# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol title:** | **An open-label study for sutimlimab in participants with cold agglutinin disease (CAD) who have completed the CARDINAL study (BIVV009-03/EFC16215, Part B) or CADENZA study (BIVV009-04/EFC16216, Part B) in Japan.** |
| **Protocol number:** | **LTS17352** |
| **Compound number (INN/Trademark):** | **BIVV009 (sutimlimab)** |
| **Study phase:** | **Phase 3** |
| **Short title:** | **Sutimlimab for the adult participants with cold agglutinin disease (CAD) who have completed Phase 3 studies (CARDINAL or CADENZA) in Japan.** |
| **Statistician:** | [redacted] |
| **Statistical project leader:** | [redacted] |
| **Date of issue:** | **07-Oct-2022** |

**Regulatory agency identifier number(s):**

| | |
|---|---|
| IND: | Not applicable |
| EudraCT: | Not applicable (TBC) |
| NCT: | Not applicable |
| WHO: | U1111-1266-5421 |
| EUDAMED: | Not applicable (TBC) |
| Other: | Not applicable (TBC) |

Total number of pages: 12

## SIGNATURE

| Approver | | Signature and Signature Date |
|---|---|---|
| Sanofi K.K. | Statistical Analysis Manager | [redacted] |
| A2 Healthcare Corp. | Biostatistics Head | [redacted] |
| **Author** | | **Signature and Signature Date** |
| A2 Healthcare Corp. | Biostatistics Lead | [redacted] |

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# VERSION HISTORY

This Statistical Analysis Plan (SAP) for study LTS17352 is based on the protocol dated 30-Jun-2021. This section summarizes major changes to the statistical analysis features in the SAP. The first participant was enrolled on 30-Oct-2021.

**Table 1 - Major changes in statistical analysis plan**

| SAP Version | Approval Date | Changes | Rationale |
|---|---|---|---|
| 1.0 | 07-Oct-2022 | Not Applicable | Original version |

# 1 INTRODUCTION

## 1.1 STUDY DESIGN

This is a multi-center, single treatment-group, open-label study with repeated dose design.

## 1.2 INTERVENTION GROUP

Sutimlimab dose is 6.5 g for participants whose weight is ≥39 kg to <75 kg or 7.5 g for participants ≥75 kg at baseline.

## 1.3 OBJECTIVE AND ENDPOINTS

**Table 2 - Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • Evaluation of overall safety profile for sutimlimab | • Adverse event (AE) /serious adverse event (SAE) / Adverse event of special interest (AESI) |
| **Secondary** | |
| • Not applicable | • Not applicable |

# 2 SAMPLE SIZE DETERMINATION

Up to 7 participants will be enrolled to this study.

Up to 7 participants are expected to complete CARDINAL study or CADENZA study, and to be enrolled to this study.

# 3 ANALYSIS POPULATIONS

The following population for analyses is defined:

**Table 3- Populations for analyses**

| Population | Description |
|---|---|
| Safety | All enrolled participants who take at least 1 dose of study intervention. |

# 4 STATISTICAL ANALYSES

## 4.1 GENERAL CONSIDERATIONS

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.

Baseline is defined as the day of the first dose (Day 0).

Unless otherwise specified, analyses will be performed by intervention group and overall for baseline and demographics characteristics.

Among the descriptive statistics, the mean, standard deviation, and median should be rounded to one more digit than the number of digits in the measurement data, and the minimum and maximum values should have the same number of digits as in the measurement data. Percentages should be expressed to the first decimal place.

## 4.2 BASELINE AND DEMOGRAPHICS CHARACTERISTICS

Descriptive statistics will be calculated for age (year), height (cm), weight (kg), BMI (kg/m^2) and Presence of CAD circulatory symptoms at baseline by intervention group and overall.

## 4.3 PRIMARY ENDPOINT(S) ANALYSIS

### 4.3.1 General common rules for primary endpoint(s) analysis

The primary analyses will be performed on the safety population as defined in Section 3.

TEAEs are defined as AEs that developed, worsened or became serious during the treatment-emergent period.

The primary focus of AE reporting will be on TEAEs.

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.

Multiple occurrences of the same event in the same participant will be counted only once in the tables.

