Statistical analysis plan

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

Sponsor:	**Hansa Biopharma**
Contract research organisation:	**Larix A/S**
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List of abbreviations and definition of terms

ADA	Antidrug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AMR	Antibody Mediated Rejection
ANOVA	Analysis Of Variance
AUC	Area Under the Concentration Versus Time Curve
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CL	Total systemic clearance of drug
C_{max}	Maximum Serum Concentration
CRF	Case Report Form
CV	Coefficient of Variation
DSA	Donor Specific Antibody
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HLA	Human Leukocyte Antigen
HR	Heart Rate
IA	Immunoadsorption
IgG	Immunoglobin G
IMP	Investigational Medicinal Product
LLQ	Lower Limit of Quantification
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity
[redacted]	[redacted]
NCA	Non-Compartment Analysis
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PE	Plasma Exchange
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PPS	Per-protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
Screened	Patient who enters the screening phase of the study
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
STDM	Study data Tabulation Model
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
T_{max}	Time of observed C_{max}

$T_{½}$	Elimination half-life
TM	Trial Master
Vz	Apparent Volume of Distribution during the terminal phase
WHO	World Health Organization

1 Introduction

This document describes the planned statistical analyses for 16-HMedIdeS-12 which will include data processing, data analyses and data presentation. This Statistical Analysis Plan (SAP) is based on the study protocol version 4.3, 5.3, 6.3, 7.3 and 8.3 (1). These are country-specific protocols for 5 different countries (France, Austria, US, Australia and Germany), allowing the countries to have minor differences regarding some exclusion criteria. These differences are deemed to not influence the analysis specified in this SAP.

1.1 Study objectives and endpoints

These are the objectives as stated in the protocols above.

1.1.1 Objectives

The primary objective of this study is to:

- Investigate the efficacy of imlifidase compared with plasma exchange (PE) in removal of Donor Specific Antibody (DSA) in patients who are experiencing an active or chronic active Antibody Mediated Rejection (AMR) episode after kidney transplantation

The secondary objectives of this study are to:

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

1.1.2 Endpoints

The primary endpoint of this study is:

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

The secondary endpoints of this study are:

- DSA levels up to 180 days after treatment
- HLA-antibodies levels up to 180 days after treatment
- Kidney function change from baseline (at screening) as evaluated by estimated Glomerular Filtration Rate (eGFR), P-creatinine and albumin/creatinine ratio in urine up to 180 days after treatment

- Proportion of patients with graft loss within 180 days of treatment
- Signs of transplant glomerulopathy 180 days post treatment
- Change from baseline (at screening) in histopathology per Banff Criteria at 29 and 180 days
- Change from baseline (at screening) in mRNA levels in kidney biopsies evaluated by [redacted] at 29 and 180 days from baseline. If kidney biopsy is performed before screening, mRNA levels will be evaluated on day 29 and day 180 (no baseline will be available)
- Safety parameters (adverse events [AEs], safety laboratory tests, vital signs and electrocardiogram [ECG])
- Type, frequency and intensity of adverse events
- Number of sessions with PE
- Total Serum Immunoglobin G (IgG) levels over time
- Presence of intact IgG on SDS-page until start of IVIg treatment
- DSA functionality determined by C1q or C3d analysis pre- and post-treatment
- PK profile of imlifidase (C_{max}, T_{max}, $t_{½}$, AUC, CL, V_z)
- Presence of anti-imlifidase IgG (ADA)
- Number of patients with resolution of AMR at day 180
- Patient survival at day 180

2 Study design

The study is a phase II, randomized, open-label, multi-centre study with an active control investigating the efficacy and safety of imlifidase compared with PE, in removing anti-HLA antibodies to treat active and chronic active AMR post-transplant. A total of 30 male and/or female patients will be included in the study. The 30 patients are planned to be distributed in 5 countries (France, Austria, US, Australia and Germany) and 14 sites.

DSA measurements and biopsies will be done at screening. If deemed eligible for the study during the screening visit, patients will be randomized in ratio 2:1 in the following way:

- 20 patients will be randomized to treatment with a single dose of 0.25 mg/kg imlifidase. The 20 patients will receive treatment with 0.25 mg/kg imlifidase at visit 2 (Day 1). On day 4 the 20 patients will be given high dose IVIg (may be given over 2 days). A single dose of rituximab will be given 5 days after completion of the high dose of IVIg. DSA will be measured at multiple timepoints during visit 2, and at all following visits. On day 29 and 180 kidney biopsies will be performed.
- 10 patients will be randomized to be treated with 5-10 sessions of PEs. The 10 patients will start the treatment with PEs at visit 2. After the last PE session, the 10 patients will be given high dose IVIg (may be given over 2 days). A single dose of rituximab will be given 5 days after completion of the high dose of IVIg. DSA will be measured at multiple timepoints during visit 2, and at all following visits. On day 29 and 180 kidney biopsies will be performed.

Figure 1 and 2 below shows a summarized outline in the study for the imlifidase arm and PE arm.

