudice to further treatment. Patients who withdraw prior to trial treatment may be replaced.

Patients who discontinue after trial drug administration will always be asked about the reason(s) for discontinuation and the presence of any AEs. The patients will be asked to allow follow-up for 6 months for safety measurements and at least graft and patient survival information even if consent is withdrawn. If a patient refuses any follow-up visit, if possible, the patient should undergo the assessments and procedures scheduled for the last trial visit (as defined in Section 6, Trial Procedures). Even if the patient is not able to attend, the End-of-Trial Form must be completed. Patients who, for a medical reason, cannot comply with the protocol procedures will be followed by best procedure to retrieve safety and efficacy data. Patients who are treated with imlifidase but not transplanted will be handled in the same way as discontinued patients.

If the trial is prematurely terminated, the sponsor will promptly inform the investigator and the FDA of the termination and the reason(s) for the termination. The IRB will also be promptly informed and provided the reason(s) for the termination either by sponsor or investigator, depending on local requirements. All patients, those in the trial at the time for termination as well as those that have completed the trial, will be informed about the trial termination and the reason(s) for it by the investigator. The monitor must also be informed about the trial termination.

5. TRIAL TREATMENT

5.1 Investigational Medicinal Product (IMP)

5.1.1 Imlifidase

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

Imlifidase for infusion will be prepared by the pharmacist and the administration will be performed by a qualified nurse at the site. Details on preparation, labeling, administration and accountability of imlifidase are described in the Pharmacy Manual that will be provided to the site and pharmacy prior to inclusion of the first patient.

Imlifidase will be administered intravenously as one dose of 0.25 mg/kg over 15 minutes within the 24-hour period prior to transplantation. The infusion may be interrupted if needed and resumed. An infusion that is interrupted and then resumed will not be regarded as a protocol deviation. A second dose may be given if the crossmatch test at 4 hours after the first dose remains positive.

5.2 Non-investigational medicinal products (NIMPs)

5.2.1 Pre-medications

To reduce the risk of infusion reactions all patients will receive pre-medication with a corticosteroid, methylprednisolone 250 mg intravenously, and an antihistamine, loratadine 10 mg orally or an equipotent antihistamine, prior to imlifidase infusion.

All patients will receive premedication prior thymoglobulin, IVIg, and rituximab according to standard of care.

5.2.2 Prophylactic antibiotic, antiviral and antifungal

All patients will receive standard prophylaxis for pneumocystis, CMV, and candida infections. Therapeutic alternatives may be used if allergies or intolerance are present. Prophylaxis for bacterial infections according to clinical practice will be administered prior to imlifidase infusion until IVIg is administered or until serum IgG level is back within normal range as judged by the investigator.

5.2.3 Belatacept

Belatacept will be provided as the commercially available product and administered intravenously (IV) with the dose of 10 mg/kg.

Belatacept will be administered on days -21, -16 and -7 prior to transplantation, and after transplantation on days 6, 10, 22, 33, 64 and 91.

The belatacept dosing can be moved, interrupted or skipped for safety reasons at any time. This is done based on the physician's judgement and is not considered a protocol deviation. However, the change must be noted in the eCRF together with the reason.

5.2.4 Bortezomib

Bortezomib will be provided as the commercially available product and administered subcutaneously (SQ) with the dose of 1.3 mg/m^2.

Bortezomib will be administered in three 21-day cycles, the first on the days -21, -18, -14, and -11 prior to transplantation, the second after transplantation on days 3, 6, 9, and 12, and the third on days 22, 25, 29, and 33.

The bortezomib dosing can be moved, interrupted or skipped for safety reasons at any time, see Section 3.1.4 for bortezomib-associated discontinuation criteria. Consecutive doses should be separated by at least 72 hours. This is done based on the physician's judgement and is not considered a protocol deviation. However, the change must be noted in the eCRF together with the reason.

5.2.5 Rituximab

Rituximab will be provided as the commercially available product and administered intravenously (IV) to all patients as a single dose of 375 mg/m^2 [redacted]

5.2.6 IVIg

High dose IVIg 10% solution will be provided as the commercially available product and administered to all patients with the dose 2 g/kg (max 140 g for >70 kg) [redacted] (as a single dose or in divided doses administered on two consecutive days).

5.2.7 Induction immunosuppressants

All patients will be given the following commercially available medications:

1. High dose corticosteroids, methylprednisolone, 1000 mg intravenously at the day of transplantation and 500 mg for at least 3 days. The high dose corticosteroids will then be tapered over several days and converted to prednisone as maintenance therapy, starting at 30 mg orally.
2. rATG (Thymoglobulin® 1.5 mg/kg) IV given over at least 3 days starting [redacted], to achieve a cumulative dose of 4.5 mg/kg. [redacted]

The induction therapy dosing can be moved, interrupted, or skipped for safety reasons at any time. This is done based on the physician's judgement and is not considered a protocol deviation. However, the change must be noted in the eCRF together with the reason.

5.2.8 Maintenance immunosuppressants

Once bortezomib is administered (3 weeks prior to transplantation), tacrolimus will be given with a trough goal of 8-10 ng/mL and mycophenolate mofetil 1000 mg twice daily.

After transplantation, all patients will receive tacrolimus with a trough goal of 8-12 ng/mL, mycophenolate mofetil, 1000 mg twice daily, and prednisone daily, tapered from 30 mg to 5 mg over a 3-months' period.

5.3 Concomitant medications and therapies

Maintenance immunosuppressant medications and standard of care transplant therapies other than those described above and other concomitant medications and/or other therapies considered necessary for the patient's welfare will be prescribed at the discretion of the investigator.

