### 16.1.9 Documentation of statistical methods

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# STATISTICAL ANALYSIS PLAN

## COMPOUND: Dupilumab/SAR231893

## Open-label, interventional, cohort study to evaluate long-term safety of dupilumab in patients with moderate to severe asthma who completed the TRAVERSE LTS12551 clinical trial

## STUDY NUMBER: LPS15023

## STUDY NAME: LONG-TERM FOLLOW-UP

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AEs: | adverse events |
| AESIs: | adverse events of special interest |
| eCRF: | electronic case report form |
| EOS: | end-of-study |
| EOT: | end-of-treatment |
| HLGT: | high level group term |
| ICF: | informed consent form |
| IMP: | investigational medicinal product |
| IRT: | interactive response technology |
| NIMP: | noninvestigational medicinal products |
| PT: | preferred term |
| q2w: | every 2 weeks |
| SAEs: | serious adverse events |
| SD: | standard deviation |
| SOC: | system organ class |
| TEAEs: | treatment-emergent adverse events |
| WOCBP: | women of child-bearing potential |

# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN AND RANDOMIZATION

The LPS15023 study is a Phase IIIb, non-randomized, open-label, interventional, outpatient, prospective, multinational, multicenter, noncomparative, single-arm, safety study in patients with moderate to severe asthma who completed the parent study, TRAVERSE-LTS12551, from here on referred to as TRAVERSE.

This study will evaluate the long-term safety of dupilumab 300 mg q2w administered subcutaneously (SC) over a maximum of 144 weeks.

It is expected that approximately 750 patients will enroll in this study.

## 1.2 OBJECTIVES

### Primary objectives

The primary objective of this study is to describe the long-term safety of dupilumab in the treatment of patients with moderate to severe asthma who completed the previous asthma clinical trial, TRAVERSE-LTS12551.

### Secondary objectives

Not applicable

## 1.3 DETERMINATION OF SAMPLE SIZE

The objective of the study is to continue to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in the previous long-term study TRAVERSE. Therefore, all qualifying patients completing the treatment period in TRAVERSE will be offered to enroll in this study.

It is expected that approximately 750 patients will enroll in this study.

## 1.4 STUDY PLAN

The LPS15023 study consists of 3 periods:

- Start-of-treatment Visit (Visit 1): After completing the EOT Visit (Visit 17) in TRAVERSE, eligible patients should rollover into LPS15023.
- Treatment period (Visit 2 to Visit 12): Open-label treatment for up to 144 weeks (Visit 13, approximately 3 years).
- End-of-treatment/End-of-study (Visit 13).

Patients who prematurely and/or permanently discontinue treatment will be scheduled for the EOT Visit, and the EOS Visit will be scheduled for 12 weeks later for follow-up on AEs.

After completing the treatment period in TRAVERSE, eligible patients who have signed the informed consent form (ICF) should perform the assessments of the Start-of-treatment Visit (Visit 1). Patients will receive treatment until dupilumab approval for use in asthma and market availability to patients, or for a maximum of 144 weeks (i.e. about 3 years) after the Start of treatment (Visit 1), whichever comes first.

The end of clinical trial is defined as the "last patient last visit" planned in the protocol, i.e. the EOT/EOS Visit (Visit 13). The Sponsor reserves the right to discontinue the study at any time.

Study Flow Chart (copied from section 1.1 of protocol)

| **Study periods** | **Start-of-Treatment** | **Treatment Period (144 weeks)** | **End-of-Treatment / End-of-Study** |
|---|---|---|---|
| **Week (W)** | **W0** | **W12-W132 (Visit every 12 weeks)** | **W144** |
| **VISIT** | **V1**[a] | **V2–V12**[b] | **V13**[c] |
| **Enrollment** | | | |
| Informed consent | X | | |
| Patient demography | X | | |
| Eligibility criteria | X | | |
| **Treatment** | | | |
| Contact IRT | X | X | X |
| IMP dispensation/administration[d] | X | X | |
| IMP accountability | X | X | X |
| Injection training/technique observation[e] | X | X | |
| Dispense home-dosing diary[f] | X | X | |
| **Safety** | | | |
| Clinical laboratory[g] | X[h] | X | X |
| Adverse event reporting | X | X | X |
| Symptom-driven physical examination and vital signs | X | X | X |
| Concomitant medications | X | X | X |

AE = adverse events; eCRF = electronic case report form; EOS = end-of-study; EOT = end-of-treatment; IMP = investigational medicinal product; IRT = interactive response technology; q2w = every 2 weeks; V = (study) visit; W = (study) week; WOCBP = women of child-bearing potential.

