STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 1b/2 study to evaluate the safety, pharmacokinetics, and preliminary efficacy of isatuximab (SAR650984) in patients awaiting kidney transplantation (Amendment 2)**
Protocol number:	**TED16414**
Compound number (INN/Trademark):	**SAR650984 isatuximab/SARCLISA**
Study phase:	**Phase 1/Phase 2**
Short title:	**Safety, pharmacokinetics, and preliminary efficacy of isatuximab in patients awaiting kidney transplantation**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study TED16414 is based on the protocol amendment #2 dated 01-Feb-2022. This section summarizes the major changes to the statistical analysis features in the SAP.

The first participant was enrolled on 22-Jun-2020. The first interim analysis was performed on 26-Aug-2021.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	22-Apr-2021	Not Applicable	Original version
2	Current version	Criteria for cPRA reduction is corrected from “at least 50% increase of likelihood” to “at least 100% increase of likelihood”.	To clarify that the target cPRA is defined as achieving at least 100% increase in the likelihood of finding a compatible donor, but this will not affect any mathematical derivations/calculations already in place.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 1b/2 open-label, non-randomized, multi-center study to evaluate the safety, pharmacokinetics (PK), and preliminary efficacy of isatuximab in patients awaiting kidney transplantation.

Patients sensitized to the human leukocyte antigen (HLA) with a high calculated panel reactive antibodies (cPRA) have low likelihood of finding a compatible donor. Currently no approved or standard therapy is available for desensitization. An effective desensitization therapy with a durable response has the potential to increase the likelihood for transplant candidates to find a compatible donor, reduce time on dialysis, and a better clinical outcome.

The study will be conducted in 2 phases (see Figure 1 for study design schema).

Phase 1 (safety run-in)

As the safety profile of isatuximab is well-established, Phase 1 (safety run-in) is designed to characterize the safety and tolerability of isatuximab in patients with chronic kidney disease (CKD), and to confirm the Phase 2 dose in this patient population. A minimum of 6 safety evaluable participants with cPRA ≥80% will be enrolled at the dose level to be tested without interruption in Phase 1. In order to be considered as safety evaluable, participants must have received at least 90% of the planned cumulative doses of the first cycle (unless they discontinue investigational medicinal product (IMP) due to pre-defined unacceptable toxicity).

Pre-defined unacceptable toxicity is defined as any verified Grade 4 adverse events (AEs) or laboratory abnormalities (except infusion reactions (IRs)) occurring during the first cycle of treatment, unless solely due to the underlying disease or due to a cause obviously unrelated to IMP, if confirmed by the Sponsor and recruiting Investigators.

The starting dose of IMP is 10 mg/kg QW for 4 weeks followed by Q2W. If the starting dose is determined not to be sufficiently well-tolerated, 6 additional (minimum) safety evaluable participants will be enrolled at dose level (DL) -1 (ie, 5 mg/kg QW for 4 weeks followed by Q2W) (see protocol Table 4 for details on the DLs and schedule for Phase 1).

Overall safety monitoring will also be performed throughout the conduct of the study. The totality of the safety findings, including all AEs occurring during treatment, unless solely due to the underlying disease or due to a cause obviously unrelated to IMP, will be taken into consideration for confirming the Phase 2 dose. Phase 2 of the study will be initiated after 6 safety evaluable participants have completed first cycle observation period where the dose level is determined to be sufficiently well-tolerated.

Upon completion of the first cycle safety observation period for each participant enrolled in Phase 1, participants will continue study procedures until study completion.

Phase 2

Phase 2 is designed to assess preliminary efficacy of isatuximab in desensitizing HLA sensitized patients awaiting kidney transplantation, which includes assessing change in cPRA and anti-HLA antibody levels. Approximately 24 to 36 participants (Phase 1 and Phase 2) are expected to be enrolled if the starting dose (10 mg/kg) is retained as the Phase 2 dose, or approximately 30 to 42 participants are expected to be enrolled if DL-1 (5 mg/kg) is the Phase 2 dose.

In Phase 2, two cohorts will be included:

Cohort A: Participants with cPRA ≥99.90%; active candidates on the kidney waitlist. Up to 6 participants with living donor can be enrolled into Cohort A.

Cohort B: Participants with cPRA 80.00% to 99.89%; active candidates on the kidney waitlist with no living donor cleared for donation.

The study will have a screening period of up to 28 days, a treatment period of up to 12 weeks, a site visit follow-up period (FUP) of up to 26 weeks, and an extended FUP which include telephone contacts every 90 days and information collection until study cut-off, death, or lost to follow-up. The study cut-off is planned at 26 weeks after the last participant completes the treatment period, or when the last ongoing participant is lost to follow-up, whichever is earlier. The Sponsor (Sanofi) may choose to extend the study cut-off date depending on the enrollment rate observed to facilitate adequate follow-up data collection. Participants who wish to proceed to transplantation when a compatible donor becomes available while on study must discontinue IMP immediately, complete an early discontinuation (E/D) visit prior to transplantation if clinically feasible, and proceed to extended FUP. The study duration that involves site visit per participant (ie, screening, treatment, site visit FUP) will be approximately 42 weeks. The study duration including extended FUP per participant will be approximately 78 weeks (depending when the participant is enrolled).

Treatment period: The cycle duration is 28 days and a complete treatment period is comprised of 3 cycles of IMP treatment. Participants will continue treatment until receiving 3 cycles of IMP, unacceptable AE per Investigator's judgment, or participants' decision to stop the treatment.

Site visit FUP: Participants completing the treatment period and who are able to remain on study will return to the study sites for study procedures.

Extended FUP: The following participants will be followed-up every 90 days by phone calls, until study cut-off date, death, or lost to follow-up, whichever comes first:

- Participants who completed or discontinued from site visit FUP
- Participants who proceed to transplantation during treatment period or site visit FUP.

During extended FUP, specified information per protocol will also be collected by study site (see protocol section 1.3).

Below figures show the study schema and duration of study period:

Figure 1 - Graphical study design

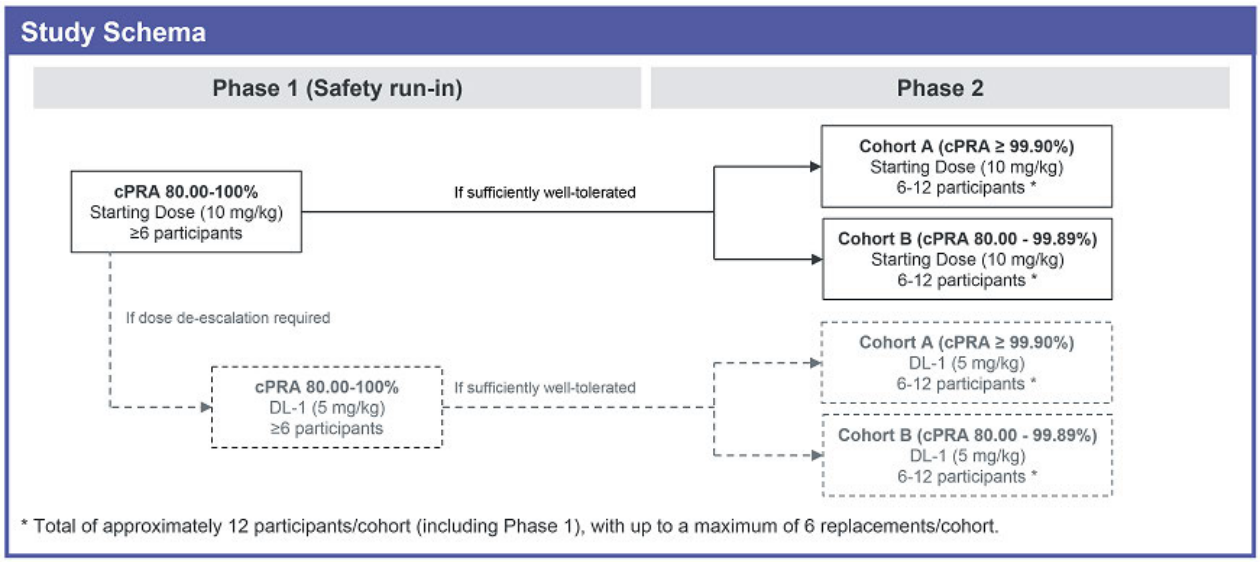
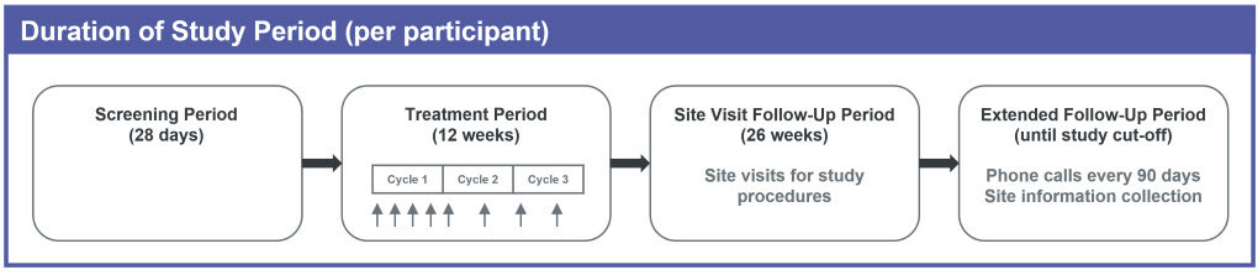