All concomitant medications must be recorded on the concomitant medication page in the eCRF throughout the trial, beginning from screening to end of trial. Recorded information will include indication, name of drug, dose (if available), route of administration and start and stop date.

5.4 Characteristics and Source of Supply

Imlifidase will be provided by Hansa Biopharma and will be handled according to the principles of Good Manufacturing Practice (GMP). Hansa Biopharma will provide the investigational pharmacy at trial site with the drug in amounts sufficient for the trial. All commercially available NIMPs will be provided by the main pharmacy at the investigational site.

5.4.1 Investigational Medicinal Product

Imlifidase is supplied as a freeze-dried (lyophilized) powder for concentrate for solution for infusion. The excipients are mannitol, polysorbate 80, trometamol, disodium edetate dihydrate (EDTA) and hydrochloric acid (for pH adjustment). The excipients are all of pharmacopeial quality.

5.4.2 Non-investigational medicinal products

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

5.5 Conditions for Storage and Use

5.5.1 Investigational product

The investigator will ensure that the IMP will be stored in appropriate conditions in a secure location with controlled access. The storage compartment must be monitored on a regular basis and the temperature documented.

Until reconstitution imlifidase should be stored refrigerated at +5°C (±3°C) (+41.0°F [±37.4°F]). Reconstitution and dilution should be performed under aseptic conditions. If not used immediately, the solution for infusion can be kept for up to 24 hours if refrigerated

(+5°C (±3°C)). During this 24-hour period, the solution for infusion may be kept outside the refrigerator, below 25°C (+77.0°F), for a maximum of 4 hours. The solution should be stored protected from light. Neither powder, nor solution for infusion should be frozen. Prior to administration, the solution for infusion should be inspected visually for particulate matter or discoloration. The solution should be discarded if any particulate matter or discoloration is observed. The entire, fully diluted infusion should be administered with an infusion set and a sterile, inline, non-pyrogenic, low protein binding filter (pore size of 0.2 µm). Unused portions of the solution for infusion must not be re-used.

5.5.2 Non-investigational medicinal products

The investigator will ensure that the NIMPs will be stored according to Prescribing Information in a secure location with controlled access and prepared according to label.

5.6 Packaging and Labeling

Packaging and labeling of the IMP will be performed in accordance with GMP and national regulatory requirements.

5.7 Blinding

This is a single arm open-label trial.

5.8 Compliance, Accountability and Destruction of IMP

5.8.1 Compliance

The administration of all medication will be done by a qualified nurse and must be recorded in the appropriate sections of the eCRF. The investigational treatment must be documented also in the accountability logs. Treatment compliance will be assured by supervised administration of the IMP by the investigator or delegate. The dose, date and time of administration of the IMP will be checked by the monitor at monitoring visits.

5.8.2 Accountability and destruction of IMP

It is the principal investigator's/institution's responsibility to establish a system for handling trial treatments, including the IMP, to ensure that:

1. Deliveries are correctly received by a responsible person (e.g. pharmacist or designated trial personnel).
2. Deliveries are recorded.
3. The IMP is handled and stored safely and properly.
4. The IMP provided for this trial will be used only as directed in the trial protocol.
5. The trial personnel will account for all drugs dispensed and returned. Any discrepancies must be documented, investigated, and appropriately resolved.
6. The Investigational pharmacist will maintain and keep the total accountability records. Used and unused IMP will be returned or destroyed according to the site's Investigational Pharmacy's SOP.

5.9 Product Quality Complaints

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

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

6. TRIAL PROCEDURES

6.1 Trial Visits

For each patient the planned duration of the trial, including the screening period and the follow-up visit, is about 7 months. A trial flowchart is presented in Appendix 1 and the trial procedures/assessments are presented in Appendix 2.

Assessments of concomitant medication and AEs will be performed at all visits throughout the trial.

Visit 1, [redacted]

Patients will be informed about the trial, the anticipated benefits and theoretical risks, in writing and verbally and sign the informed consent form. The time window for the screening visit is [redacted].

The screening visit will include the following:

- Signing of informed consent form
- SARS-CoV-2 test
- Demographics (age, gender, race, height, weight)
- Medical and surgical history (see Section 7.4.6)
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- Pregnancy test for women of childbearing potential
- ECG and echocardiogram
- Safety laboratory tests (Table 1)
- Virus screening; HIV 1 and 2 antigen/antibody, 4th generation, Hepatitis B and Hepatitis C serologies, CMV and EBV serologies
- Sampling for DSA
- FCXM test and if possible, CDCXM test
- Baseline peripheral neuropathy assessment
- Inclusion and exclusion criteria
- HRQoL questionnaires

Visit 2, [redacted]

The following activities and assessments will be performed:
[redacted]

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)

- Bone marrow biopsy and contemporaneous blood sample prior to initiating bortezomib and other medications
- Start of maintenance immunosuppression prior to bortezomib and belatacept (tacrolimus; MMF twice daily)
- Start of standard prophylaxis for pneumocystis, CMV, and candida infections prior to bortezomib when deemed medically appropriate by investigator
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered
- Belatacept administered

[redacted]

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered

[redacted]

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Belatacept administered

[redacted]

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered

[redacted]

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered
- ECG and echocardiogram

[redacted]

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Belatacept administered

Visit 3, [redacted]

The following activities and assessments will be performed [redacted]

- Review of inclusion/exclusion criteria
- SARS-CoV-2 test (completed within 5 days before IMP administration)
- Safety laboratory tests (Table 1)