*a* After completing the EOT Visit (V17) in study TRAVERSE-LTS12551, eligible patients should perform Start-of-treatment (V1) in LPS15023. Additional on-site IMP administration visits may be scheduled at the Investigator's discretion for patients who experience hypersensitivity reactions upon retreatment at this visit, or for patients with long off-treatment interval after the completion of study TRAVERSE-LTS12551.

*b* Visit window is ±7 days with respect to V1, ensuring at least an 11-day interval between 2 consecutive dupilumab administrations.

*c* Patients who prematurely and/or permanently discontinue treatment will be scheduled for the EOT Visit, and the EOS Visit will be scheduled for 12 weeks later for follow-up on AEs.

*d* Dispensation of IMP at every visit (except at EOT/EOS). Administration of 300 mg q2w. Loading dose of 600 mg at V1 for patients who discontinued treatment for ≥6 weeks after TRAVERSE-LTS12551. For administrations coinciding with site visits, patients will be monitored at the study site for a minimum of 30 minutes after injections.

*e* The Investigator or delegate must train the patient (or parent/caregiver[s]) at V1, if starting self-administration, on the preparation and injection of IMP, and review the patient's administration technique at subsequent visits if needed.

*f* The home-dosing diary should be dispensed at the time of injection training/technique observation.

*g* Local laboratory tests: Hematology (blood count: erythrocytes, hemoglobin, hematocrit, leukocytes with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelets), and pregnancy test (urine or blood, for WOCBP only). Only clinically significant values will be captured in the eCRF.

*h* Only for patients who do not roll-over into the study within 4 weeks of EOT or EOS Visit for study TRAVERSE-LTS12551 (see protocol Section 10.1.1).

## 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable

## 1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

| Date | Modification | Reviewer |
|---|---|---|
| March 3, 2021 | Added COVID-based analysis section (section 2.4.5.6) | [redacted] |

# 2 STATISTICAL AND ANALYTICAL PROCEDURES

## 2.1 ANALYSIS ENDPOINTS

### 2.1.1 Demographic and baseline characteristics

***Demographic characteristics***

Demographic variables include:

- Age in years
  - Continuous
  - Categorical (age <18, 18≤ age <65, 65≤ age <75, 75≤ age < 85, age ≥85 years)
- Sex (Male, Female)
- Weight in kilograms
  - Continuous
  - Categorical (<50, ≥50-<100, ≥100)
- BMI in kg/m2
  - Continuous
  - Categorical (<18.5, ≥18.5-<25, ≥25-<30, ≥30)
- Subject enrollment status after ending parent study (within 4 weeks, more than 4 weeks)
- Alcohol Habits
  - How often subject has a drink containing alcohol in the last 12 months? (Never, At least monthly, At least weekly, At least daily)
  - How many standard drinks containing alcohol subject has on a typical day when drinking? (1 or 2, Greater than 2)
- Smoking History
  - Smoking Status (Never, Former)
  - Average Consumption (pack per day) – continuous
  - Number of Years Smoked (years) – continuous
- Pregnancy Test
  - Performed (Yes, No)
  - Results (Positive, Negative)

***Medical history and disease characteristics at baseline***

Relevant medical and surgical history is collected on corresponding CRF.

### 2.1.2 Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

A concomitant medication is any treatment received by the patient concomitantly to the IMP.

Details related to computation, dates, imputation for missing dates are described in Section 2.5.

### 2.1.3 Efficacy endpoints

Not applicable

### 2.1.4 Safety endpoints

Primary endpoint:

- Incidence rates, defined as the percentage of patients reporting any treatment-emergent adverse events (TEAEs), and event rates defined as number of TEAEs per 100 person-years.