Figure 1: Overall study outline imlifidase arm

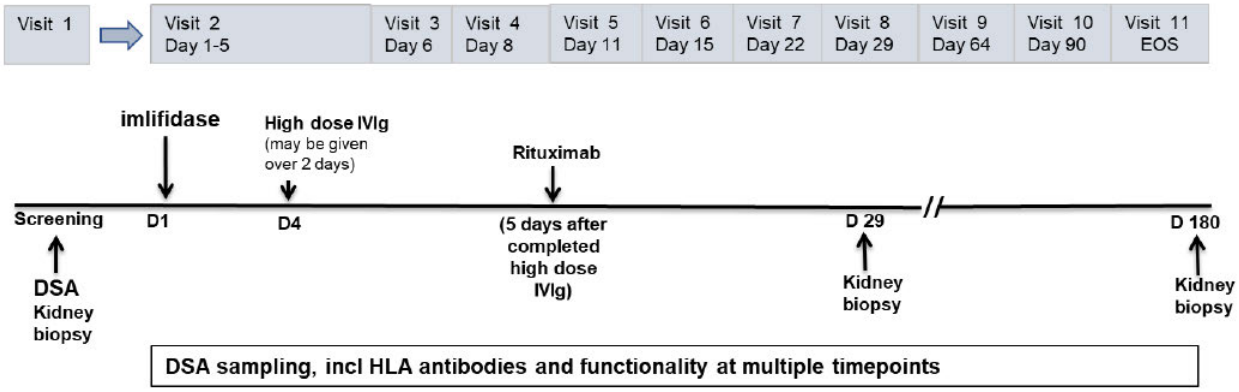
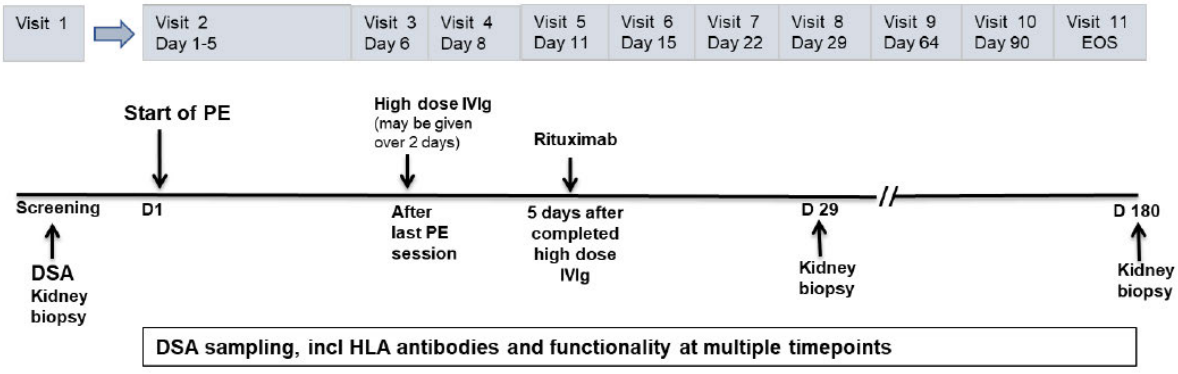


Figure 2: Overall study outline PE arm



2.1 Overview of study procedures

2.1.1 Flow Chart imlifidase arm

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

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

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

[a] Sample will be taken pre-dose but no need to wait for result before start of treatment
[b] One DSA sample will be sent to local lab for evaluation for inclusion and one DSA sample will be collected for central analysis at Hansa Biopharma
[c] One piece of tissue will be sent to local pathology lab and one piece of tissue will be sent for analysis at [redacted] If kidney biopsy is performed prior to screening, a piece of tissue cannot be sent for [redacted] analysis unless site stores tissue in mRNA later as standard of care. Then the tissue may be sent for [redacted] analysis after informed consent is signed.
[d] Rituximab will be given 5 days after completed high dose of IVIg

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

Visit Number	**2**									
Time	Pre-dose	Treat-ment	30 min	1 h	2 h	6 h	24 h	48 h	72 h	96 h
Assessment /Time window			±10 min	±10 min	±15 min	±30 min	±2h	±2h	±6h	±6h
Blood pressure and pulse rate	X				X	X	X	X	X	X
Respiratory frequency	X						X	X	X	X
Body temperature	X						X	X	X	X
Safety laboratory tests (incl creatinine)							X	X	X	X
Methylprednisolone/ prednisolone[a]	X						X	X	X	X
Antihistamine	X									

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

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

2.1.2 Flow Chart PE arm

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

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Type of visit	**Screening**	**Treat-ment**	**Assessments**								**FU/End of study**
Day		**1-5**	**6**	**8**	**11**	**15**	**22**	**29**	**64**	**90**	**180**
Assessment /Time window			0	0	±2d	±2 d	±3 d	±3 d	±7d	±7d	±14d
Informed Consent	X	See									
Demographics	X										
Medical/surgical history, incl transplantation and previous AMRs	X										

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Type of visit	**Screening**	**Treat-ment**	**Assessments**								**FU/End of study**
Day		**1-5**	**6**	**8**	**11**	**15**	**22**	**29**	**64**	**90**	**180**
Assessment /Time window			0	0	±2d	±2 d	±3 d	±3 d	±7d	±7d	±14d
Record historical creatinine values	X										
Record number of pregnancies *(if applicable)*	X										
Inclusion/exclusion criteria	X										
Randomization	X										
Physical examination	X										X
Height and weight	X										
Blood pressure and pulse rate	X		X	X	X	X	X	X	X	X	X
Respiratory frequency	X										
Body temperature	X		X	X	X	X	X	X	X	X	X
PCR test for SARS-CoV-2 virus	X										
ECG	X										X
Pregnancy test (serum)	X										X
Safety laboratory tests (incl creatinine for eGFR)	X		X	X	X	X	X	X	X	X	X
Urine sample for measurement of albumin/creatinine ratio	X		X	X	X	X	X	X	X	X	X
ADA (IgE)	X[a]										
DSA, incl HLA antibodies and functionality (*if applicable, taken before PE)*	X[b]		X	X	X	X	X	X	X	X	X
PK sampling			X	X	X	X					
PD sampling (*if applicable, taken before PE)*			X[d]	X[d,e]	X[d,e]	X	X	X	X	X	X
ADA(IgG)				X	X	X	X	X	X	X	X
Kidney biopsy	X[c]							X[c]			X[c]
Methylprednisolone /Prednisolone			Will be given according to treatment schedule (section 5.3 in protocols) and continue as long as prescribed by investigator								
Antibiotic prophylaxis			Treatment will continue until IgG levels return to acceptable values, as judged by the investigator								
High dose IVIg			High dose IVIg will be given after last PE session. Dose may be given over two days								
Rituximab				Will be given 3 to 4 days after completed high dose IVIg							