- Pregnancy test for women of childbearing potential, unless woman has been hospitalized between V1 and V3
- Review of medical/surgical history
- Donor demographics and characteristics, donor kidney conditions and donor HLA-typing
- Vital signs (blood pressure, pulse rate, body temperature)
- Weight
- Baseline sampling for DSA, PK, PD, and ADA (IgG)
- FCXM test and if possible, CDCXM test
- Methylprednisolone and antihistamine will be administered prior to the imlifidase infusion. Antibiotic prophylaxis will start prior to imlifidase infusion and the treatment will continue until IVIg has been administered or until IgG levels return to acceptable values as judged by the investigator. Methylprednisolone will be administered according to treatment schedule, see Section 5.2
- **Imlifidase administered, 0.25 mg/kg**

The following activities will be performed [redacted]

- Blood pressure and pulse rate at 30 minutes, 1, 2, 4, 24, 48 and 72 hours
- Body temperature at 2, 4, 24 and 48 hours
- Safety laboratory tests (Table 1) at 2, 4, 24, 48 and 72 hours
- Sampling for DSA at 1, 2, 4, 24 and 48 hours
- Sampling for FCXM test at 1, 2, 4 and 24 hours. The 24-hour sample may be drawn between 20-24 hours post-imlifidase.
- Sampling for PK and PD at 30 minutes, 1, 2, 4, 8, 24, 48 and 72 hours
- Sampling for ADA (IgG) at 48 hours
- [redacted]
- [redacted]
- [redacted]
- Methylprednisolone 1000 mg at day of transplantation and thereafter 500 mg daily for three days; POD 1-3
- **Transplantation within 24 hours from imlifidase administration**
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered on day 3 (POD 1)

If the first dose of imlifidase does not have sufficient effect (4-hour crossmatch still positive), a second dose of 0.25 mg/kg can be given. If a second dose is administered, methylprednisolone and antihistamine treatments prior to imlifidase infusion will be repeated. Sampling for a FCXM test will be performed prior to the second dose and at 2 hours after dosing. At the same time point sampling for DSA analysis will be performed.

PK samples will be drawn just prior to the second infusion and 30 minutes after the end of the infusion. No other blood samples will be drawn. All subsequent samplings will follow the time schedules initiated after the first dosing of imlifidase.

Visit 4, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for DSA, PK and PD
- Methylprednisolone administered
- rATG administered

Visit 5, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for PK, PD and ADA (IgG)
- Belatacept administered
- rATG administered [redacted]
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered

Visit 6, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- rATG administered

Visit 7, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for DSA, PK, PD and ADA (IgG) [redacted]

Visit 8, [redacted]

The following activities and assessments will be performed:

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Rituximab administered
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered

Visit 9, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for PK, PD and ADA (IgG) [redacted]
- Belatacept administered

Visit 10, [redacted]

The following activities and assessments will be performed:

- High dose IVIg administered intravenously. IVIg can be split into two doses given over 2 days.

Visit 11, [redacted]

The following activities and assessments will be performed:

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Sampling for ADA (IgG)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered
- ECG and echocardiogram

Visit 12, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for DSA, PK and ADA (IgG)
- Sampling for CMV, EBV and BKV PCRs

Visit 13, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for DSA and ADA (IgG)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered
- Belatacept administered

Visit 14, [redacted]

The following activities and assessments will be performed:

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered

Visit 15, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for DSA and ADA (IgG)
- Sampling for CMV, EBV and BKV PCRs
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered
- [redacted]

Visit 16, [redacted]

The following activities and assessments will be performed:

- Small safety laboratory test; hemoglobin, leucocytes with differential count, CRP, creatinine/eGFR (calculated)
- Peripheral neuropathy assessment prior to bortezomib treatment
- Bortezomib administered
- Belatacept administered
- ECG and echocardiogram

Visit 17, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- [redacted]

Visit 18, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Sampling for DSA and ADA (IgG)
- Sampling for CMV, EBV and BKV PCRs
- Belatacept administered
- [redacted]

Visit 19, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Vital signs (blood pressure and pulse rate)
- Sampling for DSA and ADA (IgG)
- Sampling for CMV, EBV and BKV PCRs
- Belatacept administered
- [redacted]
- [redacted]

Visit 20, [redacted]

The following activities and assessments will be performed:

- Safety laboratory tests (Table 1)
- Sampling for DSA and ADA (IgG)
- [redacted]

Visit 21, [redacted]

The following activities and assessments will be performed:

- Physical examination
- Vital signs (blood pressure and pulse rate)
- Body temperature
- ECG and echocardiogram
- Safety laboratory tests (Table 1)
- Peripheral neuropathy assessment
- Sampling for DSA and ADA (IgG)
- Sampling for CMV, EBV and BKV PCRs
- Pregnancy test for women of child-bearing potential
- [redacted]
- Quality of Life as measured by [redacted] PROMIS-SF-8a patient questionnaires
- [redacted]

[redacted]

7. TRIAL ASSESSMENTS

The trial assessments are described in the sections below and the timing of these assessments are detailed in the trial schedule of events (Appendix 2). The PK sampling must occur as close to the scheduled time as possible. To achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The timing priority order at each timepoint is:

1. Blood samples for PK and PD
2. Blood samples for DSA, and FCXM test and if possible, CDCXM
3. Vital signs
4. Safety laboratory
5. Additional laboratory samples

Whenever possible, all blood and urine samples should be collected in the morning prior to administration of any medication.

