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STATISTICAL TECHNICAL DOCUMENT

SAR650984-ACT16832

A multicenter, open-label, non-randomized, Phase 1b/2 study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with warm autoimmune hemolytic anemia

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibodies
AE:	adverse event
AUC:	area under the plasma concentration versus time curve
Cmax:	maximum plasma concentration observed
CTCAE:	common terminology criteria for adverse events
CV:	coefficient of variation
IMP:	investigational medicinal product
LLOQ:	lower limit of quantification
MedDRA:	Medical Dictionary for Regulatory Authorities
NCI:	National Cancer Institute
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PK:	pharmacokinetic
PKDM:	Pharmacokinetics, Dynamics and Metabolism
PT:	preferred term
SD:	standard deviation
SEM:	standard error of the mean
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization Drug Dictionary

1 STATISTICAL AND ANALYTICAL PROCEDURES

1.1 INTRODUCTION

The purpose of this document is to provide additional technical details.

A comprehensive and detailed description of strategy and statistical technique used to perform the analysis of data was provided in Section 9 of the protocol (Amended Clinical Trial Protocol, Version 06, dated 28-Mar-2022).

Modifications from analyses specified in the protocol are defined in Section 1.2.

Details for analyses defined in the protocol and additional analyses are further specified in Section 1.3.

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version currently in effect at the time of database lock, version 26.0 or later).

Previous and concomitant medication records will be coded according to the World Health Organization Drug Dictionary (WHO-DD version currently in effect at the time of database lock, version 2023MAR B3 or later).

For laboratory variables, analyses according to National Cancer Institute (NCI) grading will be made according to the NCI common terminology criteria for AEs (CTCAE) version currently in effect at the time of database lock. In addition, for laboratory variables for which NCI-CTCAE scale is not applicable, and vital sign variables, potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list from BTD-0090536 version 3.0 dated May 2014 (“Analysis and reporting of safety data from Clinical Trials through the Clinical Study Report”, Appendix 3).

1.2 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

This study stopped early and, as a result, Part B was not performed. Therefore, all protocol defined analyses planned for Part B will not be presented.

1.2.1 Modification on ‘9.4.1 General considerations’

Inter quartile range will not be included in descriptive analyses. Standard error of the mean (SEM) will be provided instead. Hence, unless otherwise specified, descriptive statistics will be provided using number of observations, mean, standard deviation (SD), SEM, minimum, maximum and median for quantitative variables.

Because of the likelihood of hemolysis in samples obtained, it has been deemed sufficient to analyze all laboratory assessments (including the primary efficacy endpoint) using local laboratory assessments primarily and if not available using central laboratory assessments.

1.2.2 Modification on '9.4.2.1.1 Adverse events'

An additional listing of all AEs will be generated. This detailed listing means the following protocol defined summaries and listings will not be presented:

- Treatment-emergent AEs (TEAEs) described according to seriousness, maximum intensity (ie, grade), relation to the investigational medicinal product (IMP) and action taken.
- Summary of post-treatment AEs.
- Participants presenting TEAEs listed sorted by primary system organ class (SOC) and preferred term (PT).

An additional summary of COVID19 related TEAEs will be generated by study intervention group with number (%) of participants experiencing at least one treatment emergent COVID19 related AE, sorted by the internationally agreed SOC order and decreasing frequency of PTs.

1.2.3 Modification on '9.4.2.1.2 Laboratory data' and '9.4.2.1.3 Vital signs and physical examinations'

In addition to the protocol defined outputs the following listings will be presented:

- Listing of participants with combined PCSAs for liver function – Safety population.
- Listing of laboratory data.
- Vital signs - Listing of participants with post-baseline abnormality (PCSA).

With the addition of the detailed listing of laboratory data noted above, which will include flags for PCSAs and abnormalities based on normal ranges, the protocol defined summary of out-of-normal laboratory range values will not be presented.

With the addition of the vital signs listing of participants with post-baseline abnormality (PCSA) noted above, the protocol defined descriptive statistics of vital signs will not be presented.

1.2.4 Modification on '9.3 Populations for analyses'

In addition to the populations for analyses defined in the protocol Table 7, the population without trial impact (disruption) due to COVID19 is defined as any participant:

- without any critical or major deviation related to COVID19
- and who didn't permanently discontinue treatment due to COVID19
- and who didn't permanently discontinue study due to COVID19.

The pharmacodynamic (PD) and pharmacokinetic (PK)/PD populations will not be considered due to the study stopping early and the fact that consequently the PD and PK/PD analyses will not be performed.

1.2.5 Modification on '9.4.3.3.3 Immunogenicity'

Due to the study stopping early, the protocol defined anti-drug antibodies (ADA) incidence will not be presented. Instead, a listing of ADA data will be provided.

1.2.6 Modification on '9.4.4 Tertiary/exploratory endpoint(s)'

Due to the study stopping early, the analyses described within Section 9.4.4 of the protocol for Part A will not be performed.