Visit Number	1	2	3	4	5	6	7	8	9	10	11
Type of visit	Screening	Treat-ment	Assessments								FU/End of study
Day		1-5	6	8	11	15	22	29	64	90	180
Assessment /Time window			0	0	±2d	±2 d	±3 d	±3 d	±7d	±7d	±14d
Concomitant medication and other treatment	Throughout the study										
Adverse events	Throughout the study										

[a] Sample will be taken pre-dose but no need to wait for result before start of treatment
[b] One DSA sample will be sent to local lab for evaluation of inclusion and one DSA sample will be collected for central analysis at Hansa Biopharma
[c] One piece of tissue will be sent to local pathology lab and one piece of tissue will be sent for analysis at [redacted] If kidney biopsy is performed prior to screening, a piece of tissue cannot be sent for [redacted] analysis unless site stores tissue in mRNA later as standard of care. Then the tissue may be sent for [redacted] analysis after informed consent is signed.
[d] If high dose IVIG is given, the PD sample must be taken prior to IVIg.
[e] If high dose IVIg is completed and there is no scheduled PD sample at the latest the following day, an additional PD sample will be taken

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

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

Visit Number	**2**									
Time	**Pre-dose**	**Treat-ment**	**30 min**	**1 h**	**2 h**	**6 h**	**24 h**	**48 h**	**72 h**	**96 h**
P-creatinine *(for calculation of eGFR)*	X									
Urine sample for measurement of albumin/creatinine ratio	X						X	X	X	X
PE		X								
Concomitant medication and other treatment	Throughout the visit									
Adverse events	Throughout the visit									

a) Methylprednisolone/prednisolone will be given according to the treatment schedule in Section 5.3 in section 5.3 in the protocols

2.2 Determination of sample size

No formal calculation has been done for the sample size. A sample size of totally 30 patients is chosen where 20 patients are treated with imlifidase and 10 patients are treated with PE.

The standard deviations for the two previous studies 14-HMedIdeS-04 and 15-HMedIdeS-06 can be considered to argue for the sample size of 30 patients. The standard deviations for the reduction of the IgG were 6% in the 14-HMedIdeS-04 and 4% in the 15-HMedIdeS-06 study. If the standard deviations are assumed to be similar in this study, it will give approximately an 8% point wide Confidence Interval (CI) when the sample size on 10+20 patients are considered. The 8% point wide of the CI is an acceptable wide and therefore the sample size on 30 patients can be used.

2.3 Blinding

The study is an open-label study. The study is fully unblinded.

2.4 Randomisation

The 30 patients will be allocated to the treatments by using block randomization. The randomizing will be 2:1 where 20 patients are treated with imlifidase and 10 patients are treated with PE. No stratification is used in this study.

2.5 Data pre-processing

The export data sets from the Larix data management Trial Master (TM) will be transformed into Study Data Tabulation Model (SDTM) structure and format following the implementation guide version 3.3 (current version) and also following "Therapeutic Area Data Standards User Guide for Kidney Transplant Version 1.0 (Provisional)". Analysis Data Model (ADaM) data sets will be prepared based on the SDTM data sets following implementation guide version 1.1 (current version). Tables, figures, and listings will be prepared from the ADaM data sets.

3 Analysis sets

Every patient will be classified according to the below definitions of the Full analysis set (FAS), Per-Protocol analysis set (PPS), Safety analysis set (SAF) and Pharmacokinetic analysis set (PKS). The analysis sets will be determined at the data review prior to database lock. Decisions will be documented in the database lock minutes.

3.1 Full Analysis Set

FAS will consist of all patients treated with any amount of study medication. Patients will contribute to the analysis ‘as randomized’.

3.2 Per Protocol Analysis Set

PPS will include all patients in the FAS who have no major protocol deviations. Examples of major deviations are:

- Violations of inclusion/exclusion criteria
- The use of prohibited or discourage medication
- Gross violation of visit schedules

Patients will contribute to the analysis ‘as treated’.

3.3 Safety Analysis Set

The SAF consists of all treated patients that received any amount of study medication (imlifidase or PE). Patients will contribute to the analysis ‘as treated’.

3.4 Pharmacokinetic Analysis Set

PKS will include patients receiving any amount of imlifidase. It will also be further defined by the PK analyst taking admission criteria, protocol deviations and other non-compliance into consideration.

4 Statistical analyses and presentation of data

4.1 General considerations

In general FAS and PPS are used to efficacy data, SAF are used on safety data and PKS is used on Pharmacokinetics (PK) data.

4.1.1 Data presentation

No formal statistical hypothesis testing will be performed in this study.

The data will be presented descriptive and for some of the endpoints 95% confidence intervals for the treatment difference will be presented.

Numerical data will be presented in summary tables by number of patients, arithmetic mean, median, standard deviation (SD), minimum and maximum.

When numerical data are recorded at different time points, absolute values at each time point and changes from baseline may be presented in the summary tables.

Categorical data will be presented by frequency and percent of patients. Number of events will also be reported where applicable.

Summary tables will in general be presented by treatment group and total across treatment groups unless this is not appropriate for specific tables.

Data will be listed by treatment group, patient and time point (if applicable).

4.1.2 Baseline definition

Baseline value is defined as the last non-missing assessment before the patients start on the treatment. Change from baseline will be calculated as the difference between values for a given timepoint after baseline and baseline values (timepoint after baseline value minus baseline value). If the post-baseline value or baseline value are missing, then the change from baseline will also be missing.