7.1 Assessments related to Primary Endpoint

The primary endpoint is the proportion of patients with DSA rebound during the first 3 months after transplantation. The definition of rebound is the following (Appendix 3):

1. When the positive FCXM at screening is due to low titer, non-complement binding (C1q-negative) DSAs, rebound is measured as:
    a. Immuno-dominant DSA: a post-transplant MFI value that is ≥50% the pre-imlifidase value

    OR

    b. Total DSAs: a post-transplant serum where ≥50% of the DSA DSA prior to imlifidase treatment have an MFI value that is ≥50% of the pre-transplant MFI value AND the sum MFI must be ≥50% of the pre-transplant value
2. When the positive FCXM at screening is due to high titer, complement binding (C1q-positive) DSAs, rebound is measured as:
    a. Immuno-dominant DSA: a post-transplant MFI value at 1:16 dilution that is ≥8000 MFI

    OR

    b. Total DSAs: a post-transplant 1:16 diluted serum where ≥50% of the DSA prior to imlifidase treatment have an MFI value that is ≥50% of the pre-transplant MFI value AND the sum MFI must be ≥8000

An HLA antibody is considered a DSA when the MFI value is at least 3000 in the serum analyzed prior to imlifidase treatment. Either a or b must be fulfilled for the increase in DSA to be defined as rebound.

7.2 Assessments related to Secondary Endpoints

7.2.1 Frequency of AMR

The proportion of patients with biopsy proven AMR will be calculated at the following time points:

- During the first 3 months after transplantation (for-cause and protocol biopsy)
- From transplantation up to 6 months (for-cause and protocol biopsies)

All biopsies will be evaluated according to Banff 2019 (Loupy et al. 2020). The biopsies will be performed and evaluated at the site. The date of collection of the biopsies, result of the biopsies and the Banff scores will be entered in the eCRF together with the contemporaneous DSA measurements performed locally. Contemporaneous kidney function parameters will also be collected/calculated in connection with the AMR (p-creatinine/eGFR).

AMR findings from the kidney biopsies will be reported as AEs/SAEs.

7.2.2 Proportion of patients with DSA rebound

The proportion of patients with DSA rebound up to 6 months after transplantation will be calculated. The DSA rebound definition is presented in Section 7.1.

7.2.3 Determination of DSA and complement binding DSA levels

Samples for determination of anti-HLA-antibodies, titer and complement (C1q) binding DSAs will be analyzed centrally, in immunoglobulin (Ig) G single antigen solid-phase immunoassay for antibodies to HLA class I and class II (SAB-HLA, C1qScreen, One Lambda), to obtain full antibody profiles. The assay allows determination of the mean fluorescence intensity (MFI) of antibodies in patient serum reacting to an array of individual HLA immobilized to beads. DSAs will be identified by the site using HLA profile data from the donor and the patients obtained at the screening visit, together with the SAB analysis data. DSAs and HLA-mismatches between donor and patients will be entered in the eCRF.

The levels of anti-HLA specific DSA will be evaluated at several timepoints from the screening visit and throughout the trial. In addition, C1q and titers will be analyzed if an MFI level of a DSA is high enough to result in a meaningful analysis (Tambur et al. 2015; Zeevi et al. 2013). All subjects will be analyzed for both titers and C1q pre-imlifidase treatment regardless of MFI level.

7.2.4 Analysis of crossmatch tests

Two crossmatch tests will be performed, flow cytometry (FCXM) and complement dependent cytotoxicity (CDC). CDC will only be performed at the screening visit and prior to imlifidase dosing, if it is possible. The test(s) will be performed locally.

7.2.5 Graft survival

Graft survival 6 months after transplantation, death censored, will be calculated.

7.2.6 Patient survival
Patient survival 6 months after transplantation will be calculated.

7.2.7 Kidney function
Evaluation of kidney function will be based on p-creatinine and eGFR according to the modification of diet in renal disease (MDRD) equation:

eGFR (mL/min/1.73 m2) = 175 x (Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American) (conventional units)

The ratio protein/creatinine in urine will also be measured unless patients are anuric. The kidney function variables will be analyzed locally.

7.2.8 Pharmacokinetics
Determination of concentrations of imlifidase in serum will be analyzed centrally by a validated electrochemiluminescence based immunoassay using the MSD technology. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report. The actual date and time of collection of each sample will be recorded in the eCRF.

7.2.9 Pharmacodynamics
The IgG levels in serum (pharmacodynamics) will be analyzed centrally by a validated electrochemiluminescence based immunoassays using the MSD (Meso Scale Diagnostic) technology. Full details of the analytical method and the analysis results will be detailed in a separate bioanalytical report. IgG-fragments will be analyzed by protein electrophoresis. The sampling date and time will be recorded in the eCRF.

7.2.10 Immunogenicity
Determination of anti-drug antibodies (ADA) will be analyzed centrally. Determination of anti-imlifidase IgG concentration in serum will be performed using a customized ImmunoCAP. Anti-imlifidase IgG will be analyzed throughout the trial. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report.

7.2.11 Safety Laboratory
The blood samples for determination of clinical chemistry (plasma), hematology (whole blood), coagulation (plasma) and urine analysis are presented in Table 1.