Figure 2 - Duration of study period (per participant)



Details on schedule of activities (SoA) are provided in protocol section 1.3.

1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Phase 1: To characterize the safety and tolerability of isatuximab in kidney transplant candidates. • Phase 2: To evaluate the efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	• AEs/serious AEs (SAEs) and laboratory abnormalities. • Response rate (RR defined as the proportion of participants meeting at least one of the predefined desensitization efficacy criteria, from baseline up to 26 weeks after treatment period, measured by single antigen bead (SAB) assay per central laboratory assessment as follows:

Objectives	Endpoints
	1. Reduction in cPRA resulting in at least 100% increase of likelihood of finding a compatible donor (for target cPRA, see protocol section 10.9). 2. Reduction in antibody titer (≥75% reduction from baseline) to achieve target cPRA (see protocol section 10.9). 3. Elimination of ≥1 anti-HLA-antibody (ie, mean fluorescence intensity [MFI] reduced to <2000) as measured by a SAB assay, for antibodies with baseline MFI ≥3000.
Secondary	
• Phase 2: To characterize the safety profile of isatuximab in kidney transplant candidates.	• AEs/SAEs, and laboratory abnormalities.
• To characterize the PK profile of isatuximab in kidney transplant candidates.	• PK parameters of isatuximab (see protocol Table 7)
• To evaluate the immunogenicity of isatuximab.	• Incidence of anti-drug antibodies (ADA) against isatuximab.
• To assess the overall efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	• Duration of response (DoR) per central laboratory assessment. • Proportions of participants and duration achieving target cPRA per local laboratory assessment. • Number of anti-HLA-antibody with baseline MFI ≥3000 reduced to <2000 as measured in a SAB assay per central laboratory assessment. • Transplantability including time to first transplant offer, time to transplant, and number of transplant offers, if applicable. • Time to first antibody mediated rejection (AMR) episode and rate of AMR, if applicable. • Graft survival at 6 months post-transplant, if applicable.
Tertiary/exploratory	
• To assess other preliminary efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	[redacted]
• To assess the biological effects of isatuximab on immune cell populations and identify potential predictive and/or PD biomarkers	[redacted]
• To perform PK/PD analysis.	[redacted]

1.2.1 Estimands

Primary estimand defined for the main efficacy endpoint is summarized in below Table 2.

Table 2 - Summary of primary estimand for main efficacy endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary efficacy objective: Phase 2: To evaluate the efficacy of isatuximab in desensitization of patients awaiting kidney transplantation				
Primary efficacy endpoint (Estimand 1)	Response rate	Efficacy-evaluable	Interruption/discontinuation of study intervention: Response rate will be analyzed regardless of intervention discontinuation (treatment policy)	Response rate, defined as proportion of participants meeting at least one of the predefined desensitization efficacy criteria, from baseline up to 26 weeks after treatment period and two-sided 95% confidence intervals using the Clopper-Pearson method (1)

2 SAMPLE SIZE DETERMINATION

Statistical hypotheses and sample size determination:

Phase 1: There is no formal statistical hypothesis. Approximately 6 to 12 safety evaluable participants are expected to be enrolled.

Phase 2:

- Null hypothesis: True RR[redacted]
- Alternative hypothesis: True RR [redacted]

With a minimum sample size of 12 participants per cohort and 1-sided alpha of 0.025, the analysis will have at least 80% power to demonstrate that RR is significantly better than [redacted] assuming the true RR is [redacted], based on exact test. A null hypothesis of [redacted] is selected representing placebo control as there is currently no approved or standard therapy for desensitization, and there is no expected decrease in anti-HLA antibody levels or cPRA in patients who do not undergo desensitization therapy.

A maximum of 6 replacements per cohort is allowed for participants who:

- enroll in Phase 1 and receive <90% of the planned cumulative doses within the first cycle (unless they discontinue IMP due to pre-defined unacceptable toxicity), or
- receive <75% of planned cumulative doses within 3 cycles, or
- have consecutive dose interruption of >28 days, or
- do not complete site visit FUP, after agreement with Medical Monitor.

Participants treated at the Phase 2 dose during Phase 1 will be included in the analysis together with the participants in Phase 2.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form (ICF).
Enrolled	Includes all participants from screened population who plan to continue in the treatment phase upon completion of screening, regardless of whether the study intervention (isatuximab) was received or not.
All treated	Includes all participants who receive at least 1 dose of isatuximab-. This population is the primary population for the analyses of safety parameters, unless otherwise noted. All analyses using this population will be based on the dose level actually received.
Safety-evaluable (Phase 1)	Includes all participants enrolled in Phase 1 who receive ≥90% planned cumulative doses of isatuximab within Cycle 1 (unless IMP is discontinued due to pre-defined unacceptable toxicity).
Efficacy-evaluable	Includes All Treated population who fulfill the study eligibility criteria, with an evaluable baseline and at least 1 evaluable postbaseline efficacy assessment and receive ≥75% of planned cumulative doses. This is the primary population for efficacy analyses.
PK	Includes All Treated population with at least 1 available concentration result post-treatment (whichever the cycle and even if dosing is incomplete) with adequate documentation of date and time of dosing and date and time of sampling.
ADA	Includes All Treated population with at least 1 available ADA result (negative, positive, or inconclusive) post-treatment (whichever the cycle and even if dosing is incomplete).

Participants exposed to isatuximab before or without being enrolled will not be considered enrolled and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Enrolled participants for whom it is unclear whether they took isatuximab will be considered as treated and will be included in the safety population.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants. Time to event variables will be analyzed using the Kaplan-Meier method.

The baseline value is defined as the last available value before the first dose of IMP. For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Analyses will be performed by cohort (and overall) within Phase 2, for demographics and baseline characteristics. If Phase 1 dose level is reduced due to unacceptable toxicities, summaries may also be performed on Phase 1 participants, by dose level group.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the time from when the participants give informed consent to first IMP administration.
- The **on-treatment period** (ie, treatment-emergent [TE] period) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the time starting 31 days after the last dose of IMP to study cut-off.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. If applicable, the number (%) of screen failures will be provided in the screened population.

Enrolled participants will include screened participants who plan to continue in the treatment phase, ie, those for whom the investigator ticked “Yes” to the question “Will the subject continue in the Treatment phase?” in the Completion of Screening eCRF page.