4.1.3 Multiplicity

The study is descriptive so no multiple testing will be done. This study will not include any interim analyses.

4.1.4 Data imputation

In general, missing data will remain as missing and the missing values will not be adjusted. There are some exceptions described below.

Adverse events

Missing values will be treated as missing except for causality, toxicity, intensity, seriousness and outcome of an AE, in which case a “worst case” approach will be taken. If causality is missing, it will be set to “related”. If intensity is missing, it will be set to “severe”. If seriousness is missing, it will be considered as a Serious Adverse Event (SAE). If outcome is missing and no date is given for the outcome it will set to “not yet recovered”.

Dates for adverse event and concomitant medication

Missing or partial start dates for AEs and concomitant medication data will be handled in the following way:

- If the start date is totally missing, the date will still be missing.
- If the start date is partial where only months and year are given, then the two cases are considered:
  1 If the available partial date (month and year) is before the month and year of treatment start date, then the AE/medication will be considered as pre-treatment and the date will be imputed as the start (1st) of the month.
  2 If the available partial date does not indicate that the AE/medication has started before the treatment start, then the AE/medication will be considered as treatment emergent/concomitant. The date will be imputed as the start (1st) of the month (if the month is not same as that of the treatment start date) or treatment start date (if the month is same as the treatment start date).
- If the start date is partial where only the year is given, then the two cases are considered:
  3 If the available partial date (year) is clearly before the year of treatment start date, then the start date is imputed as start of the year (1st January YYYY).
  4 If the available partial date (year) is equal to or after the year of treatment start date, then the start date will be imputed as start of the year (1st January YYYY) (if the year is not same as that of the treatment start date) or treatment start date (if the year is same as the treatment start date).
- For the partial end dates, similar procedure will be used as for the start dates. The only difference is the imputation for missing days and months. Missing days is imputed to the end of the month instead of the start of the month. If only year is available, the end date is set to 31st December YYYY. It will be checked that the imputed end dates fall after the corresponding start dates.

All completely missing end dates will be missing.

4.2 Patient disposition

The summary table for patient disposition will be presented in the following way:

The number of patients screened, the number of patients in the FAS, PPS, PKS and SAF analysis sets, completers and withdrawals with reason for withdrawal will be summarised with frequency and percentage by treatment.

The patient disposition will also be listed by patient.

The patients screened but not allocated to treatment will be presented with the reason(s) for screening failure in a listing.

4.3 Protocol deviations

Deviations from the protocol, as continuously tracked by investigator and sponsor, will be classified as ‘minor’ or ‘major’. The final classification of the deviations will be done before the database lock.

All protocol deviations will be summarised with frequency and percentage for each category of protocol deviation. The FAS dataset will be applied. The protocol deviations will also be listed by patient.

4.4 Demographics and other baseline characteristics

The following demographic variables will be summarised by treatment: Age, sex, race, height, weight and Body Mass Index (BMI). The table will be made for FAS. The demographics variables will also be listed by patient.

Medical and surgical history and concomitant illness will be summarised by using latest effective version of Medical Dictionary for Regulatory Activities (MedDRA), System Organ Class (SOC) and Preferred Term (PT). The FAS dataset will be used. Medical and surgical history and concomitant illness will also be presented in a list by patient.

Only concomitant medication during the treatment will be tabulated by World Health Organization (WHO) drug version 153E, level 4 (chemical/therapeutic/pharmacological subgroup) and level 5 (Chemical substance). The FAS dataset will be used. Concomitant medication during the treatment and before the start of the treatment will be presented in a list.

Previous kidney transplant history will be presented in a summary table by treatment and listed by patient. The FAS set will be used.

The donor type (living or deceasing) will be listed by patient.

4.5 Compliance and exposure

A summary table will be presented for exposure. In the table we will have the total dose and percentage of planned dose. The time point for IVIg and Rituximab will also be included in the table. Compliance and the drug exposure will be presented in a list by patient. The list will show start date of treatment, end date of treatment, number of doses or sessions (as applicable), planned dose and actual dose.

4.6 Efficacy

4.6.1 Primary efficacy analysis

The primary endpoint is the maximum reduction in DSA at any time point during 5 days following start of treatment. No formal statistical hypothesis will be tested for the primary endpoint. The FAS and PPS set will both be used for the primary endpoint. The primary endpoint will be calculated as part of the ADaM programming.

The DSAs are given as levels of mean fluorescence intensity (MFI) and genetic region of interest. These parameters are used to calculate the reduction in DSA for individual patients in the following steps:

1) Determine the DSAs having MFI levels larger than or equal to 1000 at baseline for the considered patient. Calculate DSA_0 as the sum of these MFI levels.
2) Calculate DSA_t for each patient as the sum of the MFI levels for the time point t, using the DSAs from step 1.
3) The reduction (%) is calculated as $100\times(DSA_0 - DSA_t)/DSA_0$ for each patient and time point. In the formula DSA_t is the total MFI level at time t.
4) The time point with maximum reduction within 5 days is found and chosen for each patient.

5) The maximum reduction per patient is a single value as the primary endpoint for the patient.

The difference in reduction between the two treatments will be presented with 95% CI in a table. The confidence interval for the difference in the reduction is found by using an Analysis of variance (ANOVA) model with treatment as fixed effect.
The reduction of DSAs calculated per patient will also be presented in a summary table by treatment and visit and presented in a mean plot by treatment and time point. The maximum reduction per patient will be listed by patient.
If the normality assumption is violated, sensitivity analyses using transformations of the primary endpoint will be performed.