Table 1. Safety laboratory tests

Clinical chemistry	Hematology	Coagulation	Urine
IgG, total	Hemoglobin	PT-INR	Protein/creatinine ratio (unless anuric)
Alkaline phosphatase	Leucocytes, total	APTT	
Alanine aminotransferase	Thrombocytes		
Aspartate aminotransferase	Differential analysis of leucocytes		
Bilirubin, total			
Glucose, fasting			
Sodium			
C-reactive protein (CRP)			
Albumin			
Triglycerides			
Creatinine			
eGFR (calculated from creatinine by MDRD formula)			

A small safety laboratory test will be performed and analyzed prior to administration of bortezomib and/or belatacept: hemoglobin, leukocytes with differential count, CRP, creatinine/eGFR (calculated).

All safety samples listed in Table 1 (including small safety laboratory test kit) will be analyzed locally at the hospital laboratory. The investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are non-clinically or clinically significant. Clinically significant abnormal findings will be reported as AEs.

7.2.12 Vital Signs

Blood pressure, pulse rate, and body temperature will be measured at several time points throughout the trial.

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

7.2.13 Adverse Events

See Section 9.

7.2.14 Health Related Quality of Life Questionnaires (HR-QoL)

At the screening visit and at the last visit, visit 21, the following patient questionnaire will be used to assess life participation; PROMIS Social Health domain "Ability to participate in social roles & activities, PROMIS-SF-8a" (PROMIS Short Form v2.0) (Appendix 4). The guideline for the questionnaire will be followed.

7.3 Assessments related to Exploratory Endpoints

7.4 Other Assessments

7.4.1 Physical Examination

A complete physical examination will be performed at the first and last trial visits and include an assessment of the following: general appearance, head and neck, lymph nodes, abdomen, musculo-skeletal, cardiovascular, respiratory and gross neurological examination. The physical examination shall be performed by an investigator. The results will be reported as normal or abnormal in the eCRF. Abnormal findings will be assessed as clinically significant or not clinically significant. Clinically significant abnormal findings will be reported as AEs.

7.4.2 ECG and Echocardiogram

ECG according to standard procedure at the clinic, will be measured after 10 minutes'-rest at the first and the last trial visit. ECG and echocardiogram will be measured after each completed bortezomib cycle. Additional ECGs and echocardiograms may be performed by the Investigator for safety reasons.

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

7.4.3 Peripheral Neuropathy Assessment

Peripheral motor neuropathy and peripheral sensory neuropathy will be assessed by the Investigator at screening and prior to each bortezomib infusion and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The Investigator or designee will evaluate the Grade and whether any change in Grade is clinically significant. Clinically significant Grades will be reported as AEs and evaluated for trial stopping criteria.

7.4.4 Viral surveillance

Virus screening performed at the screening visit will be HIV 1 and 2 antigen/antibody, 4th generation, Hepatitis B and Hepatitis C serologies, CMV and EBV serologies and a SARS-CoV-2 test. The SARS-CoV-2 test will be repeated prior to administration of imlifidase. During the trial CMV, EBV and BKV PCRs will be performed for early diagnosis of viral activations/reactivations and early treatment. Extra samples should be taken if indicated. At screening, results not older than 6 months can be used.

7.4.5 Demographics and Baseline Data

Information about gender, race, age at inclusion, weight and height will be collected at the screening visit and the weight will be measured again prior to imlifidase administration. Measurements should be taken without shoes. Body Mass Index will be calculated from the height and the weight.

7.4.6 Medical and Surgical History

Medical and surgical history will be recorded at screening visit, including blood group, female history of pregnancy, previous transplantation(s) including all previous donor HLA-type (if available), previous analyzed DSAs, relationship with donor, previous desensitization therapies prior to transplantations, time on dialyses pre- and post-transplantations including the present, number of dialyses and number of transfusions within the year of current transplantation. HLA-typing of the patient will be performed (complete genotyping; 11 loci; A, B, C, DRB1, DRB3/4/5, DQA, DQB, DPA, DPB), and historical calculated PRA collected. Clinically significant findings at the screening visit will be documented as Medical History in the eCRF.

7.4.7 Donor data

Donor demographics and characteristics will be collected as well as donor HLA-typing (complete genotyping; 11 loci; A, B, C, DRB1, DRB3/4/5, DQA, DQB, DPA, DPB) and kidney condition. Data collection will include the following: demographics (age, gender, race), body measurements (weight, height), history of hypertension and diabetes (including HbA1c), serum creatinine, HCV screen, CMV and EBV serostatus, blood group, risk evaluation of donor, surgical complications, acute kidney injury including acute hemodialysis, kidney biopsy performed (date, time and information from the biopsy report). Other data than the ones listed here may be collected depending on donor/kidney condition. Total cold

ischemia time (if applicable), warm ischemia time (if applicable), whether machine perfusion has been used, will also influence the condition of the kidney and will be documented in the eCRF.

All intended donors must be tested for SARS-CoV-2 as soon as possible in accordance with the latest version of the "Summary of Current Evidence and Information – Donor SARS-CoV-2 Testing & Organ Recovery from Donors with a History of COVID-19" by the OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC) (Summary of Evidence and Information: SARS-CoV-2 (hrsa.gov))[a].

All data collected will be de-identified. The reason for collecting these data is to evaluate the conditions of the donated kidney, which may impact the kidney function, possible rejection episodes and severity and graft survival after transplantation.

7.4.8 Pregnancy Test

Serum β-hCG will be determined for all females of childbearing potential at screening, at visit 3 unless the woman has been hospitalized between visit 1 and 3 and at the last visit, using validated standard methods.

[a] The document is updated quarterly by DTAC (COVID-19 - OPTN (hrsa.gov) and https://optn.transplant.hrsa.gov/media/kkhnlwah/sars-cov-2-summary-of-evidence.pdf).

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of Blood

The total blood volume obtained will be about 850 mL over 6 months.