1.2.7 Modification on '9.5 Interim analyses'

Due to the study stopping early, the study analyses will now be conducted as one step (as Part B is no longer applicable), at the end of the study.

1.3 DATA HANDLING CONVENTIONS

This section describes the rules and conventions used in the presentation and analysis of data.

The data will be analyzed following the Sanofi guideline for reporting of Phase 1b/2 studies 'Conventions for analyzing and reporting standard Early Development clinical trial data (except Oncology)' (BTD-009094 v4.0). In the statistical appendices and in-text tables, the following treatment labels will be used:

- Isatuximab 140 mg SC Q2W x2
- Isatuximab 280 mg SC Q2W x6
- Isatuximab 560 mg SC Q2W x6

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only the data associated with the final re-screen for a participant will be considered for the definition of analysis populations.

As permitted in the protocol, one participant in Cohort 1 who met retreatment criteria and agreed to be retreated, was retreated as part of Cohort 2. The retreatment period will not be included for any analyses other than listings and will be reported separately. Furthermore, only the data associated with the first treatment period will be considered for the definition of analysis populations. For the retreated participant, the treatment-emergent period is defined as the period from the first IMP administration of the considered study period up to the last IMP administration of the considered study period + 30 days or up to the next study period (excluded), whatever occurred first. For the retreated participant, the following treatment label will be used when applicable:

- Isatuximab 280 mg Retreated SC Q2W x6

For parameters with evaluations before administration and in cases of rechecked value(s) for one participant, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values.

After baseline, only observations planned in the protocol will be used in descriptive statistics.

For clinical laboratory parameters with nonnumeric values, the imputed values used for the descriptive statistics and/or the flags will be determined by considering the following rules:

- If database value is ' < X', the value used will be X/2
- If database value is ' > X', the value used will be $X + 10^{[-\text{number of digits of the considered parameter in the database}]}$
- If database value is a range (eg, 'X – Y'), the values used will be (Y + X)/2

If not otherwise stated in the statistical section of the protocol:

- Missing data other than protocol-planned baseline values will not be replaced.
- Descriptive statistics for quantitative parameters will be provided using number of non-missing observations, mean, SD, SEM, minimum, maximum and median.
- Descriptive statistics for qualitative parameters will be provided using frequencies (N) and percent (%).

Laboratory and vital signs variables

For the following laboratory variables, descriptive statistics and individual plots for results and changes from baseline (absolute or percent change, as applicable) will be provided by planned visit and time and presented by study intervention group.

- Hemoglobin (g/L)
- Markers of hemolysis
  - LDH (µkat/L)
  - Haptoglobin (mg/L)
  - Reticulocytes (%)
  - Total bilirubin (µmol/L)

The variables will be converted into standard international units.

For all laboratory variables, listings will be provided. For vital sign variables, a listing of participants with PCSA will be provided.

Data below the lower limit of quantitation/detection limit (LLOQ) will be treated as LLOQ/2 and values above the upper limit of quantification (ULOQ) will be treated as ULOQ in descriptive statistics.

Pharmacokinetic analysis

For ease of presentation, mean values will be arithmetic mean unless specified otherwise. Plasma concentration values below the plasma assay limit will be treated as zero in calculating mean values. Mean values below the LLOQ will be reported as LLOQ in the tables and not plotted in the figures if after maximum plasma concentration observed (Cmax). Mean calculations and their associated statistics will be generated from unrounded numbers and may differ slightly from those values that would be determined using the rounded numbers displayed in the tables. Values expressed in all tables will be for ease of presentation and will not be meant to imply accuracy to more than 3 significant figures.

Area under the plasma concentration versus time curve (AUC) values extrapolated to infinity by more than 30% will be excluded from any PK statistical analysis.

Plasma concentrations and PK parameters of Isatuximab will be summarized by descriptive statistics (such as arithmetic mean, geometric mean, SD, SEM, coefficient of variation (CV[%]), median, minimum, maximum, and number of observations), for each study intervention group. These descriptive statistics will be performed under the responsibility of the Pharmacokinetics, Dynamics and Metabolism (PKDM) department at Sanofi.

Handling missing data for adverse events

In case of missing or inconsistent information, an AE will be counted as a TEAE, unless it can clearly be ruled out that it is not a TEAE (eg, by partial dates or other information).

If the start date (or time) of an AE is incomplete or missing, then the AE will be considered as a TEAE unless a partial date (or time) or comment shows it as a pre- or post-treatment event.

If the relationship to study drug is missing, the AE will be assessed as unrelated if it started before administration of study medication; in all other cases it will be assumed to be related.

If the severity is missing for one of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity 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.

2 SOFTWARE DOCUMENTATION

The analysis of clinical data will be performed under the responsibility of the Sanofi Biostatistics Department, using SAS® (SAS Institute, NC USA). Statistical analysis of PK parameters will be performed by the Sanofi PKDM Department, using DatAssist_NCA 1.0 and Phoenix 8.2.