4.6.2 Secondary efficacy analyses

DSA levels up to 180 days after treatment
DSAs will be measured using SAB-HLA assay and a functional assay e.g. C1q or C3d assay. A summary table for the C1q assay will be generated for the sum of MFI levels for DSAs from step 1 for primary endpoint (see Section 4.6.1) by treatment and time point. MFI levels will be listed per patient and time point. Spaghetti plots will show the DSA level versus time for each patient. A mean plot by treatment and time point will be presented.
A list with all DSA by patient and time point will be presented.

HLA-antibodies levels up to 180 days after treatment
Patient listings of MFI values for all HLAs will be presented.

Kidney function change from baseline
The kidney function will be evaluated by the parameters eGFR, P-creatinine and albumin/creatinine ratio in urine. The laboratory parameters will be summarised as part of the safety data tabulation.

The eGFR will be calculated as a part of ADaM programming, using the Modification of Diet in Renal Disease Study (MDRD) equation (2):

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}),$$

where Cr stands for creatinine value and Age are measured in years from birth to screening visit. This formula assumes that Cr is given in the mg/dL unit.

Proportion of patients with graft loss at day 180
The number of patients with graft loss at day 180 will be handled as a binary variable. Graft loss is defined as permanent return to dialysis for at least 6 weeks, re-transplantation, or transplantectomy. The endpoint is a success if the patients have absence of graft loss at day 180. The proportion of patients, which satisfy the success criterium, will be summarized by treatment and listed by patient. The FAS set will be applied.

Signs of transplant glomerulopathy 180 days post treatment
Possible transplant glomerulopathy 180 days post treatment will be handled as a binary variable. The endpoint is a success if the patients have no possible transplant glomerulopathy 180 days post treatment. The proportion of patients, which satisfy the success criterium, will be tabulated by treatment. A list will also be created by patient. The FAS set will be applied.

Change from baseline in histopathology per Banff Criteria at 29 and 180 days
Kidney biopsies will be assessed according to the Banff (2017 or later version) criteria pre-dose and at day 29 and 180. The biopsy data are measured as scores. The scores will be presented by time point in

a summary table. The change from baseline will be summarised by treatment, Banff lesion score and time point.

The overall interpretations for the biopsies will be presented in a summary table by time point. Shift tables will also be presented for overall interpretation from the biopsies. The possible categories for the overall interpretation are: Active AMR, Chronic Active AMR, CMR, Borderline CMR and No rejection. Possible combinations for the overall interpretation are: Active AMR + CMR, Active AMR + Borderline CMR, Chronic Active AMR + CMR and Chronic Active AMR + Borderline CMR.

A list will also be presented by patient where the scores and diagnosis are presented.

Change from baseline in mRNA levels in kidney biopsies evaluated by [redacted] at 29 and 180 days from baseline

[redacted] data will be presented in a summary table and in a list for day 29 and day 180. The [redacted] data is also given as score. The change from baseline will also be presented in a summary table. If baseline data is not available for [redacted], only the values on day 29 and 180 will be presented.

Number of sessions with PE for 180 days

The number of PE and immunoadsorption (IA) sessions within 180 days will be summarized by treatment and listed by patient. In addition, the number of PE and IA sessions after start of IVIg administration and up to 180 days after start of study treatment will be summarized by treatment. The FAS set will be applied.

Total serum IgG over time

The FAS set will be applied when analysing total serum IgG.

The IgG levels in serum will be analyzed centrally by a validated ECL based immunoassay using the Meso Scale Diagnostic technology. The total serum IgG levels will be summarized by time point. Total serum IgG levels will also be presented by mean and spaghetti plots. Finally, data will be listed by patient.

In addition, the reduction of total serum IgG levels will be analyzed as a binary endpoint. The binary endpoint is defined as a success, if the minimum IgG value at any time point during the 5 days following the start of treatment is less than 5% of baseline for the patient. The proportion of patients, which satisfy the success criterium, will be presented in a summary table by treatment. The difference in proportion between the two treatments will be presented with a 95% CI in a summary table. The 95% CI for the difference between the two treatments will be based on exact Confidence Limits. In addition, the proportion of patients which satisfy the success criterium will be presented by treatment and time point.

The composition of IgG-fragments will be analyzed centrally using SDS-PAGE. Each sample will be assigned a score depending on the observed composition of fragments as follows:

0=no intact IgG, scIgG or $F(ab')_2$
1=only $F(ab')_2$
2=mix of scIgG and $F(ab')_2$
3=only scIgG
4=mix of intact IgG and scIgG
5=only intact IgG

SDS-PAGE scores will be summarized by time point.

Presence of intact IgG on SDS-PAGE until start of IVIg treatment

The endpoint is a success for a patient if no detectable intact IgG is found by the SDS-PAGE assay for at least one time point between the start of study medication (imlifidase) treatment and start of administration of IVIg. No detectable intact IgG is defined as SDS-PAGE scores 0, 1, 2 or 3. The

proportion of patients, who reached the success criterium, will be summarized in a table using the PKS set.

Number of patients with resolution of AMR at day 180
The number of patients with resolution of AMR at day 180 will be handled as a binary variable. Resolution is defined as "Active AMR" or "Chronic active AMR" not being selected from the biopsy protocol.
The endpoint is a success if the patients have resolution of AMR at day 180. The proportion of patients, which satisfy the success criterium, will be tabulated by treatment. A list will be created by patient. The FAS set will be applied.

Patient survival at day 180
The patient survival on day 180 will be handled as a binary variable.
The endpoint is a success if the patients have survived on day 180. The proportion of patients, which satisfy the success criterium, will be summarized and listed by patient. The FAS set will be applied.

Pharmacokinetic
The Pharmacokinetic (PK) characteristics of imlifidase will be analyzed using the PKS. Imlifidase concentration in serum will be analyzed centrally using a validated electrochemiluminescence (ECL) based immunoassay (Meso Scale Diagnostic) technology. Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalysis report.