The number (%) of participants in the following categories will be provided:

- Screened participants, and screen failures (if applicable)
- Enrolled participants

- Enrolled but not treated participants
- Enrolled and treated participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for definitive treatment discontinuation
- Participants who completed the site visit follow-up period.
- Participants who did not complete the site visit follow-up period and main reason for site visit follow-up discontinuation
- Participants who completed the study/extended follow-up period.
- Participants who did not complete the study/extended follow-up period and main reason for study/extended follow-up discontinuation
- Participant status at last study contact

If applicable, the number (%) of treated but not enrolled participants will also be presented.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the enrolled and/or treated population.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

The primary endpoint in the Phase 1 portion of the study will focus on safety, ie, AEs/SAEs and laboratory abnormalities. Analysis details of these safety parameters are presented in Section 4.7.2 and Section 4.7.3.1.

In the Phase 2 portion of the study, the primary efficacy endpoint will be RR, to be defined as the proportion of participants meeting at least one of the predefined desensitization efficacy criteria, from baseline up to 26 weeks after treatment period, measured by SAB assay per central laboratory assessment as follows:

- Reduction in cPRA resulting in at least 100% increase of likelihood of finding a compatible donor for target cPRA
- Reduction in antibody titer (≥75% reduction from baseline) to achieve target cPRA
- Elimination of ≥1 anti-HLA-antibody (ie, MFI reduced to <2000) as measured by a SAB assay, for antibodies with baseline MFI ≥3000

RR criterion 1: target cPRA

The target cPRA, defined as the reduction of cPRA required to achieve at least 100% increase of likelihood of compatible donor (LCD), is calculated according to the following equation:

$$LCD = 1\ in\ \frac{1}{1 - cPRA}$$

Participants with baseline cPRA 100.00% will be assigned with cPRA 99.99% for computational purpose. In addition, cPRA values will be rounded to 2 decimal places prior to LCD calculation (≥xx.xx5=round up, <xx.xx5=round down).

RR criterion 2: antibody titer

Antibody titer is defined as the last dilution of serum at which positive results is obtained (eg, MFI ≥2000). To potentially meet the second RR criterion, serial dilution of the serum collected at baseline is performed until the target cPRA is achieved. If subsequent post-treatment serum is diluted at ≥75% reduction from the baseline dilution that achieved target cPRA, and again meet target cPRA anytime within the 26-week post-treatment period, participant will have met RR criterion 2.

RR criterion 3: anti-HLA-antibody

An anti-HLA-antibody is considered to be eliminated if its MFI is reduced to <2000 at post-treatment. Only antibodies with baseline MFI ≥3000 will be included for assessment under this criterion.

4.3.2 Main analytical approach

The primary efficacy analysis is based on a treatment policy estimand introduced in Section 1.2.1.

This primary estimand is defined according to the following attributes:

- The endpoint is RR, as defined in Section 4.3.1.
- The treatment condition of interest is isatuximab
- The analysis population is the efficacy-evaluable population (defined in Section 3)
- The study intervention interruption/discontinuation intercurrent event will be handled with the treatment policy strategy. RR will be assessed based on the 3 criteria irrespective of study intervention interruption/discontinuation.
- Population-level summary will be RR, defined as the proportion of participants meeting at least one of the predefined desensitization efficacy criteria (refer to Section 4.3.1), along with and two-sided 95% confidence intervals using the Clopper-Pearson method.

Proportion of participants meeting each criterion will also be tabulated.

Calculation details and examples on RR criteria 1 and 2 are provided in Appendix 4, Section 5.4.2 (DESENSITIZATION response criteria).

For RR criterion 3, elimination of anti-HLA-antibody will be determined for each applicable molecular specificity.

4.3.3 Sensitivity analysis

In addition to planned protocol analysis of the primary endpoint, if cohort assignment based on local laboratory's cPRA value collected at screening visit varies from the corresponding central laboratory's baseline cPRA value in greater than 10% of the efficacy-evaluable participants per cohort, a sensitivity analysis of the primary efficacy endpoint will be conducted assigning participants to the respective cohort based on the central laboratory's cPRA value.

4.3.4 Supplementary analyses

Not applicable.

4.3.5 Subgroup analyses

Not applicable.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Key/Confirmatory secondary endpoint(s)

No key/confirmatory secondary endpoint.

4.4.2 Supportive secondary endpoints

4.4.2.1 Definition of endpoints

The following secondary endpoints in the Phase 2 portion of the study are defined below, with the exception of PK parameters and immunogenicity/ADA against isatuximab which are described in Section 4.8.1 and Section 4.8.2, respectively:

DoR per central laboratory assessment

DoR (based on central laboratory assessment): defined as time from laboratory sample collection date used in determining a participant to be a responder up to the laboratory sample collection date when participant is no longer meeting any response criterion (ie, non-responder) or the date of death due to any cause, whichever occurs first.

For participants with ongoing response at the time of the analysis, DoR will be censored at the date of the last available laboratory assessment showing response. Non-responders will be excluded in the DoR summaries.

For responders meeting more than 1 criterion, DoR will be calculated from: [(earliest of start dates) up to (latest of end dates) + 1] across any response criteria durations.

For responders having multiple DoRs within the same criterion but with gaps, only the 1st DoR (or 1st set of DoRs for those meeting more than 1 criterion) will be summarized. A sensitivity analysis may be performed using the longest DoR (in lieu of 1st DoR), if applicable.

Proportion of participants and duration achieving target cPRA per local laboratory assessment (using OPTN-calculated and using locally reported cPRA values)

Proportion of participants achieving target cPRA: will be summarized separately for cPRA values, based on OPTN calculator and based on locally reported values

Duration of achieving target cPRA: defined as time from laboratory sample collection date of achieving target cPRA the first time up to the laboratory sample collection date when no longer achieving target cPRA or the date of death due to any cause, whichever occurs first.

Participants who retain their target cPRA values will be censored at the date of the last available laboratory assessment achieving their target cPRA. Participants who do not achieve target cPRA will be excluded from the analysis.

For participants with multiple durations (with gaps), only the 1st duration will be summarized. A sensitivity analysis may be performed using the longest duration (in lieu of the 1st duration), if applicable.

Refer to Section 5.4.2, Table 8 for a table of target cPRA.

Number of anti-HLA-antibody with baseline MFI ≥3000 reduced to <2000 as measured in a SAB assay per central laboratory assessment

Reduction of anti-HLA-antibody is defined similarly as in RR criterion 3 (Section 4.3.1), and will be summarized by the proportion of participants with pre-specified ranges of anti-HLA-antibody reduction (eg, none, 1-5, >5-10, >10-15, … >x).

Transplantability including time to first transplant offer, time to transplant, and number of transplant offers, if applicable

Time to first transplant offer: defined as time from date of first IMP dose up to date of first transplant offer. Study eCRF folder/page for transplant offer: TRANSPLANT/TRANSPLANT STATUS

Time to transplant: defined as time from date of first IMP dose up to date of kidney transplant on/after first IMP start date. Study eCRF FOLDER/page for date of kidney transplant surgery during study: TRANSPLANT/TRANSPLANT STATUS; KIDNEY TRANSPLANT SURGERIES [Transplant and Patient status subcategory=During study, and corresponding Date of kidney transplant]

Participants who do not receive any transplant offer or any transplant, and:

- who died will be censored at the longest follow-up date across all participants in the study prior to the analysis cut-off date.
- who are still alive will be censored at the participant's last laboratory assessment date collected in the study or at the analysis cut-off date, whichever is earlier.

Time to first AMR episode and rate of AMR (if applicable)

Time to first AMR: defined as time from date of first IMP dose up to date of biopsy with first AMR. Study eCRF FOLDER/page for date of biopsy with AMR: TRANSPLANT/GRAFT REJECTION BIOPSY

Transplanted participants without any AMR will be censored at the participant's last assessment/contact date collected in the study or at the analysis cut-off date, whichever is earlier. Participants who do not receive a transplant in the study will be excluded from this analysis.

Rate of AMR: defined as proportion of participants with AMR field ticked as "yes" based on graft rejection biopsy eCRF page. Study eCRF FOLDER/page for AMR: TRANSPLANT/GRAFT REJECTION BIOPSY

Graft survival rate at 6 months post-transplant (if applicable)

Graft survival rate at 6 months post-transplant: defined as proportion of participants with graft survival status at ≤6 months post-transplant="Functioning". Study eCRF FOLDER/page for date of biopsy with AMR: TRANSPLANT/GRAFT SURVIVAL AT LESS THAN OR EQUAL TO 6 MONTHS

In addition, the proportion of participants with a functioning graft beyond 6 months post-transplant may be tabulated, if data are available. An adhoc analysis of graft survival may also be performed using the Kaplan-Meier method.