Secondary endpoints:

- Incidence rates and event rates per 100 person-years for AESIs over the study.
- Incidence rates for SAEs/death over the study.
- Incidence rates for AEs leading to study discontinuation over the study.

#### *2.1.4.1 Adverse events variables*

AEs and SAEs are defined in Protocol Section 10.4.1.

Adverse events reported in this study will be coded using the version of the Medical Dictionary for Regulatory Activities in effect at Sanofi at the time of database lock. Adverse events occurred during the treatment-emergent period will be considered as TEAE.

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them; AESIs may be added, modified or removed during a study by protocol amendment.

The following is a list of AESIs for this study. For these AESIs, the Sponsor will be informed immediately (i.e. within 24 hours), per SAE notification described in Protocol Section 10.4.1.2, even if not fulfilling a seriousness criterion, using the corresponding screens of the eCRF:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment (see Protocol Appendix F).
- Injection site reactions that are severe and last longer than 24 hours.

- Any serious infection, any bacterial infection requiring treatment with parenteral antibiotics for longer than 2 weeks, any parasitic infection, any systemic opportunistic infection (see Protocol Appendix E), any viral infection requiring antiviral treatment, or any uncommon, atypical, or unusually frequent or persistent infection and TB that requires anti-TB medication. For details, refer to Protocol Section 10.6.3.

Note: Candidiasis – all cases should be collected as AEs (or SAEs if requirements met), however, only cases which are NOT cutaneous (systemic or mucous membranes involved) unless involvement is extensive, will be considered as AESI.

- Pregnancy (female patient or female partner):
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Protocol Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be permanently discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with the IMP/NIMP.
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the planned dose during an interval of less than 11 days. The circumstances (i.e. accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
  - Of note, asymptomatic overdose has to be reported as a standard AE.

#### *2.1.4.2 Deaths*

Deaths will be collected from the time of informed consent signature and then at each visit until the EOT/EOS (Visit 13).

#### *2.1.4.3 Laboratory safety variables*

Clinical laboratory data will be limited to hematology (blood count: erythrocytes, hemoglobin, hematocrit, leukocytes with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils] and platelets), and pregnancy testing.

Only clinically significant laboratory test results will be recorded as AEs in the eCRF.

#### *2.1.4.4 Vital signs variables*

Symptom-driven physical examination and vital signs will be performed in patients presenting with signs or symptoms.

#### *2.1.4.5 Electrocardiogram variables*

Not applicable

## 2.2 DISPOSITION OF PATIENTS

Enrolled patients consist of all the patients who signed informed consent and had a treatment kit number allocated and recorded in IRT database, and regardless of whether the treatment kit was used or not.

The safety population consists of the patients who actually received at least one dose or part of a dose of dupilumab in the current study.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Enrolled patients
- Safety population: patients who received at least one dose in the current study
- Patients who did not complete the study treatment period as per protocol
- Patients who permanently discontinued study treatment by main reason
- Patients who did not complete study follow-up period as per protocol
- Patients who discontinued study by main reason

For all categories of patients, percentages will be calculated using the number of enrolled patients. Reasons for treatment and/or study discontinuations will be supplied in tables giving numbers and percentages.

All critical or major deviations potentially impacting analyses, enrollment, and drug-dispensing irregularities, and other major or critical deviations will be listed.

A patient is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit.

### 2.2.1 Randomization and drug dispensing irregularities

Not applicable

## 2.3 ANALYSIS POPULATIONS

The enrolled population includes all enrolled patients and will be used to summarize demographics and baseline characteristics.

### 2.3.1 Efficacy populations

Not applicable

### 2.3.2 Safety population

The primary analysis population is the safety population, defined as all patients who have received at least one dose or part of a dose of dupilumab during this study.

The treatment-emergent period is defined as the time from the first dose of dupilumab up to the last dose of dupilumab plus 2 weeks for completers, or plus 12 weeks for prematurely discontinued subjects.