8.2 Handling, Storage and Destruction of Biological Samples

Locally analyzed samples will be discarded immediately after analysis according to local laboratory practice.

Blood, urine, and kidney biopsy samples collected for central analysis will be stored coded by the sponsor or by the sponsors contracted laboratory, until completion of the trial report. Residual biological specimen will then be discarded or anonymized so that they cannot be linked to the patient any longer. Kidney biopsies/stained glass will be sent back to the hospital or will be anonymized. Biobank/data protection and local legislation will be adhered to. Anonymized samples will be used for methodology development.

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

8.3 Chain of Custody of Biological Samples

A full chain of custody will be maintained for all samples until they are anonymized.

The principal investigator will have the responsibility to keep full traceability of collected biological samples from the patients while in storage at the site until shipment, and keep documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage during the study until used, discarded or anonymized.

Hansa Biopharma will keep 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 patient withdraws consent to the use of biological samples during the study, all samples that has not yet been analyzed will be discarded.

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, whether or not considered causally related to the product. Relationship to the trial drug will be deemed as not related, unlikely related, possibly related or probably related. 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.

9.1.1.1 Pre-treatment adverse event

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

9.1.1.2 Treatment emergent adverse event

A treatment emergent adverse event is any adverse event occurring after the administration of the IMP and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after administration of the IMP and within the time of residual drug effect. The time of residual drug effect is the estimated period of time after the administration of the IMP, where the effect of the product is still considered to be present based on pharmacokinetic, pharmacodynamic or other substance characteristics.

The residual drug effect of imlifidase is governed by the PD effect and return of IgG, which starts 1-2 weeks after treatment. Since the IgG levels are not immediately back to normal, the time of residual drug effect is set to 30 days.

9.1.1.3 Post-treatment emergent adverse event

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

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 hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above. 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.

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

9.2 Collection and Recording of Adverse Events

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

AEs will therefore be collected on the AE CRF from the time of signing of the informed consent and throughout the trial including the follow-up period.
Adverse events can be collected by:

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

9.2.1 Variables

The following variables will be recorded in the CRF for each AE; description of the AE, the date and time (if applicable) when the AE started and stopped, severity based on Common Terminology Criteria for Adverse Events grading (CTCAE v.5.0) whether the AE is serious or not, causality assessment, action taken, and outcome.

9.2.1.1 Causality Assessment

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

- **Not related:** applicable to an AE that occurs when the patient was not exposed to trial treatment or another cause is obvious.
- **Unlikely related:** applicable to an AE that meets the following criteria
    - Does not follow a reasonable temporal sequence from trial drug dosing
    - May readily have been produced by the patient's clinical state, environmental, or toxic factors, or other therapy administered to the subject
- **Possibly related:** applicable to AEs where connection with dosing of trial drug appears unlikely but cannot be ruled out. Applicable to AEs where:
    - It follows a reasonable temporal sequence dosing with trial drug
    - It follows a known pattern of response to trial drug dosing
- **Probably related**: applicable to AEs that are considered, with a high degree of certainty, to be related to the trial drug. Applicable to AEs where
    - It follows a reasonable temporal sequence trial drug dosing
    - It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy
    - It follows a known pattern of response to trial drug dosing.
- For SAEs causal relationship will also be assessed for any trial procedure.

9.2.2 Adverse Events Based on Signs and Symptoms

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

9.2.3 Adverse Events Based on Examinations and Tests

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

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

Findings from the kidney biopsies (AMR, CMR) will be captured as AEs and if SAE criteria are fulfilled, they will also be considered as SAEs.

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

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

9.2.4 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the patient's last AE assessment in the trial are followed up by the investigator until stabilization, for as long as medically indicated or until the overall clinical outcome of the patient is known, unless the patient 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 patient with ongoing AE(s)/SAE(s) at the end of the trial, if judged necessary.

9.2.5 Reporting of Serious Adverse Events

SAEs will be recorded from the time of informed consent.

All SAEs have to be reported, whether or not considered related to the investigational product, or to the trial procedure(s), on a separate safety form. It will be recorded in the AE module of the eCRF that the AE is considered serious.

An assigned contract research organization (CRO), PrimeVigilance, will be responsible for the SAE handling in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulations.

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

Contact Information:

CRO: **PrimeVigilance**

[redacted] [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 PrimeVigilance of any follow-up information on a previously reported SAE immediately but no later than within 24 hours of when he or she becomes aware of it.

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

9.2.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

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 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.

PrimeVigilance will be responsible for ensuring reporting of all SUSAR to RA in accordance with ICH GCP and local regulations. The CRO managing the trial sites, VCLS – Voisin Consulting Life Sciences, is responsible for informing all participating trial investigators of any SUSAR on an expedited basis and in accordance with applicable regulations.

In addition, Hansa Biopharma is responsible for ensuring information about all SUSAR to all investigators, IRB, and ethics committees, as applicable, in all other ongoing studies involving imlifidase. In US, it is the responsibility of the site investigator to promptly notify the IRB and other appropriate institutional regulatory bodies of all SUSAR received involving risk to human subjects as per their applicable requirements.

The SUSAR reporting procedures are detailed in the trial Safety Management Plan. This plan is an agreement between Hansa Biopharma and PrimeVigilance.

9.3 Adverse Events of Special Interest

The following events will be assessed as AESI:

- infusion-related reactions that occurs within 48 hours of imlifidase treatment
- all events resulting in interruption (pause and/or discontinuation) of imlifidase dose (exempted are all interruptions due to problems with e.g. infusion line or pump)
- severe or serious infections within 30 days after transplantation

Events resulting in interruption of the imlifidase dose should be reported within 24 hours, as described for SAEs in section 9.2.5, and submitted to the sponsor using a safety form.