4.4.2.2 Main analytical approach

All secondary efficacy endpoints (if applicable) during Phase 2 will be summarized descriptively and presented by cohort. Categorical variables (eg, rates and proportions) will be tabulated via frequency distributions (ie, number and percents). Continuous variables (eg, change from baseline) will be summarized by providing the number of observations (n), mean, median, SD, minimum, and maximum.

DoR and other time to event variables will be analyzed using the Kaplan-Meier method (ie, median and associated 95% confidence interval). No hypothesis/significance testing will be performed.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoints

The following tertiary/exploratory efficacy endpoints will be explored in the Phase 2 portion of the study:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4.5.2 Main analytical approach

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.6 MULTIPLICITY ISSUES

No multiplicity issues are anticipated in this study.

4.7 SAFETY ANALYSES

For the Phase 1 portion of the study, pre-defined unacceptable toxicities) will be listed by participant using the Safety-evaluable Phase 1 population defined in Section 3.

All safety analyses detailed below will be performed on the All Treated population as defined in Section 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong in the All treated (eg, treated but not enrolled) will be provided.

4.7.1 Extent of exposure

4.7.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any study interventions is administered.
- Duration of IMP exposure (in weeks) is defined as [(last date of IMP administration) – (first date of IMP administration)] / 7.

- The first day of IMP administration is defined as the first administration date with non-zero dose for the IMP. The last date of IMP administration is defined as follows:
  - date of the last IMP dose + 7 if the last cycle is a QW cycle or date of death + 1, whichever is earlier
  - date of the last IMP dose + 14 if the last cycle is a Q2W cycle or date of death + 1, whichever is earlier

The total number of cycles started, number of cycles started by participants will be summarized as a quantitative variable and by category (number (%) of participants receiving 1 cycle, 2 cycles, 3 cycles). The duration of overall exposure will be summarized quantitatively.

The following variables will be computed to describe overall dose modification (cycle delay):

- Cycle delay: A cycle is deemed as delayed if the (start date of the current cycle – start date of the previous cycle) – duration of a cycle (ie, 28) is >2 days. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the participant (with number of participants used as denominator) and cycle (with number of cycles used as denominator) levels, as follows:

- Number (%) of participants with a least 1 cycle delayed
  - Number (%) of participants with a cycle delayed between 3 and 7 days (using maximum delay across all cycles)
  - Number (%) of participants with a cycle delayed between 8 and 14 days (using maximum delay across all cycles)
  - Number (%) of participants with a cycle delayed >14 days (using maximum delay across all cycles)
- Number (%) of cycles delayed
  - Number (%) of cycles delayed between 3 and 7 days
  - Number (%) of cycles delayed between 8 and 14 days
  - Number (%) of cycles delayed >14 days
- Dose delay: within a cycle, the treatment window is ±1 day for each of the weekly administrations and ±2 days for each of the Q2W administrations. Within a cycle, a dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, or ≥3 days beyond the theoretical day of treatment for Q2W dose.

4.7.1.2 IMP exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant

- Duration of IMP exposure (in weeks) is defined as [(last date of IMP administration) – (first date of IMP administration)] / 7.
- The first day of IMP administration is defined as the first administration date with non-zero dose for the IMP. The last date of IMP administration is defined as follows:
  - date of the last IMP dose + 7 if the last cycle is a QW cycle or date of death + 1, whichever is earlier
  - date of the last IMP dose + 14 if the last cycle is a Q2W cycle or date of death + 1, whichever is earlier
- Actual dose (mg/kg): is defined as the actual dose (mg) administered divided by the body weight at the time
- Cumulative dose (mg/kg): the cumulative dose is the sum of all actual doses (mg/kg) of IMP, given from first to last administration
- Actual dose intensity (ADI [mg/kg/week]): defined as the cumulative dose (mg/kg) divided by the duration of IMP exposure (weeks)
- Planned dose intensity (PDI [mg/kg/week]): corresponds to the planned dose (mg/kg) multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{PDI (mg/kg/week)}}$

The total number of doses, total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving 1 cycle, 2 cycles, 3 cycles). Duration of IMP exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications:

- Dose reduction: The first IMP administration will not be counted as a dose reduction. For the second and subsequent IMP administrations, dose reduction will be determined using the dose level intervals provided in Table 4, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 4 - IMP dose reduction criteria

Actual dose level	Dose level interval
Starting dose (10 mg/kg)	>7.5 mg/kg
Dose level -1 (5 mg/kg)	>0 mg/kg and ≤7.5 mg/kg

- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered as interrupted if the IMP administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose delayed
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
    - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose delayed
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
    - Number (%) of cycles with at least 1 dose interruption

4.7.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National cancer institute common terminology for adverse events [(NCI-CTCAE) version 5.0] and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the on-treatment period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the toxicity grade is missing for 1 of the treatment-emergent occurrences of an AE, the toxicity grade will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the toxicity grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the overall incidence.
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE (any grade)
- Any grade ≥3 TEAE
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)
- Any TE SAE (any grade)
- Any serious, treatment-related, TE SAE (any grade)
- Any TEAE leading to definitive study treatment discontinuation
- Any TE AESI
- Any TE AESI grade ≥3
- Any treatment-related TEAE (any grade)
- Any grade ≥3 treatment-related TEAE

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
	Primary SOC
	PT
TEAE related to IMP treatment as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE	Primary SOC and PT
Treatment-emergent SAE related to IMP treatment as per Investigator's judgment	Primary SOC and PT
TEAE leading to definitive study treatment discontinuation	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
	Primary SOC and PT
Pretreatment AEs & SAEs	Overview[a]
	Primary SOC and PT
Post-treatment AEs & SAEs	Overview[a]
	Primary SOC and PT
TEAE leading to dose reduction	Primary SOC and PT
TEAE leading to dose interruption	Primary SOC and PT

a Will include the following AE categories: any AEs, any SAEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by reason for death
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment).
  - Fatal TEAE (regardless of date of death/period).
    - Grade 5 TEAE with a fatal outcome during the treatment period,
    - Any Grade TEAE with a fatal outcome during the post-treatment period.
  - Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).
- Deaths in enrolled but not treated participants

Analysis of infusion reactions (IRs) classified as an AESI

IR analysis will include all adverse events regardless of relationship to isatuximab. The IRs will be summarized as follow:

- Number (%) of participants experiencing IRs according to investigator reported AEs presented by primary SOC and PT will be summarized by grade.
- Description of the IR diagnoses (using the diagnosis reported and excluding symptoms).
  - Number (%) of participants' action taken,
  - Number (%) of participants with only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes,
  - Number (%) of participants with first occurrence of IR at the first infusion and subsequent infusions,
  - Number (%) of participants with IR at the first and subsequent infusions,
  - Number (%) of participants with at least two episodes of IRs at the same infusion,
  - Day of onset from infusion,
  - Duration (in days).
- Number of participants with symptoms of IRs (as reported by investigator) by SOC and PT.

Analysis of other adverse events of special interest (AESIs)

Other adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 7. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 5.

Table 7 - Selections for other AESIs

AESIs	Selection
Symptomatic overdose	e-CRF specific tick box on the AE page
Pregnancy	e-CRF specific tick box on the AE page

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following routine laboratory variables (performed by local laboratories) and vital signs variables will be analyzed. Electrocardiogram (ECG), performed only at screening visit, will not be summarized. Left ventricular ejection fraction (LVEF) collected in the screening echocardiography will be summarized in the baseline characteristics table.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count (erythrocytes), platelet count, prothrombin time (expressed as international normalized ratio)
  - White blood cells: neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose (fasting), HbA1c*, total protein, albumin
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate, magnesium
  - Renal function: creatinine*, urea, blood urea nitrogen (BUN), uric acid*, eGFR (MDRD equation)*
  - Liver function*: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total and direct bilirubin
  - Hepatitis screen: hepatitis B surface antigen, anti-hepatitis-C antibody
  - Parathyroid hormone (intact)

  ** Local laboratory normal ranges will be used for these laboratory variables.*
- Vital signs: heart rate, systolic and diastolic blood pressure, as well as, weight, respiratory rate, and body temperature (and route)

Data below the lower limit of quantification limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification (ULOQ) will be replaced by ULOQ value.