## 2.4 STATISTICAL METHODS

### 2.4.1 Demographics and baseline characteristics

Parameters will be summarized on the enrolled population.

Continuous data will be summarized using the number of available data (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

Parameters described in Section 2.1.1 will be summarized for the safety population using descriptive statistics.

Relevant medical or surgical history is collected on CRFs and will be summarized. The alcohol habits, smoking history, and pregnancy test data at baseline will also be summarized.

### 2.4.2 Concomitant medications

A concomitant medication is any treatment received by the patient concomitantly to the IMP. Concomitant medications will be presented for the safety population.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted more than once for the same medication if it was prescribed for different indications.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

### 2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized within the safety population (Section 2.3.2).

#### *2.4.3.1 Extent of investigational medicinal product exposure*

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of exposure to IMP is defined as: last dose date – first dose date of dupilumab + 14, regardless of unplanned intermittent discontinuations. Duration of exposure will be

summarized using descriptive statistics such as mean, standard deviation (SD), median, minimum, and maximum.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories in days: >0-4, >4-12, >12-24, >24-48, >48-72, >72-96, >96-120, >120-142, >142.

#### *2.4.3.2 Compliance*

A given administration of IMP will be considered "noncompliant" if the patient did not take the planned dose of treatment as required by the protocol.

**Percentage of compliance** for a patient will be defined as 100 x (the number of administrations the patient was compliant divided by the total number of administrations the patient was to take during the treatment period).

**Above-planned dosing percentage** for a patient will be defined as the number of administrations that the patient took a higher dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

**Under-planned dosing percentage** for a patient will be defined as the number of administrations that the patient took a lower dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Note: Percentage of compliance + above-planned dosing percentage + under-planned dosing percentage will be lower than or equal to 100%, depending upon the definition of compliance (for instance, the required quantity may be administered, but too rapidly, so that the administration will not be counted as compliant or above-planned dose or under-planned dose).

Treatment compliance will be summarized by categories (eg, >80% compliant, >60 - 80% compliant, >40-60% compliant, <40% compliant). The percentage of patients with compliance <80% will be summarized.

In addition, the number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, >0 - 20%, and >20% under-planned dosing administrations. In addition, overall compliance will be summarized descriptively (N, mean, SD, median, minimum, and maximum).

### 2.4.4 Analyses of efficacy endpoints

Not applicable

### 2.4.5 Analyses of safety data

The primary and secondary analyses are safety related. All safety analysis will be performed on the safety population.

Treatment-emergent AE is defined as any AE with onset on or after the first dose of dupilumab up to the last dose of dupilumab plus 14 days for completers, or plus 84 days for prematurely discontinued subjects.

Primary endpoint:

- Incidence rates, defined as the percentage of patients reporting any treatment-emergent adverse events (TEAEs), and event rates, defined as the number of TEAE events per 100 person-years.

Secondary endpoints:

- Incidence rates and event rates per 100 person-years for AESIs over the study.
- Incidence rates for SAEs/death over the study.
- Incidence rates for AEs leading to study discontinuation over the study.

#### *2.4.5.1 Analyses of adverse events*

***Analysis of Primary Safety Endpoint***

Incidence rates of TEAEs with corresponding 95% CI (by the Clopper-Pearson method) will be calculated as follows:

- Incidence Rate (IR) = number patients with one or more TEAEs / number of subjects at risk (i.e. safety population) × 100

Event rates per 100 person-years of TEAEs with corresponding 95% CI (two-sided exact Poisson CIs) will be calculated. All events reported during the study follow-up period will be counted, regardless of whether they are reported in the same subject (i.e., multiple events per subjects), or different subjects. The person-years at follow-up will be calculated using the standard on-treatment duration formula: (the date of last IMP – date of first dose of IMP + 14 days)/365.25. Note that date of first dose of IMP, is in regards to first dose of this study, not first dose of the parent study. Event rate per person-years will be calculated as follows:

- Event rate (ER) = number of TEAEs / number of person−years at follow up

***Analysis of Secondary Safety Endpoints***

Incidence rates with corresponding 95% CI (Clopper-Pearson method) and event rates with corresponding 95% CI (exact Poisson method) will be presented for AESIs, described in section 2.1.4.1, using the same methodology described above.

