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|---|---|
| Document type: | Statistical Analysis Plan |
| Title: | Effects of oral levosimendan (ODM-109) on respiratory function in patients with ALS: open-label extension for patients completing study 3119002 |
| NCT Number: | NCT03948178 |
| Document Date: | 16 December 2020 |

# STATISTICAL ANALYSIS PLAN

# EFFECTS OF ORAL LEVOSIMENDAN (ODM-109) ON RESPIRATORY FUNCTION IN PATIENTS WITH ALS: OPEN-LABEL EXTENSION FOR PATIENTS COMPLETING STUDY 3119002

**3119003**

**REFALS-ES**

Phase III study

Standard: GCP

[redacted]

Sponsor: ORION PHARMA

[redacted]

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## ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AESI | Treatment-emergent adverse event of special interest |
| ALS | Amyotrophic lateral sclerosis |
| ALSFRS-R | Revised ALS Functional Rating Scale |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| AST | Asparate transaminase |
| ATC | Anatomical therapeutic chemical |
| BMI | Body mass index |
| BP | Blood pressure |
| CAFS | Combined assessment of function and survival |
| CGI | Clinical Global Impression |
| CI | Confidence interval |
| CR10 | Category Ratio 10 |
| CRF | Case report form |
| DSMB | Data and safety monitoring board |
| ECG | Electrocardiogram |
| eGFR | Creatinine clearance |
| FAS | Full analysis set |
| HR | Heart rate |
| IHSC | In-house search category |
| ITT | Intent-to-treat |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed model for repeated measures |
| NIV | Non-invasive mask ventilation |

| | |
|---|---|
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PP | Per-protocol |
| PR | Pulse rate |
| PT | Preferred term |
| RMST | Restricted mean survival time |
| RTSM | Randomization and trial supply management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SMQ | Standardised MedDRA Query |
| SOC | System organ class |
| SVC | Slow vital capacity |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| ULN | Upper limit of normal |
| VAS | Visual analogue scale |

# 1. GENERAL REMARKS

The purpose of this document is to describe the statistical methodology for this clinical study, including also plans of analysis datasets to be used and the plans how the results will be presented.

# 2. OVERALL STUDY DESIGN AND PLAN

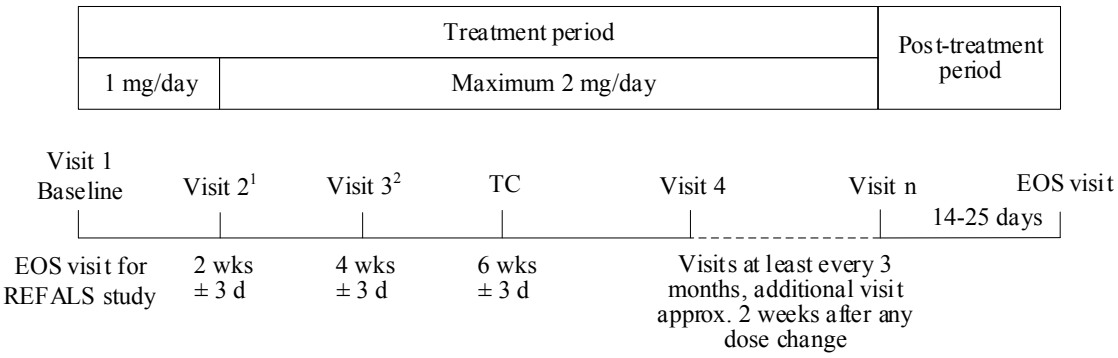
This is an open, non-randomised, uncontrolled, multicentre phase III extension study to the REFALS study.

The subjects will give informed consent (IC) to continue in this open-label extension study at the 48-week or end-of-study visit of the REFALS (or between these visits). The REFALS end-of-study visit will double as the REFALS-ES baseline visit. Visits to the study centre are flexible but occur at least every 3 months. Subject assessments will be conducted 2 weeks after starting the study treatment and after each change in the dose: such visits may be at study centre or conducted remotely where feasible (see section 6.1.3 in the protocol). A telephone contact will be performed for all subjects 6 weeks after starting the treatment.

The subject may continue the treatment as long as clinically indicated (see withdrawal criteria in section 4.5 in the protocol) or until the study ends.

An end-of-study visit will take place 14-25 days after the last study treatment administration for each subject.

The study design is presented in Figure 1.




TC = telephone contact, EOS = end-of-study

[1] Dose increased to 1 mg b.i.d. if the 1 mg/day dosing was well tolerated

[2] Additional visit approx. 2 weeks after any dose change at visit 2

Figure 1. Study design

# 3. STUDY OBJECTIVES

## 3.1 Primary objective

The primary objective, in addition to continuing treatment for subjects in REFALS study, is to evaluate long-term safety of oral levosimendan in ALS patients.

## 3.2 Secondary objectives

The secondary objective is to explore long-term effectiveness of oral levosimendan in the treatment of patients with ALS, by continuing to observe rate of disease progression during the treatment.