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges [lower limit of normal (LLN), upper limit of normal (ULN)] are defined and will be used for grading (see list of parameters in Section 5.4.5). For other biochemistry parameters (noted with * in laboratory variable list above), grading will be derived using local laboratory normal ranges.

For serology and viral load parameters, results may be summarized via shift tables at baseline and at participant's worst post-baseline visit.

Analyses according to PCSA and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version specified in the protocol. For laboratory variables for which NCI-CTCAE scale is not applicable, potentially clinically significant abnormality (PCSA) summaries may be performed using sponsor or local laboratory normal ranges.

In addition, for vital signs (ie, heart rate, systolic and diastolic blood pressure), PCSA analyses will be performed based on the PCSA criteria listed below.

Vital signs parameter	PCSA criteria
Systolic Blood Pressure (mmHg)	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg
	≥ 160 mmHg and increase from baseline ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg
	≥ 110 mmHg and increase from baseline ≥ 10 mmHg
Heart Rate (beats/min)	≤ 50 beats/min and decrease from baseline ≥ 20 beats/min
	≥ 120 beats/min and increase from baseline ≥ 20 beats/min

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables and vital signs above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For laboratory variables graded by NCI-CTCAE,

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

4.8 OTHER ANALYSES

4.8.1 PK analyses

4.8.1.1 Non-compartmental analysis: following the 1st administration

Individual concentrations and PK parameters of drug at Cycle 1 will be listed and summarized by descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, SD, standard error (SE), coefficient of variation (CV)%, minimum, and maximum) by cohort and possibly overall.

Mean concentration profiles over time will be plotted by cohort and possibly overall under the responsibility of Sanofi, Pharmacokinetic, Dynamic and Metabolism (PKDM), Translational Medicine and Early Development (TMED) department.

4.8.1.2 Over treatment concentrations: C_{trough} and C_{eoi}

C_{trough} defined as a sample collected before dosing, in a time window of 6 to 8 days after the previous infusion for the QW administration, in a time window of 12 to 16 days after the previous infusion for the Q2W administration, will be included in the descriptive analysis irrespectively of interruption of infusion. However, C_{trough} drawn outside time collection window described in the protocol PK flowcharts or collected after a dose deviation higher than ±50% from intended dose will be excluded from the analyses.

C_{eoi} collected after significant infusion interruption, drawn outside collection of time window described in the PK flowcharts of the protocol or collected after a dose deviation higher than ±50% from intended dose will be excluded from the analyses.

Individual C_{trough} and C_{eoi} will be listed and summarized with descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, SD, SE, CV%, minimum, and maximum) by cohort and possibly overall.

Mean (±SE) of C_{trough} will be plotted over treatment phase by cohort and possibly overall.

Individual C_{trough} ratio (C2D1 vs C1D8 and C3D1 vs C1D8) and C_{eoi} ratio (C2D1 vs C1D1 and C3D1 vs C1D1) will be listed and summarized by descriptive statistics as described above by cohort and possibly overall.

All concentration values below the LLOQ will be treated as zero in individual listing and respective descriptive statistics and will be replaced by LLOQ value for individual ratio and respective descriptive statistics.

4.8.1.3 Population PK analysis

Details of the population PK analysis plan will be provided in a separate document.

4.8.2 Immunogenicity analyses

Immunogenicity impact on PK analysis may be explored, depending on the ADA prevalence.

Descriptive statistics of C_{trough} as described above will be provided at each cycle in the subset of negative participants by cohort and possibly overall where positive or inconclusive participants will be observed.

The impact of immunogenicity on PK will be assessed graphically by plotting individual C_{trough} profiles of ADA positive participants (and the concentration of the administered drug at the same time as ADA positive result will be notified) along with mean (+/-SD) C_{trough} profile of ADA negative participants by cohort and possibly overall. Descriptive statistics of C_{trough} of ADA negative participants will be provided by cycle at the bottom of the plot.

The impact on safety and efficacy endpoints may be further explored by graphical methods or descriptively, depending on the ADA prevalence.

4.8.2.1 Analysis of Immunogenicity variables

A summary table by cohort and possibly overall with the number (%) of pre-existing ADA and negative participants at baseline, number (%) of boosted and induced participants (either transient, persistent or indeterminate) will be reported, along with descriptive statistics of titer. Prevalence and incidence will also be presented.

In addition, for positive ADA participants, time to onset, duration of ADA response, and the characterization of the immune response (transient, persistent, indeterminate) will be provided using a summary table by cohort and possibly overall.

An individual data listing with ADA samples status (positive, negative or inconclusive), the titer if applicable, date of first/last dose, duration of exposure, study period (cycle), time point and date/time of sampling along with C_{trough} value of the drug will be provided for positive and inconclusive ADA participants.

Note that treatment-boosted ADA are excluded from the analyses of ADA kinetics because this type of immune response differs mechanistically.

4.8.3 Biomarker analyses

Blood samples before and after treatment with IMP (isatuximab) will be collected from all participants for the:

- flow cytometric analysis of immune cells: the percentage and the cell count of each immune cell population and sub-population will be summarized using descriptive statistics at each timepoint. Change from baseline will be also described to assess the biological effects of IMP on immune cell populations. A specific focus will be done on CD38 expressing cells in blood to evaluate its alteration upon IMP treatment. Baseline expression of immune cells, especially CD38 expression cells, may be also associated with the observed clinical responses in reduced anti-HLA antibodies to anti-CD38 treatment.
- possible functional assessment of memory B-cells depletion: peripheral B-cells will be processed for subsequent analysis of anti-HLA alloreactivity upon IMP treatment
- measurement of total immunoglobulin levels: descriptive statistics will be used to summarize the total immunoglobulin levels and the levels of ImmunoglobulinG (IgG) at each timepoint and the change over time in order to estimate the impact of IMP treatment on the total IgG pool. Baseline levels of immunoglobulin may be also associated with the observed clinical responses in reduced anti-HLA antibodies to anti-CD38 treatment.

4.9 INTERIM ANALYSES

Not applicable.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA: anti-drug antibodies
ADI: actual dose intensity
AEs: adverse events
AESIs: adverse events of special interest
AMR: antibody mediated rejection
CKD: chronic kidney disease
cPRA: calculated panel reactive antibodies
CV: coefficient of variation
DL: dose level
DoR: duration of response
E/D: early discontinuation
ECG: electrocardiogram
eHR: electronic health record
FUP: follow-up period
HLA: human leukocyte antigen
HLGT: high level group term
HLT: high level term
ICF: informed consent form
IgG: ImmunoglobulinG
IMP: investigational medicinal product
IRs: infusion reactions
LCD: likelihood of compatible donor
LLN: lower limit of normal
LLOQ: lower limit of quantification
LLT: lower level term
MedDRA: Medical Dictionary for Regulatory Activities
MFI: mean fluorescence intensity
NCI-CTCAE: National cancer institute common terminology for adverse events
OPO: Organ Procurement Organizations
OPTN: Organ Procurement and Transplant Network
PCSA: potentially clinically significant abnormality
PDI: planned dose intensity
PK: pharmacokinetics
PKDM: Pharmacokinetic, Dynamic and Metabolism
PT: preferred term
RDI: relative dose intensity
RR: response rate
SAB: single antigen bead
SAEs: serious adverse events
SAP: statistical analysis plan

SD:	standard deviation
SE:	standard error
SoA:	schedule of activities
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TMED:	Translational Medicine and Early Development
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
UNOS:	United Network for Organ Sharing
US:	United States
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical/surgical history

The following demographics and baseline characteristics, medical/surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the enrolled population.