9.4 Overdose

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

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF

- An overdose without associated symptoms is only reported in the patient file

The actual dose administered must be reported in the appropriate module of the eCRF.

9.5 Pregnancy and Pregnancy Outcome

Pregnancy is an exclusion criterion, and a pregnancy test is performed at the screening visit and prior to infusion of the IMP unless the patient has been hospitalized between the screening visit and the infusion. A pregnancy test is also performed at the last trial visit.

If a patient becomes pregnant during the follow up phase of the trial, the patient will continue in the trial according to the trial 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 patient has completed or discontinued the trial. 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-trial pregnancy and considered possibly or probably related to the trial drug by the investigator will be reported to Hansa Biopharma (or designee).

10. STATISTICAL METHODS

The statistical analyses will be outsourced to a CRO. Prior to clean file, a Statistical Analysis Plan (SAP) with details on statistical analysis and data presentation will be established. No formal statistical hypothesis testing will be performed in this trial. The statistical analyzes will include descriptive statistics reflecting the explorative nature of the trial.

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

For categorical data frequencies and percentages will be presented.

Due to the exploratory nature of the trial, missing data will remain missing and no substitution of missing data will be performed.

Patients treated with imlifidase but not transplanted will be included in the safety analysis set but not in the full analysis set. These patients will be included in the patient disposition presentation.

10.1 Analysis Sets

The analysis sets used in the trial are defined below. The decision to exclude patients from any of the analysis sets for reasons not covered by the definition will be taken by the clinical trial team before database lock and documented in the database lock minutes. Further details will be specified in the SAP.

10.1.1 Full Analysis Set (FAS)

The FAS will be used to present efficacy endpoints and include all imlifidase treated patients who were transplanted.

10.1.2 Safety Analysis Set

The safety analysis set comprises of all patients treated with at least one dose of imlifidase, belatacept and/or bortezomib and will be used in all presentations of safety data.

10.1.3 Pharmacokinetic Analysis Set

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

10.2 Patient characteristics

The data from the clinical assessments, including demographics and other baseline characteristics, will be summarized and listed for each time point using descriptive statistics.

10.2.1 Patient disposition

The patient disposition will present number of patients as screened, enrolled, exposed, transplanted, completed, withdrawn overall and by reason for withdrawal and finally by each of the analysis set.

10.2.2 Demographics and Other Baseline Characteristics
The patient's demographics and other baseline characteristics will be summarized and listed.

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

10.2.4 Exposure and Compliance
Exposure of imlifidase will be tabulated and listed.

10.3 Statistical analysis of Primary Endpoint
Patients with DSA rebound will be listed and summarized from the time of transplantation up to 3 months after transplantation.

10.4 Statistical analysis of Secondary Endpoints

10.4.1 Proportion of patients with DSA rebound
Patients with DSA rebound will be listed and summarized from the time of transplantation up to 6 months after transplantation.

10.4.2 Proportion of patients with biopsy proven AMR
Patients with AMR will be listed and summarized from the time of transplantation up to 3 months and up to 6 months after transplantation.

10.4.3 Proportion of patients with negative crossmatch tests
Results of crossmatch tests (FCXM) will be listed by patient and summarized.

10.4.4 Measurements of DSA and complement binding (C1q) DSA levels
All DSA and complement binding (C1q) DSA MFI values before and after imlifidase administration will be summarized by patient and time point and presented as listings.

10.4.5 Graft survival
Graft survival will be listed by patient and summarized by end of trial.

10.4.6 Patient survival
Patient survival is listed by patient and summarized by end of trial.

10.4.7 Kidney function
Kidney function assessed by p-creatinine, eGFR and urine protein/creatinine levels will be listed by patient and time point and summarized.

10.4.8 Pharmacokinetics
The PK analysis will be performed by Hansa Biopharma. The PK parameters will be calculated by non-compartmental analysis (NCA) or compartmental analysis using the software WinNonlin® (Pharsight Corporation, US). Actual sampling time points relative to dosing will be used for the calculations and on the individual plots of plasma concentration versus time. Plasma concentration values below LLQ and missing values (e.g. no blood

sample collected or no value obtained at analysis) will be excluded from the calculations. Values below LLQ will be represented by '0' (zero) in the arithmetic descriptive statistics and as LLQ/2 in the plots. No formal analysis of "outliers" is planned.

PK parameters will be estimated based on measurements of the plasma concentration-time data of imlifidase, and the following parameters will be estimated, if possible, but not limited to; AUC, C_{max}, t_{max}, $t_{½}$, CL, V_z.

PK parameters will be presented with number of measurements, number of missing data, arithmetic mean, standard deviation, %CV (arithmetic), median, minimum, maximum, geometric mean, and %CV (geometric mean). For $t_{½}$, the harmonic mean will be listed instead of the arithmetic and geometric means, and for t_{max} only the median, minimum, and maximum will be presented.

10.4.9 Pharmacodynamic

Concentration of IgG will be listed by patient and timepoint and summarized. Scoring of IgG fragments will be listed by patient and timepoint and summarized.

10.4.10 Anti-drug antibody level

Concentration of anti-imlifidase antibodies will be listed by patient and timepoint and summarized.