The PK parameters will be calculated by non-compartmental analysis (NCA) and/or compartmental analysis using the software WinNonlin (Pharsight Corporation, USA). Actual sampling time points relative to dosing will be used for the calculation and on the individual plots of plasma concentration versus time. Plasma concentration values missing (e.g., no blood sample collected, or no value obtained at analysis) will be excluded from the calculations. Values below lower limit of quantification (LLQ) will be represented by '0' (zero) in the 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, and V_z.

Imlifidase concentrations will be listed by patient, visit and time point. Imlifidase concentrations will also be presented in a summary table by time point. PK parameters including but not limited to AUC, C_{max}, t_{max}, $t_{½}$, CL, and V_z, will be listed by patient and visit, by treatment arm, and summarized with number of measurements, arithmetic mean, standard deviation, percentage coefficient of variation (%CV) (arithmetic), median, minimum, maximum, geometric mean, and %CV (geometric mean). For $t_{½}$, the harmonic mean, median, minimum, and maximum will be presented, and for t_{max} only the median, minimum, and maximum will be displayed.

Further, the PK concentrations will be presented graphically as mean profile plots and as spaghetti (individual lines) plots. Semi-log format with log10 on the y-axis and a linear time on the x-axis will be presented in the plots. Linear-linear plots may also be presented.

4.6.3 Additional analyses

No additional analyses are applied.

4.7 Safety

Safety parameters will be evaluated for the safety analysis data set.

4.7.1 Adverse events

Adverse events (AEs) will be classified according to the latest effective version of MedDRA.

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

An AE overview summary table will be prepared including the number of patients reporting an AE, the percentage of patients (%) with an AE, and the number of events (E) reported for the following categories:

- TEAEs
- Related TEAEs (TEAEs considered to be possibly or probably related to IMP as judged by the investigator)
- Related Serious TEAEs
- Deaths
- Treatment-emergent Serious Adverse Events (SAEs)
- TEAEs leading to withdrawal
- Severe and life-threatening AEs

Treatment-emergent AEs will be summarised in a table by dictionary level, i.e., System Organ Class (SOC) and Preferred Term (PT) for MedDRA. The table will display the total number of patients reporting a TEAE, the percentage of patients (%) with a TEAE and the number of events (E) reported. TEAEs will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence. For the summary tables the SAF set will be applied.

Summary tables will be prepared for:

- All TEAEs
- TEAEs by causality (related/unrelated)
- TEAEs by intensity
- Related TEAEs by intensity
- SAEs
- SAEs by causality (related/unrelated)
- Treatment-emergent SAEs
- Treatment-emergent SAEs by causality (related/unrelated)

- Treatment-emergent SAEs leading to death
- TEAEs leading to withdrawal

Data listings will be provided for:

- All TEAEs sorted by patient number
- All TEAEs sorted by MedDRA SOC and PT
- SAEs
- Treatment-emergent SAEs
- Treatment-emergent SAEs leading to death
- TEAEs leading to withdrawal
- Pre-treatment emergent AEs
- Post-treatment emergent AEs

4.7.2 Other safety endpoints

The clinical safety laboratory tests, vital signs, and ECG parameters will be summarised for both absolute values and changes from baseline by treatment and time point. The SAF set will be applied. The parameters will also be listed by patient. Values outside the reference ranges will be flagged in listings.

A list for physical examination will be created.

The results for the Polymerase Chain Reaction (PCR) tests for SARS-CoV-2 and pregnancy tests will be listed by patient.

Anti-imlifidase antibody data (ADA) is numerical and will be summarized by time point in a summary table, where PKS is used. Anti-imlifidase antibody data will also be presented graphically as boxplots and listed by patient.

4.8 Other endpoints

No other endpoints are included in the study.

5 Deviations from protocol analysis

The primary endpoint from the protocol was: “Maximum reduction in mean DSA level at any time point during the 5 days following the start of treatment.” This has been changed to: “Maximum reduction in DSA level at any time point during the 5 days following the start of treatment” to avoid a misinterpretation that it is a mean across patients.

The Western blot is not applied for detectable intact IgG. Instead, the scoring is done on the SDS-PAGE where the scores 0, 1, 2, 3 mean no detectable intact IgG. The Western blot does not generate any quantifiable data as SDS-PAGE does. Therefore, it is not applied in the analyses.

The difference in proportion between treatments and 95% CI are not done for detectable intact IgG. The treatment group (not including imlifidase) will only generate score 5. Therefore, no additional information will be gained by comparing the two groups.

The time for the endpoint “Presence of intact IgG on SDS-PAGE until start of IVIg treatment”, also referred to as “Detectable intact IgG on a Western blot” in protocol, is changed. Instead of over 180 days, the endpoint is considered between the start of treatment and start of administration of IVIg. This is changed because the high dose IVIg will lead to detectable intact IgG, i.e. no meaningful conclusions on remaining intact IgG can be drawn after the administration on IVIg.

PKS is updated to only include patients treated with imlifidase. Blood samples will still be taken as planned for central analysis for non-imlifidase patients, but no portion will be used for PK and ADA analysis, as this is not applicable for non-imlifidase patients.

IA has been added to the endpoint “Number of sessions with PE within 180 days” as it is used for the same purpose as PE.

6 Quality control

SDTM data sets will be generated by programs in SAS software by reading in lab data and export data from Trial Master and converting to SDTM formats following the SDTM specifications. The QC will include:

- Independent Code review
- CRF annotation review vs SDTM content
- Direct QC of input vs output in SDTM on a sample of data
- Apply the Pinnacle 21 validator for STDM and ADAM

This three-pronged approach has proven to give a high-quality level corresponding to the expected for SDTM data

ADaM data sets will be based on the SDTM data sets. The programming of the ADaM datasets will be performed in SAS and the programs will be reviewed by an independent person.