Demographic and baseline characteristics

- age (in years) as continuous variable and age group categorical variable
- sex (Male, Female)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Other baseline characteristics (renal disease status, CPRA value [from local lab: OPTN-calculated, locally reported; from central lab], blood type, height, weight, body mass index [BMI], LVEF, number of prior kidney transplants, sensitizing events)

Renal disease status at study entry includes renal disease stage and duration, origin of renal insufficiency, dialysis time, and kidney waitlist information.

Other baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical/surgical history includes any past and/or concomitant diseases or past surgeries (except previous transplantation). Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version in effect at Sanofi at the time of database lock.

Other procedures

Other procedures include those not planned in the protocol that are related to or performed as a result of any AE or following a pre-existing condition. Other procedures will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version in effect at Sanofi at the time of database lock.

Prior or concomitant medications, and other medications

All medications (including IR medications, prior/post-transplant immunosuppression treatments, desensitization/AMR medications) will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant took during the post-treatment period (Section 4.1) up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications and other specific medications/treatments (ie, administered for IRs, prior/post-transplant immunosuppression treatments, desensitization/AMR medications) will be summarized separately, for the enrolled and treated population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 General conventions

Time since CKD stage diagnosis at study entry: (date of first IMP dose - date of diagnosis for most recent CKD stage at study entry) + 1, and convert to years

Dialysis time: (date of first IMP dose – start date of most recent start/restart chronic dialysis) + 1, and convert to years

Waitlist time: (date of first IMP dose – waitlist registration date (from transplant status at study entry)) + 1, and convert to years

Creatinine clearance (eGFR) using the equation of MDRD formula:

$$GFR = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if African American})$$

with serum creatinine in mg/dL and age in year.

Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of participants with non-missing observation in the considered population. When relevant, the number of participants with missing data is presented.

When incomplete or missing dates are found in the eCRF, attempts will be made to retrieve the complete date, especially for dates within the month prior to first IMP dose. However, if some dates remain incomplete, the following rules will be applied:

Handling of disease characteristics missing/partial dates (including medical/surgical history, renal disease status at study entry)

- If the day is missing, impute day with 1.
- If the month is missing, impute month with 1.
- If the year is missing, no imputation will be performed.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For prior transplant immunosuppression treatments, following rules will be applied:

Missing/partial start date will be imputed as follows:

- If year and month exist, day is missing, impute day with 1.
- If only year exists, month and day are missing, impute both month and day with 1.
- If year, month, and day are all missing, no imputation will be applied.

Missing/partial end date will be imputed in a two-step approach as follows:

- Step 1: Use the following rule to impute end date:
  - If year and month exist, day is missing, impute day with 1.
  - If only year exists, month and day are missing, impute both month and day with 1.
  - If year, month, and day are all missing, no imputation will be applied.
- Step 2: If imputed end date is earlier than start date, set the imputed end date the same as start date.

Imputation of incomplete start date for post-transplant immunosuppression treatments and desensitization/AMR treatments/procedures

For post-transplant immunosuppression treatments and desensitization/AMR treatments/procedures, if the start date is missing, it will be imputed as follows:

- If start day and month are missing and start year is the same as treatment end year, start date will be set equal to treatment end date + 1.
- If start day and month are missing and start year is after the treatment end year, start day and month will each be set to 01.
- If start day is missing and start year and month is the same as the treatment end year and month, start day will be set equal to the treatment end day + 1.
- If start day is missing and start month is before the treatment end month and start year is the same as treatment end year, start day will be set to 01.
- If start day is missing and start month is after the treatment end month and start year is the same as treatment end year, the medication start day will be set to 01.
- If start day is missing and start month is not missing and start year is after the treatment end year, start day will be set to 01.
- If start day, start month and start year are all missing, start date will be set equal to the treatment end date + 1.

No imputation will be done for missing/partial end dates.

Handling of AEs with missing or partial date of onset

Missing or partial AE onset dates (occurrence or becoming serious) will be imputed so that if the partial AE onset date information does not indicate that the adverse event started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. In case of AEs worsening during the study, the emergence will also be based on the cycle of worsening. No imputation of AE end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of AE resolution.

Handling of death with missing or partial date of death

The imputation for missing or partial death date will proceed as follows:

- If the death day is missing and the death month and year are the same as the last month and year the participant was last known to be alive, the death day will be set equal to the last day the participant was known to be alive + 1.
- If the death day is missing and the death month is after the month the participant was last known to be alive and the death year is the same as the year the participant was last known to be alive, the death day will be set to 01.
- If the death day and month are missing and the death year is the same as the year the participant was last known to be alive, the death date will be set equal to the date the participant was last known to be alive + 1.
- If the death day and month are missing and the death year is after the year the participant was last known to be alive, the death day and month will both be set to 01.

If the date the participant was last known to be alive is partial or missing, no imputation for missing or partial death date will be performed. The last date the participant was known to be alive is the latest of the following: date of last IMP dose, date of last visit performed (when the participant is known to be alive according to subject status), date of last laboratory assessment, and date of last vital signs recorded.

Handling of AEs with missing grade

If the grade is missing for one of the TE occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done and missing grades will be summarized in the "all grades" category.

Handling of missing assessment of relationship of AEs to IMP

If the assessment of the relationship to the regimen is missing, then the relationship to the IMP regimen has to be assumed and the AE considered as such in the frequency tables of possibly related adverse events, but no imputation will be done at the data level.

Handling of parameters expressed as inequality or approximation

For some parameters (such as laboratory parameters), if the value is expressed as "<xx", "≤xx, half of the numeric portion of the entry or limit of quantification will be used in calculations.

Analysis windows for time points

No analysis windows will be applied in the by-scheduled visit summaries.

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ADA will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs/NCI grade, and the shift summaries for safety.

5.4.2 DESENSITIZATION response criteria

The target cPRA (ie, reduction of cPRA required to achieve at least 100% increase of LCD is calculated according to the following equation (2). Examples of target cPRA reduction are presented in Table 8.

$$LCD = 1\ in\ \frac{1}{1 - cPRA}$$

Table 8 - Examples of target cPRA reduction

Baseline		Target	
cPRA	**LCD**	**cPRA**	**LCD**
99.99%	1:10000	**99.98%**	1:5000
99.90%	1:1000	**99.80%**	1:500
99.80%	1:500	**99.60%**	1:250
99.60%	1:250	**99.20%**	1:125
99.50%	1:200	**99.00%**	1:100
99.00%	1:100	**98.00%**	1:50
97.50%	1:40	**95.00%**	1:20
95.00%	1:20	**90.00%**	1:10
90.00%	1:10	**80.00%**	1:5
80.00%	1:5	**60.00%**	1:2.5

Abbreviations: cPRA = calculated panel reactive antibodies, LCD = likelihood of compatible donor

Participants with baseline cPRA 100.00% will be assigned with cPRA 99.99% for computational purpose.

Antibody titer is defined as the last dilution of serum at which positive results is obtained (eg, MFI ≥2000) (3). Examples of antibody titer based on MFI are illustrated in Table 9.

Table 9 - Examples of antibody titer

	Neat Serum	1:2	1:4	1:8	1:16	1:32	Titer
Antigen 1 MFI	13430	12492	6250	3123	1550	790	**8**
Antigen 2 MFI	18320	20820	10501	5206	2604	1302	**16**
Antigen 3 MFI	11020	5493	2750	1384	688	360	**4**

Abbreviations: MFI = mean fluorescence intensity

Using similar concept, Table 11 illustrates an example in which the second predefined desensitization criterion (ie, ≥75% reduction in antibody titer from baseline to achieve target cPRA, see Table 10) may be met. In this example, participant's baseline cPRA is measured by SAB as 97.50%, the target cPRA is therefore 95.00% as defined in Table 8. Through serial dilution of the serum collected at baseline, titer required to achieve target cPRA is 16 (ie, achieved

at 1:16 dilution). Subsequent post-treatment serum is therefore diluted at 1:4 (ie, 75% reduction from 1:16) to determine whether target cPRA is achieved. At Cycle 3 Day 1, target cPRA is reached at 1:4 dilution therefore meeting the aforementioned predefined desensitization criterion.