Incidence rates with corresponding 95% CI (Clopper-Pearson method) will be presented for SAEs/death over the study.

Incidence rates with corresponding 95% CI (Clopper-Pearson method) will be presented for AEs leading to study discontinuation over the study.

***Generalities***

The primary focus of adverse event reporting will be on treatment-emergent adverse events.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, and PT, sorted in alphabetical order, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population.

***Analysis of all treatment-emergent adverse events***

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Treatment-emergent AESIs
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse event by primary SOC, HLGT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, PT) will be presented in alphabetical order

***Analysis of all treatment emergent serious adverse event(s)***

- All SAEs by primary SOC, HLGT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, PT) will be presented in alphabetical order

***Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation***

- All TEAEs leading to treatment discontinuation by primary SOC, HLGT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, PT) will be presented in alphabetical order

#### *2.4.5.2 Deaths*

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death.
- TEAE leading to death (death as an outcome on the AE eCRF screen as reported by the Investigator) by primary SOC, HLGT, and PT showing number (%) of patients.

#### *2.4.5.3 Analyses of laboratory variables*

Continuous data will be summarized by visit using the number of available data (n), mean, standard deviation (SD), median, minimum, and maximum and change from baseline where appropriate. Categorical and ordinal data will be summarized by visit using the number and percentage of patients.

Clinically significant test results will be recorded as AEs; overall AE summaries will include the AEs reported in the study (see Protocol 11.4.3.1) and the clinical significant test results that are recorded as AEs.

#### *2.4.5.4 Analyses of physical examination and vital sign variables*

Symptom-driven physical examination and vital signs will be performed in patients presenting with signs or symptoms. Continuous data will be summarized by visit using the number of available data (n), mean, standard deviation (SD), median, minimum, and maximum and change from baseline where appropriate. Categorical and ordinal data will be summarized by visit using the number and percentage of patients.

#### *2.4.5.5 Analyses of electrocardiogram variables*

Not applicable

#### *2.4.5.6 Analyses of COVID-19-related variables*

The number and percentage of patients with impact due to COVID-19 will be summarized using the number of patients with at least 1 impacted site visit, the number of patients with at least 1 visit with different impact type (visit not done, visit partially done, visit delayed), the number of visit types (vital signs, local laboratory hematology, pregnancy tests, physical examination and follow-up, investigational product administration, and contact form), and the number of patients impacted per visit. Wave 3 analyses will be performed by assessment and visit type, and stratified by country (France, Canada, and Israel). COVID-19-related analysis will also include Argentina and South Africa in the final analysis.

## 2.5 DATA HANDLING CONVENTIONS

### General conventions

Not applicable

### 2.5.1 Data handling conventions for secondary efficacy variables

Not applicable

### 2.5.2 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

***Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing***

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, last available dose date + 11 days will be used.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

***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 posttreatment medication.

***Handling of adverse events with missing or partial date/time of onset***

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

***Handling of adverse events when date and time of first investigational medicinal product administration is missing***

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

***Handling of missing assessment of relationship of adverse events to investigational medicinal product***

If the assessment of the relationship to IMP is missing, then the relationship to IMP is assumed to be possibly related in summary tables, but no imputation will be presented in the listings.

***Handling of missing severity of adverse events***

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

### 2.5.3 Windows for time points

Not applicable – no analysis by visit/window.

### 2.5.4 Unscheduled visits

Not applicable – no analysis by visit/window.

### 2.5.5 Pooling of centers for statistical analyses

Not applicable

### 2.5.6 Statistical technical issues

Not applicable

# 3 INTERIM ANALYSIS

Interim analyses of data may be conducted to support regulatory submissions or publication activities.

# 4 DATABASE LOCK

The database is planned to be locked at 4 weeks after last patient last visit.

Additional database snapshots/soft locks may be performed to support regulatory submissions.

# 5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Enterprise Guide 7.1 and SAS studio 3.7.

# 6 REFERENCES

Not applicable

# 7 LIST OF APPENDICES

Not applicable