Tables, listings and figures (TLF) will be created by SAS programs and based on the ADaM data sets. Summary TLFs will be QC'ed by independent code review.

On top of the actual code review for ADaM and TLF, the review includes check of execution, error log, check for warnings and important notes, and check of output. On top of reviewing individual programs and output items, an integrated review of all output will be performed by a reviewer. Since there are no formal statistical analyses, double programming will not be applied in this study.

The programming and execution of programs for producing data sets and tables, figures and listings follow the Larix SOPs 701, 702 and 703 on standard programs, programming environment and single use programs respectively.

SAS version 9.4 or later will be used for data handling and presentation.

7 Layout of output

The output will follow Larix standard output templates. Tables and listings will first be prepared as individual RTF (Rich text format, which is a standard text format) files. This file type may be opened and saved in the currently available Microsoft Word versions. Graphical output will be prepared in PNG (Portable network graphics) format, which is the standard graphical format in current Microsoft software packages and therefore easily importable into Microsoft Word documents.

Tables and figures will per default be created in portrait format while listings will be in landscape format. Margins and font will be chosen to respect the requirements for filing with EMA (European medicines agency) and FDA (the US Food and drug administration).

The output items (tables, listings, figures) will be collected in Word documents. Separate Word documents will be created for tables, figures and listings respectively.

An overview of the relevant tables, listings and figures can be seen in section 8 in this SAP.

8 Tables, Listings and figures

The table below gives an overview over planned output for the study:

		BASELINE AND DEMOGRAPHIC DATA
14.1.1	Table	Patient disposition, including reason for discontinuation
14.1.2	Table	Protocol deviations (FAS)
14.1.3	Table	Demography and body measurements (FAS)
14.1.4	Table	Medical and surgical history (FAS)
14.1.5	Table	Concomitant medication (FAS)
14.1.6	Table	Previous kidney transplant history (FAS)
14.1.7	Table	Exposure (FAS)
		EFFICACY DATA
14.2.1	Table	Difference in maximum DSA reduction and 95% CI (FAS)
14.2.2	Table	Difference in maximum DSA reduction and 95% CI (PPS)
14.2.3	Table	DSA reduction - by time point (FAS)
14.2.4	Table	DSA reduction - by time point (PPS)
14.2.5	Table	MFI levels for DSA c1q - by time point (FAS)
14.2.6	Table	Proportion of patients with absence of graft loss at day 180 (FAS)
14.2.7	Table	Proportion of patients having no signs of transplant glomerulopathy at day 180 (FAS)
14.2.8	Table	Kidney biopsy (Banff) - Scores - by time point (FAS)
14.2.9	Table	Kidney biopsy (Banff) - Change from baseline (scores) - by time point (FAS)
14.2.10	Table	Kidney biopsy (Banff) - Interpretations - by time point (FAS)
14.2.11	Table	Kidney biopsy (Banff) - Shift table - by time point (FAS)
14.2.12	Table	Kidney biopsy ([redacted]) - Scores - by time point (FAS)
14.2.13	Table	Kidney biopsy ([redacted]) - Change from baseline - by time point (FAS)
14.2.14	Table	Number of sessions of PE and IA for 180 days (FAS)
14.2.15	Table	Total IgG - by time point (FAS)
14.2.16	Table	Proportion of patients having reduction in total IgG - by time point (FAS)
14.2.17	Table	Composition of IgG-fragments (SDS-PAGE) - by time point (FAS)
14.2.18	Table	Proportion of patients having no detectable intact IgG (PKS)
14.2.19	Table	Proportion of patients with resolution of AMR at day 180 (FAS)
14.2.20	Table	Patient survival at day 180 (FAS)
14.2.21	Table	Summary of imlifidase (PK) concentrations - by time point (PKS)
14.2.22	Table	Summary of imlifidase PK parameters (PKS)
		DISPLAYS OF ADVERSE EVENTS
14.3.1	Table	Overview of treatment-emergent AEs (SAF)
14.3.2	Table	Summary of treatment-emergent AEs - by SOC and PT (SAF)
14.3.3	Table	Summary of treatment-emergent AEs - by causality (SAF)

14.3.4	Table	Summary of treatment-emergent AEs - by intensity (SAF)
14.3.5	Table	Summary of related treatment-emergent AEs - by intensity (SAF)
14.3.6	Table	Summary of SAEs (SAF)
14.3.7	Table	Summary of SAEs - by causality (SAF)
14.3.8	Table	Summary of treatment-emergent SAEs (SAF)
14.3.9	Table	Summary of treatment-emergent SAEs - by causality (SAF)
14.3.10	Table	Summary of treatment-emergent SAEs leading to death (SAF)
14.3.11	Table	Summary of treatment-emergent AEs leading to withdrawal (SAF)
		DISPLAYS OF SAFETY DATA
14.4.1	Table	Summary of clinical chemistry variables - by time point (SAF)
14.4.2	Table	Summary of haematology variables - by time point (SAF)
14.4.3	Table	Summary of coagulation variables - by time point (SAF)
14.4.4	Table	Summary of vital signs - by time point (SAF)
14.4.5	Table	Summary of ECG - by time point (SAF)
14.4.6	Table	Summary of anti-IdeS IgG (ADA) - by time point (PKS)
		EFFICACY FIGURES
15.1.1	Figure	DSA reduction vs time (FAS)
15.1.2-15.1.31	Figure	Individual plots DSA vs time (FAS)
15.1.32	Figure	Mean plot DSA level - by time point (FAS)
15.1.33	Figure	Individual IgG cleavage (PD) 0-180 days - by patient profiles (FAS)
15.1.34	Figure	Individual IgG cleavage (PD) 0-96 hours - by patient profiles (FAS)
15.1.35	Figure	Mean IgG cleavage (PD) - 0-180 days (FAS)
15.1.36	Figure	Mean IgG cleavage (PD) profile - 0-96 hours (FAS)
15.1.37	Figure	Mean log scale imlifidase concentration profiles (0-14 days) (PKS)
15.1.38	Figure	Mean log scale imlifidase concentration profiles (0-96 hours) (PKS)
15.1.39	Figure	Individual log scale PK concentration (0-14 days) - by patient profiles (PKS)
15.1.40	Figure	Individual log scale PK concentration (0-96 hours) - by patient profiles (PKS)
15.1.41	Figure	Anti-imlifidase IgG (ADA) - box plot (PKS)
		PATIENT DATA LISTINGS
		BASELINE AND DEMOGRAPHIC DATA
16.1.1.1	Listing	Patient disposition – by patient
16.1.1.2	Listing	Patients withdrawn from study – by patient
16.1.1.3	Listing	Protocol deviations - by patient (FAS)
16.1.1.4	Listing	Demography – by patient (FAS)