Table 10 - 75% reduction in antibody titer from baseline

Baseline		75% Reduction	
Titer	**Dilution**	**Titer**	**Dilution**
2	1:2	**1**	Neat
4	1:4	**1**	Neat
8	1:8	**2**	1:2
16	1:16	**4**	1:4
32	1:32	**8**	1:8
64	1:64	**16**	1:16
128	1:128	**32**	1:32
256	1:256	**64**	1:64
512	1:512	**128**	1:128

Table 11 - Example of ≥75% reduction in antibody titer from baseline to achieve target cPRA

	Neat Serum	1:2 Titer = 2	1:4 Titer = 4	1:8 Titer = 8	1:16 Titer = 16	Response Criterion Met
Baseline cPRA	97.50%	97.50%	97.50%	96.00%	95.00% (target cPRA)	
C2D1 cPRA	96.00%		96.00%			**No**
C3D1 cPRA	96.00%		95.00% (target cPRA)			**Yes**

Abbreviations: C2D1 = Cycle 2 Day 1, C3D1 = Cycle 3 Day 1, cPRA = calculated panel reactive antibodies

5.4.3 Health Resources and Services Administration (HRSA): Research Plan

This research plan provides details on the match run simulation process supporting the exploratory analysis on transplant offers (Section 4.5.2).

1. Name of primary investigator(s), co-investigators, and contact person:

Primary Investigators:

[redacted], PhD - UNOS
[redacted], PhD - Sanofi US

Co-investigators:

[redacted] - UNOS
[redacted] - UNOS
[redacted] - UNOS
[redacted] - UNOS

[redacted] - Sanofi
[redacted] - Sanofi
[redacted] - Sanofi

Contact person: [redacted], PhD [redacted]

2. Project title:

Match Run Simulations of Kidney Transplant Candidates who Underwent Desensitization Treatment

3. Project background:

Sanofi has initiated a clinical study (TED16414) to investigate activity of an anti-CD38 antibody (isatuximab) in desensitization of kidney transplant candidates. The purpose of the TED16414 clinical study is to evaluate the efficacy of isatuximab in lowering the amount of antibodies (ie, the efficacy of desensitization). Eligible patients on the TED16414 clinical study are active transplant waitlist candidates with calculated PRA (cPRA) values of 80%-100%, so patients enrolled on the TED16414 clinical study will be captured in OPTN Waiting List. The OPTN system creates a system generated ID called Waiting List ID that is unique to a patient registered on the Waiting List. Sanofi will collect and share the following information of the TED16414 clinical study patients with UNOS: OPTN Waiting List ID, anti-HLA antibody profiles, and cPRA levels at baseline and monthly thereafter for approximately 9 months after treatments starts.

UNOS will collaborate with Sanofi to explore the feasibility of using OPTN data to perform the following analytical activities:

1. Generate a reliable external control arm for the TED16414 using OPTN data merged with the Optum® EHR dataset.
    - The Optum® de-identified Electronic Health Record dataset containing information on approximately ~105 million US patients starting from 2007 across various inpatient, outpatient, and specialty settings likely contains additional health information on a subset of patients who are on the OPTN kidney waitlist. Matched control subjects will be selected from the merged dataset.
2. Perform kidney match run simulations (ie, rerun the kidney matches) of the TED16414 patients using their anti-HLA antibody profiles and cPRA values at baseline and after treatment.
    - Performing match run simulations using the algorithm based on OPTN allocation policies and TED16414 participants' data would allow a realistic assessment of potential clinical benefits as a result of the desensitization treatment effect from isatuximab.
    - Therefore, the match run simulations will be conducted to explore novel metrics or surrogate endpoints that measure transplantability of patients who received isatuximab, such as higher ranks on match run simulations or appearing on a higher number of matches. Matched control subjects selected above may also be included in the match run simulations.

4. Target population:

Adult patients on OPTN kidney waiting list and deceased donors with kidney match runs between December 2014 and December 2023.

5. Question(s) your study will address:

1. What is the overlap between OPTN waitlist and Optum EHR (ie, what is the number of OPTN waitlist patients found in Optum® EHR)?
2. Do isatuximab treated patients have higher transplantability (eg, higher ranks or more matches) compared to pre-treatment, as well as compared to matched control patients?
3. Is there a correlation between transplantability (eg, higher number of matches or higher ranks on match run simulations) and time to transplant or higher transplant rate?
4. Can comparison of TED16414 clinical study outcome against retrospective control arm selected from OPTN data merged with Optum® EHR data inform possible clinical benefits in the context of real world data, where clinical outcome may include number of transplant offers, kidney graft survival, rejection rates?

6. Hypotheses your study will test:

The overall, primary hypotheses include:

A) Isatuximab-treated patients have higher transplantability (eg, higher ranks or more matches on match run simulations) after treatment as compared to prior to treatment and matched control patients.

B) Higher ranks or increased number of matches correlate with shorter time to transplant or higher transplant rate.

7. Type of data you need for your study *(check all that apply)*:

__X_ Waiting list candidate file *(ie, all registrations on waiting list, transplanted or not – also contains donor, transplant, and follow-up data for recipients)*

__X_ Transplant recipient file *(ie, only patients who received transplants – also contains waiting list, follow-up, and donor data for recipients)*

__X_ Deceased donor file *(ie, all deceased donors)*

____ Living donor file *(ie, all living donors)*

__X_ Other *(1) PTR dataset without the "other, specify" refusal reason; 2) for each historical kidney match run, candidate and donor data elements at the time match was run)*

8. Explain why you need patient identifiers for your study. Include details on how you plan to link to any non-OPTN patient-level datasets:

1. UNOS will receive patient identified datasets with identifiers described below from OPTN.

2. UNOS will create an indicator to flag these patients in the OPTN waiting list data as the TED16414 study participants.
    - UNOS will remove TED16414 patients and the multiply listed waitlist ID from the dataset to ensure the TED16414 patients will not be selected as matched control subjects in retrospective control arm.
    - UNOS will use the encrypted OPTN Waiting List ID and remove other OPTN ID's for the data linkage described below.
3. UNOS will need the following PHI (patient last name, first name, Social Security Number, date of birth, zip code of residence, state of residence, and gender) to link OPTN data with Optum® EHR.
    - UNOS will run the tokenization software from Datavant (subcontractor of Optum - https://datavant.com/wp-content/uploads/2018/05/Datavant_De-Identifying-and-Linking-Structured-Data-Whitepaper.pdf) against the OPTN data.
        - All of the PHI will be removed by Datavant software and replaced by patient-specific tokens.
        - UNOS will verify that PHI has been removed in the tokenized dataset.
        - UNOS will send the dataset to Optum via secure File Transfer Protocol (FTP) site.
    - Optum will run the Datavant tokenization software to tokenize Optum® EHR and then merge with OPTN data that only contains encrypted Waiting List ID (**Note**: **Optum will not have access to any OPTN PHI or PII)**
        - All PHI will be removed by the software and replaced by new patient-specific tokens in the merged dataset.
        - Optum will verify that the merged dataset does not contain any PHI or PII.
        - Optum will send the merged OPTN-Optum dataset to Sanofi via secure FTP site.
        - **Optum will destroy OPTN data.**
4. Sanofi will select matched control patients from the merged OPTN-Optum dataset based on certain patient characteristics. When this is completed, Sanofi will send the Waiting List ID's of the TED16414 study patients and the encrypted Waiting List ID's of the matched control patients to UNOS via secure FTP site.
5. UNOS will use the unencrypted OPTN Waiting List ID to perform the match run simulations. **Only UNOS will have access to the crosswalk between OPTN encrypted and unencrypted Waiting List ID's**.
    - UNOS will provide Sanofi with individual level summary of the match simulations that includes the encrypted Waiting List ID and ranks for each candidate on the matches.