The AE tables will be sorted as indicated in Table 4.

**Table 4 - Sorting of AE tables**

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

*a* Appendix2 for sort order of SOC
*b* Sorting will be based on the overall incidence.
*c* 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.

### 4.3.2 Adverse event

**Analysis of all adverse events**

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

- Total number of TEAEs
- Number of subjects with at least one TEAE
- Number of subjects with at least one related TEAE
- Total number of treatment emergent AESIs
- Number of subjects with at least one treatment emergent AESI
- Number of subjects with at least one related treatment emergent AESI
- Total number of treatment emergent SAEs
- Number of subjects with at least one treatment emergent SAE
- Number of subjects with at least one related treatment emergent SAE
- Number of subjects who discontinued treatment and/or the study due to a TEAE
- Number of deaths

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event (if these types of AE are observed).

**Table 5 - Analyses of adverse events**

| Type of AE | MedDRA levels |
|---|---|
| TEAEs | Primary SOC and PT |
| Treatment emergent AESIs | Primary SOC and PT |
| Treatment emergent SAEs | Primary SOC and PT |
| TEAEs leading to permanent treatment discontinuation | Primary SOC and PT |
| Deaths | Primary SOC and PT |

**Analysis of adverse events of special interest (AESIs)**

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 6. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 4.

**Table 6 - Selections for AESIs**

| AESIs |
|---|
| Symptomatic overdose with study drug |
| Pregnancy |

## 4.4 OTHER ANALYSES

### 4.4.1 Extent of exposure

Study drug exposure, measured by the duration of study treatment and total actual BIVV009 dose, will be summarized for the Safety population. For these items, the mean, standard deviation, and median will be displayed to the second decimal place, and the minimum and maximum values will be displayed to the first decimal place.

The duration of the study treatment (in weeks) is defined as (date of last dose – date of first dose + 15)/7.

The actual dose administered at each infusion is calculated as (Total volume administered / Total volume prepared) * assigned dose.

The total BIVV009 dose is the summation of all actual dose administered.

Study drug compliance will also be summarized for Safety population.

Study drug compliance for a subject is measured by the percent of number of doses received out of the number of protocol specified doses. For example, for a subject who completes the study treatment at Day259, the number of protocol specified doses is 20. The compliance of the subject will be the number of doses received divided by 20 expressed in percentage. For a subject who discontinues early, the number of protocol specified doses is the number of scheduled doses prior to the date of discontinuation.

### 4.4.2 Hemoglobin, bilirubin and lactate dehydrogenase

Hemoglobin (g/dL), bilirubin (mg/dL) and lactate dehydrogenase (U/L) at baseline and at the last measurement will be summarized for Safety population and for the participants who completed the study.

## 4.5 INTERIM ANALYSES

Not applicable.

### 4.6 LISTING（IF ANY）

1. Informed Consent
2. Eligibility (if any violation(s))
3. Demography (including Height and Weight)
4. Presence of CAD circulatory symptoms
5. Clinical Laboratory Test
6. Medical History
7. Infusion of Study Drug
8. Date of Visit
9. Completion/Discontinuation
10. Adverse Event
11. Adverse Event of special interest (Pregnancy)
12. Adverse Event of special interest (Overdose)
13. Prior and/or Concomitant Medication(s)

# 5 SUPPORTING DOCUMENTATION

## 5.1 APPENDIX 1: ABBREVIATIONS AND DEFINITIONS

| Abbreviations | Definitions |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| CAD | cold agglutinin disease |
| -mab | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| SAE | serious adverse event |
| TEAE | treatment-emergent adverse event |

## 5.2 APPENDIX 2: MEDDRA SYSTEM ORGAN CLASS LIST – INTERNATIONALLY AGREED ORDER

Reference: MedDRA 23.1 - September 2020

1. Infections and infestations
2. Neoplasms benign and malignant (including cysts and polyps)
3. Blood and the lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic and mediastinal disorders
14. Gastrointestinal disorders
15. Hepato-biliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal, connective tissue and bone disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital and familial/genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury, poisoning and procedural complications
25. Surgical and medical procedures
26. Social circumstances
27. Product issue.