16.1.1.5	Listing	Medical and surgical history – by patient (FAS)
16.1.1.6	Listing	Concomitant medication – by patient (FAS)
16.1.1.7	Listing	Previous medication – by patient (FAS)
16.1.1.8	Listing	Previous kidney transplant history and donor type – by patient (FAS)
16.1.1.9	Listing	Compliance and exposure to study drug – by patient (FAS)
16.1.1.10	Listing	Compliance and exposure to IVIg – by patient (FAS)
16.1.1.11	Listing	Compliance and exposure to Rituximab – by patient (FAS)
		INDIVIDUAL EFFICACY RESPONSE DATA
16.2.1.1	Listing	DSA reduction - by patient and time point (FAS)
16.2.1.2	Listing	MFI levels for DSA c1q - by patient and time point (FAS)
16.2.1.3	Listing	All DSA - by patient and time point (FAS)
16.2.1.4	Listing	SAB-HLA MFI values - by patient and time point (FAS)
16.2.1.5	Listing	Patients with graft loss at day 180 - by patient (FAS)
16.2.1.6	Listing	Transplant glomerulopathy at day 180 - by patient (FAS)
16.2.1.7	Listing	Kidney Biopsy score and diagnose (Banff) - by patient and time point (FAS)
16.2.1.8	Listing	Kidney Biopsy score [redacted] - by patient and time point (FAS)
16.2.1.9	Listing	PE sessions and IA sessions for 180 days - by patient (FAS)
16.2.1.10	Listing	Total IgG - by patient and time point (FAS)
16.2.1.11	Listing	IgG scores - by patient and time point (FAS)
16.2.1.12	Listing	Resolution of AMR at day 180 - by patient (FAS)
16.2.1.13	Listing	Patient survival at day 180 - by patient (FAS)
16.2.1.14	Listing	Imlifidase (PK) concentration - by patient and time point (PKS)
16.2.1.15	Listing	Imlifidase (PK) parameters - by patient (PKS)
		ADVERSE EVENT LISTINGS
16.3.1.1	Listing	Treatment-emergent AEs - by patient (SAF)
16.3.1.2	Listing	Treatment-emergent AEs - by SOC and PT (SAF)
16.3.1.3	Listing	SAEs (SAF)
16.3.1.4	Listing	Treatment-emergent SAEs (SAF)
16.3.1.5	Listing	Treatment-emergent SAEs leading to death (SAF)
16.3.1.6	Listing	Treatment-emergent AEs leading to withdrawal (SAF)
16.3.1.7	Listing	Pre-treatment emergent AEs (SAF)
16.3.1.8	Listing	Post-treatment emergent AEs (SAF)
		LISTINGS OF SAFETY DATA
16.4.1.1	Listing	Clinical chemistry (1) - by patient and time point (SAF)
16.4.1.2	Listing	Clinical chemistry (2) - by patient and time point (SAF)
16.4.1.3	Listing	Clinical chemistry (3) - by patient and time point (SAF)
16.4.1.4	Listing	Haematology (1) - by patient and time point (SAF)
16.4.1.5	Listing	Haematology (2) - by patient and time point (SAF
16.4.1.6	Listing	Haematology (3) - by patient and time point (SAF
16.4.1.7	Listing	Coagulation - by patient and time point (SAF)
16.4.1.8	Listing	Vital signs - by patient and time point (SAF)
16.4.1.9	Listing	ECG - by patient and time point (SAF)

16.4.1.10	Listing	Physical examination - by patient and time point (SAF)
16.4.1.11	Listing	PCR test - by patient (SAF)
16.4.1.12	Listing	Pregnancy test - by patient (SAF)
16.4.1.13	Listing	Anti-Imlifidase IgG (ADA) - by patient and time point (PKS)
16.4.1.14	Listing	Anti-Imlifidase IgE (ADA) - by patient and time point (PKS)

9 References

1) Clinical study protocol 16-HMedIdes-12: A Randomized, Open-Label, Multi-Centre, Active Control Study Investigating the Efficacy and Safety of Imlifidase in Eliminating Donor Specific Anti-HLA Antibodies in the Treatment of Active Antibody-Mediated Rejection in Kidney Transplant Patients version 4.3, 5.3, 6.3, 7.3 and 8.3

2) Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9): 604-12

10 Change log

Version	Effective date	Reason for revision
1.0	29-Jun-2022	New document
2.0	29-Aug-2022	Changes in section 4.1.4 for imputation dates for concomitant medication and adverse events. Changes in title for figure 15.1.34 and 15.1.36 and section 8 is updated.