9. Type of patient identifiers you need for your study *(check all that apply)*:

__X__ Patient name

__X__ Patient Social Security Number

__X__ Patient date of birth
__X__ Patient zip code
__X__ Unencrypted waiting list ID *(encrypted ID is standard in STAR files)*
_____ Unencrypted transplant ID *(encrypted ID is standard in STAR files)*
_____ Other patient identifier *( )*
_____ Donor name
_____ Donor Social Security Number
_____ Donor date of birth
__X__ Unencrypted donor ID *(encrypted ID is standard in STAR files)*
_____ Other donor identifier *(specify: _____)*

10. List other *key* variables you need for your study. You may attach a separate list.

- All variables included in STAR files and PTR dataset
- Donor and candidate data elements that are used in match runs for each historical kidney match run (Note: these elements will only be accessed by UNOS for performing the match run simulations)

11. Describe, in general, how the data are to be analyzed:

- The number of patients on the OPTN kidney waitlist that overlap with Optum® EHR will be determined after the linkage.
- Matched control subjects will be selected by Sanofi using exact or propensity score matching methods from the merged OPTN-Optum® EHR datasets (as specified in Section 8, the merged datasets will not have any PHI or PII). Parameters for matching may include key patient characteristics used in the OPTN kidney allocation policy, such as waiting time, cPRA value, blood type, age, prior transplant, and location of transplant center.
- Match run simulations will be performed by UNOS using the kidney allocation algorithm that is in place at the time of the simulations.
  - Match run simulations will be performed for the TED16414 study participants using pre- and post-treatment anti-HLA antibody profiles and cPRA values.
  - The results of the match-reruns will be summarized and this will include the ranks for each candidate on the matches.
- The summary data from the match run simulations will be analyzed by Sanofi:
  - Number of matches will be compared among: (a) TED16414 participants pre-treatment, (b) TED16414 participants post-treatment, (c) matched control subjects.
  - Rank scores of matches will be compared among: (a) TED16414 participants pre-treatment, (b) TED16414 participants post-treatment, (c) matched control subjects.
- Additionally, Sanofi will analyze whether higher matches or rank scores are correlated with shorter time to transplant/higher transplant rate and transplant outcomes such as patient survival, graft survival, or rejection rates.

12. Describe how you plan to use the data, including any plans to present or publish the data.

Data summary will be included in the TED16414 clinical study reports and/or research study reports, which will be retained for regulatory and quality purposes. Aggregated results may also be published as an abstract and/or manuscript. The data summary and aggregated results will not contain any patient identifiers.

13. Will you need updates of these data in the future?

Yes - Every quarter for three years.

5.4.4 Propensity score analysis

Propensity score matching is commonly used to analyze observational data to reduce bias due to confounding variables that are unbalanced between groups of interest (eg, participants that received the treatment and those that did not). Propensity score matching will be utilized to attempt to select the appropriate participants from the real-world data pool (UNOS database, with the option of enriching the database by linking with participants' data in the OPTUM eHR) for inclusion in the synthetic control arm (SCA) so that the distribution of baseline characteristics would be well balanced between the SCA and the treatment arm from the study. Two SCAs will be constructed separately to match the corresponding two cohorts of Phase 2 of this study. This section provides detailed procedures to carry out the propensity score matching:

Step 1: Within the real-world data pool: (a) exclude TED16414 trial participants, (b) exclude real-world data pool participants not satisfying TED16414 study entry criteria, based on available data collected in the UNOS/OPTUM databases; and (c) keep unique patient ID that map to multiple waitlist IDs.

Step 2: Estimate propensity scores. The propensity score is the probability of assignment of the treatment conditional on the observed baseline covariates:

$$p(x) = \Pr(T = 1|X = x)$$

Where T is an indicator variable denoting the treatment received (T=1 for study treatment vs. $T = 0$ for historical control) and X is a vector representing the covariates to be included in the propensity score model. The propensity score will be estimated using a logistic regression model in which treatment status is regressed on observed baseline covariates. The baseline covariates included in the propensity score model may consist of the following disease characteristics:

1. Blood type
2. Gender
3. Days on waiting list
4. Days on dialysis
5. Age
6. cPRA
7. Distance from the transplant center

The estimated propensity score is the predicted probability of treatment derived from the fitted logistic regression model.

Step 3: Create SCA by selecting participants from the real-world data pool to match the participants enrolled in this study using the estimated propensity scores. The greedy nearest-neighbor matching without replacement and a fixed 1-to-1 matching ratio will be used. Other matching ratios may also be explored. Participants enrolled in this study will be randomly ordered within each cohort. Then each participant will be matched to a historical participant whose propensity score is the closest to that of the enrolled participant and within a prespecified caliber. A caliper width equal to 0.25 of the pooled standard deviation of logit of the propensity score from the 2 groups will be used. Matching without replacement will be conducted, that is, the matched historical participants will be removed from consideration for further matching. This process will be repeated sequentially for all the enrolled participants in each cohort separately.

Step 4: Post-matching evaluation of covariate balance. Whether the distribution of measured baseline covariates is similar between the study enrolled participants and historical SCA participants will be examined. Baseline covariates will be summarized with descriptive statistics for the study enrolled participants and SCA both before and after matching. Standardized difference in covariate means before and after matching will be computed and compared.

For a continuous covariate, the standardized difference is:

$$d = \frac{\overline{x_t} - \overline{x_h}}{\sqrt{(s_t^2 + s_h^2)/2}}$$

Where $\overline{x_t}$ and $\overline{x_h}$ denote the sample mean of the covariate for the study treatment arm and historical SCA arm, respectively; s_t^2 and s_h^2 denote the sample variance of the covariate for the study treatment arm and historical SCA arm, respectively.

For categorical variables the standardized difference is defined as:

$$d = \frac{\widehat{p_t} - \widehat{p_h}}{\sqrt{\{\widehat{p_t}(1 - \widehat{p_t}) + \widehat{p_h}(1 - \widehat{p_h})\}/2}}$$

Where $\widehat{p_t}$ and $\widehat{p_h}$ denote the category of covariate for the study treatment arm and historical SCA arm, respectively. For covariate with more than 2 categories, the standardized difference for each level of the categorical variable will be calculated. The absolute standardized differences should generally be less than 0.25.

In order to minimize the selection bias, the propensity score matching process to construct the SCA arms will be conducted by Sanofi independent B&P group who will only have access to baseline covariates of participants from both study treatment and historical pool (ie, blinded by the results of the study and historical data).

5.4.5 Generic ranges for hematological and biochemistry parameters

Table 12 - Generic ranges for hematological parameters

Test	Gender	Unit	Lower/Upper limit of normal
Hemoglobin	F	g/L	120 - 160
Hemoglobin	M	g/L	135 - 175
Lymphocytes		10^9/L	1 - 2
Neutrophils		10^9/L	1.8 - 3.15
Platelets		10^9/L	150 - 350
Leukocytes		10^9/L	4.5 - 11
Eosinophils		10^9/L	0 - 0.4
Basophils		10^9/L	0 - 0.15
Monocytes		10^9/L	0.18 - 0.5
Hematocrit	M	Ratio	0.41 - 0.53
Hematocrit	F	Ratio	0.36 - 0.46
Erythrocytes	F	10^{12}/L	4 - 5.2
Erythrocytes	M	10^{12}/L	4.5 - 5.9
INR		ratio	0.8 - 1.2

Based on Kratz et al. (4)

Table 13 - Generic ranges for biochemistry parameters

Test	Unit	Lower – Upper limit of normal
Albumin	g/L	35 - 55
BUN	mmol/L	3.6 - 7.1
Calcium	mmol/L	2.2 - 2.6
Chloride	mmol/L	80 - 115
Corrected calcium	mmol/L	2.2 - 2.6
Glucose	mmol/L	3.9 - 7
Bicarbonate (HCO3)	mmol/L	22 - 29
Carbon dioxide	mmol/L	21 - 30
Potassium	mmol/L	3.5 - 5
Magnesium	mmol/L	0.8 - 1.2
Sodium	mmol/L	136 - 145
Phosphate	mmol/L	1 - 1.4
Protein	g/L	55 - 80
Urea	mmol/L	3.6 - 7.1

6 REFERENCES

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