10.4.11 Health related quality of life

HRQoL endpoint is change in patient-reported life participation, as measured by the PROMIS Social Health domain "Ability to participate in social roles & activities, PROMIS-SF-8a", from baseline to 6 months after transplantation. HRQoL will be evaluated in the FAS by patient questionnaire PROMIS "Ability to participate in social roles activities, PROMIS-SF-8a" at the screening visit and at the last trial visits (Visit 21). The HRQoL measurements will be summarised descriptively.

10.5 Statistical analysis of Exploratory Endpoints

10.5.4 Health Related Quality of Life

[redacted]

10.6 Safety Endpoints

10.6.1 Analysis of Adverse Events

10.6.1.1 Adverse Events

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

10.6.1.2 Overview of treatment emergent adverse events

A treatment emergent AE summary table will be presented. The table will include, the number of patients reporting an AE, the percentage of patients with an AE and the number of events reported, for the following categories:

- All AEs
- Severe AEs
- SAEs
- Adverse drug reactions
- AEs leading to withdrawal
- Deaths

Adverse drug reactions (ADRs) are defined as events that are considered to be possibly or probably related to IMP as judged by the Investigator.

10.6.1.3 Incidence of treatment emergent adverse events

Summary tables will be prepared for the incidence of treatment emergent AEs by MedDRA system organ class (SOC) and preferred term (PT), presenting number of patients reporting an AE, the percentage of patients (%) with an AE and the number of events reported. Summary tables will be prepared for:

- All treatment emergent AEs by SOC and PT
- AEs by causality
- AEs by intensity
- ADRs by SOC and PT
- ADRs by intensity

Missing values will be treated as missing except for causality, intensity, seriousness and outcome of an AE, in which case, a “worst case” approach will be taken. Thus, if causality is missing, the AE will be regarded as related to the IMP, if intensity of the AE is missing, it

will be taken to be severe, if seriousness is missing, the AE will be considered to be an SAE and if the outcome is missing and no date of outcome is present, the outcome is regarded as "not yet recovered".

10.6.1.4 Serious adverse events, deaths, and other significant adverse events

Separate listings will be provided for SAEs, deaths, and other significant AEs if any such event occurs.

10.6.2 Analysis of Other Safety Variables

10.6.2.1 Vital signs

Vital signs will be listed by patient and time for each parameter and summarized.

10.6.2.2 Clinical Chemistry, Hematology, Hemostasis, and Urinalysis

Clinical chemistry, hematology, hemostasis and urinalysis parameters will be presented in the same way as the vital sign parameters.

10.6.2.3 Electrocardiography

ECG's will be categorized as "normal", "abnormal and not clinically significant", "abnormal and clinically significant" (as judged by the investigator) and summarized. ECG and echocardiogram results will be listed by patient and abnormal values will be flagged.

10.7 Determination of Sample Size

Due to the exploratory nature of the trial, there is no formal statistical hypothesis. The evaluation of DSA rebound will be descriptive. A sample size of 12 patients is considered sufficient to provide adequate information for the purpose to the trial.

11. TRIAL MANAGEMENT

11.1 Pre-trial Activities

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

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

Before the first patient 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.

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).

11.2 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 CRFs, and IMP accountability checks are being performed.
- 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 trial) including verification of informed consent of participating subjects.
- If a patient 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 patient.

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

11.3 Source Data

Except for SAEs, which must always be 100% 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 data must be defined in a source data agreement. 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 IRBs who may audit/inspect the trial and to permit trial-related monitoring.

11.4 Audit and Inspection

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

The purpose of an audit/inspection is to systematically and independently examine all trial-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the International council for Harmonisation (ICH), and any applicable regulatory requirements including the Declaration of Helsinki.

The patients must be informed by the investigator and in the Informed Consent Documents that authorized 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/subject number will appear on these copies.

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

11.5 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.

12. DATA MANAGEMENT

12.1 Case Report Form

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

After the trial database has been 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.

12.2 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.

12.3 Coding

For medical coding of AEs, medical history 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.

12.4 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.

13. CHANGES IN TRIAL CONDUCT OR PLANNED ANALYZES

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 (IRB and RA, if applicable) have been obtained.

Changes to the protocol to eliminate immediate hazard(s) to trial patients may be implemented prior to IRB and RA approval.

13.2 Protocol Deviations

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

13.3 Statistical Analysis Plan

A statistical analysis plan will be prepared and finalized before the database lock. 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 patients 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 IRB and provide them with a detailed written explanation of the termination or suspension.

If the RA terminates or suspends its approval/favorable 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 (CSR) within one year after end of trial. The report will be submitted for comments and signature to the coordinating (signatory) investigator.

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 and Hansa Biopharma. Hansa and the investigator may publish on the trial progress and outcomes of the trial once both parties have reviewed the potential manuscripts and agree on authorship prior to any submissions or publications.

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

15.2 Liabilities and Insurance

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

15.3 Institutional Review Boards

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

Hansa Biopharma will keep an updated list of submission and approval dates of all documents submitted to IRB.

15.4 Regulatory Authority

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

15.5 Patient Information and Informed Consent

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

It must be emphasized that participation is voluntary and that the patient 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 patient will receive a copy of the Patient Information and his/her signed Informed Consent Form.

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

15.6 Patient Confidentiality

Patient 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 patient.

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 without prior written approval of Hansa Biopharma.

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 patients 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 or longer if required by local law 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 patient identification code which provides the sole link between named patient source records and anonymous eCRF data for Hansa Biopharma. The investigator must arrange for the retention of this Patient Identification Log and signed Informed Consent Documents for at least 25 years or longer if required by local law 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. LIST OF REPORTS

[redacted]

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19. APPENDICES

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