# 4. STATISTICAL HYPOTHESES

No formal statistical hypotheses are specified.

# 5. DETERMINATION OF SAMPLE SIZE

No sample size estimation is done. The maximum number of participants is bounded by the number of subjects completing REFALS.

# 6. GENERAL STATISTICAL CONSIDERATIONS

## 6.1 Data sets to be analysed

All analyses will be performed in the safety population, including subjects who receive at least 1 dose of study treatment. No other analysis populations are planned.

## 6.2 Statistical issues

### 6.2.1 Randomization

No randomization is done in the extension study. Subjects were randomized to either levosimendan or placebo in a 2:1 ratio for the main study. That randomization will be used for reporting this study, dividing subjects into arms having received prior levosimendan or placebo.

### 6.2.2 Significance level and confidence intervals

Not applicable. There are no formal hypothesis tests.

### 6.2.3 Multiplicity

No adjustment for multiplicity is planned.

### 6.2.4 Intercurrent events

Not applicable.

### 6.2.5 Dropouts and missing data

Analyses are performed without missing data handling, in a complete-case manner.

### 6.2.6 Outliers

Detection of outliers will be done via visual inspection. If outliers are detected, a sensitivity analysis excluding the outliers may be performed to evaluate their impact to the results.

### 6.2.7 Baseline values

Planned pre-dose values from the baseline visit (which can be either the REFALS end-of-study visit or a separate baseline visit specifically for this study) are used as baseline values.

### 6.2.8 Multiple measurements

Here, a multiple measurement refers to a combination of analysis visit and timepoint where there are more than one value recorded for a given parameter.

If there are multiple measurements for a given parameter-visit-timepoint combination, values from the measurement that was performed last will be used.

### 6.2.9 Multiple timepoints

Visits following the Week 2 (and possible Week 4) site visit(s) and the Week 6 TC will be binned based on time elapsed since the baseline visit; visits falling into the same interval of time will be given the same label for reporting. The binning will be done on a monthly level, with visit days rounded to the nearest full month, using a conversion factor of 1 month = 30.4375 days.

### 6.2.10 Checking model assumptions

Not applicable.

### 6.2.11 Transformations

No data transformations are planned.

### 6.2.12 Multicentre studies

Subject disposition will be tabulated by centre. No additional reporting by centre will be done.

### 6.2.13 Interim analyses and data monitoring

None planned.

### 6.2.14 Subgroups

Summary of AEs and AESIs will be presented in the subgroups of: age; sex; race; BMI; acetylation status; and baseline medical history groups of interest (see 7.3).

### 6.2.15 Descriptive statistics

The following statistics will be provided for continuous variables: number of observations, mean, standard deviation (SD), minimum, median and maximum. For categorical variables, frequency counts and percentages will be presented.

Mean, median and SD values will be presented to one more decimal place than the raw values. Minima and maxima will be presented as they appear. Percentages will be rounded to the nearest single decimal place, with the exception of 0 and 100, which will be presented as integers.

When descriptive statistics are reported by treatment group, data for a pooled total arm will also be reported, unless otherwise specified.

## 7. STATISTICAL ANALYSES

The subject's assigned arm from REFALS will be used when reporting by treatment group.

## 7.1 Disposition of subjects

329 subjects completed the REFALS study. Of those, 28 were ineligible to continue to the extension study, and 54 otherwise eligible subjects did not wish to continue. Of the remaining 247 subjects who wished to continue, 20 were delayed due to COVID-19 related restrictions, and did not start the study before the recruitment was closed. In total, 227 subjects were screened and started the extension.

The number of subjects will be tabulated by treatment group for the following populations:

- Screened population
- Safety population
- Discontinued study

Separate tables by treatment group will also be provided for each country, and each study centre.

The disposition and number of subjects, along with reasons for screening failure and study discontinuations, will be listed and tabulated by treatment group.

## 7.2 Demographic and other baseline characteristics

Descriptive statistics (see 6.2.15) of demographic and other baseline characteristics will be tabulated for the safety population, stratified by treatment group. An authorised person will code medical history and concomitant diseases using standard coding dictionaries (see 7.10.1).

The following variables will be summarized:

1. Age
2. Age (< 65, 65–74, ≥ 75)
3. Sex
4. Race
5. Ethnicity
6. Height
7. Weight
8. BMI
9. BMI (< 18.5, 18.5–24.9, 25.0–29.9, ≥ 30.0)
10. Country
11. Region (North America, rest of the world)
12. Site of onset (bulbar, spinal)
13. El Escorial criteria for ALS diagnosis
14. Disease duration (time from symptom onset to baseline)
15. Below median disease duration (time from symptom onset to baseline)
16. Time from symptom onset to baseline (observed tertiles)
17. Time from symptom onset to baseline (observed quartiles)
18. Acetylation status (slow, rapid; see 7.7)
19. Acetylation status (4 groups; see 7.7)
20. Cardiac or vascular abnormality (see 7.3)
21. Ischaemic heart disease (see 7.3)
22. Cardiac arrhythmias (see 7.3)
23. Cardiac failure (see 7.3)
24. SVC (sitting) at baseline
25. Below median SVC (sitting) at baseline
26. SVC (supine) at baseline
27. Below median SVC (supine) at baseline
28. King's clinical stage at baseline (see 7.5.2.1)
29. ALSFRS-R at baseline
30. Below median ALSFRS-R at baseline
31. ALSFRS-R bulbar subdomain at baseline
32. ALSFRS-R fine motor subdomain at baseline
33. ALSFRS-R gross motor subdomain at baseline
34. ALSFRS-R respiratory subdomain at baseline
35. ALS progression rate at baseline
36. ALS progression rate at baseline (< 1 point/month, ≥ 1 point/month)
37. ALS progression rate at baseline (observed tertiles)

Values for the above variables will be summarized also at REFALS baseline as part of the additional combined reporting described in 7.10.4.

## 7.3 Medical history

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Descriptive statistics will be provided by body system organ class (SOC), and preferred term (PT), by treatment group.

Past findings, where the subject reports the condition has ended prior to their start of the study, and present findings, those ongoing at the start of the study, will be reported separately.

The following categories define groups of interest used in safety subgroup analyses:

1. Cardiac or vascular abnormality
2. Ischaemic heart disease (SMQ)
3. Cardiac arrhythmias (SMQ)
4. Cardiac failure (SMQ)

Both past and present findings at the start of the study are included in forming these groups. See Appendix 10.1 for definitions of the search categories. If an SMQ has both a broad and a narrow definition, the narrow search will be used.

## 7.4 Extent of exposure and treatment compliance

The total number of exposed subjects, the total duration of study treatment exposure (continuous, and categorized both separately and cumulatively at the thresholds of $\leq 4$, $\leq 8$, $\leq 12$, $\leq 24$, and $\leq 48$ weeks), and dose levels (in milligrams), averaged over the course of the study as well as at each study visit, will be reported as measures of extent of exposure.

Dose changes will be described by reporting the subject counts in the following categories:

1) remained at 1 mg for the entire study (“never increased”)
2) uptitrated to 2 mg and remained for the rest of the study (“increased and remained”)
3) uptitrated to 2 mg and later downtitrated to 1 mg (“increased, then decreased”)
4) downtitrated to 0.5 mg directly (“decreased directly”).

Treatment compliance will be described by reporting the number of dispensed and returned study treatment capsules at each study visit. The number of subjects with treatment interruptions longer than 7 days will be reported with descriptive statistics.

Both extent of exposure and treatment compliance will be tabulated with descriptive statistics.

## 7.5 Efficacy

All efficacy data will be listed and tabulated by treatment group for each visit.

### 7.5.1 Primary efficacy variable(s)

#### 7.5.1.1 Slow Vital Capacity

SVC is defined as the maximum volume of air that the subject can exhale slowly after slow maximum inhalation. The raw SVC volume is measured in litres. The SVC variable used in the

analyses is derived from the raw SVC volume, and measured as a percentage of the predicted (normal) volume for age, height and sex. Predicted values used for the calculation are derived based on the global lung function 2012 equations (Quanjer PH et al., 2012).

SVC will be assessed in the sitting and supine position once at each centre visit during the study including the baseline (visit 1), i.e. in the morning before the study treatment administration. The MasterScope (used in the REFALS study) with centralised reading will be used in all study centre visits during the first 3 months (so that all subjects have at least 1 post-baseline assessment with the device), after which each centre will either use its own standard pulmonary function test equipment or continue using the MasterScope without centralised reading. At baseline (visit 1), the SVC will be assessed by using both MasterScope and the local equipment.

Descriptive statistics will be reported by treatment group for SVC in both supine and sitting positions (including original values, and change from baseline) at each study visit. For supine SVC, descriptive statistics will also be further broken down by angle of measurement.

Slope of decline will be estimated for both treatment groups, using a random slope model for change from baseline. To facilitate comparison with the main study, the model will be adjusted for REFALS randomization strata, and include the baseline measurement as a covariate.

Measurements made with local devices (or MasterScope without centralised reading) and MasterScope devices with centralised reading will be reported separately, along with a third combined measurement which includes measurements from either type of device, preferring the MasterScope measurement with centralised reading if both are present on a given visit. Measurements of unacceptable quality (BTRGRCD = "U") will be excluded from reporting.

### 7.5.2 Secondary efficacy variables

#### 7.5.2.1 Revised ALS Functional Rating Scale

The ALSFRS-R (Cedarbaum JM et al., 1999) includes 12 items: speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting sheets, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each item will be scored from 0 to 4, with lower values indicating worse function. The variables derived will be the scores of the 12 separate items, the total scores of each subdomain (bulbar [items 1-3], fine motor [4-6], gross motor [7-9] and respiratory [10-12]) and the total score of ALSFRS-R.

Descriptive statistics will be reported by treatment group for all items in the scale, as well as each subdomain and the total scale at each study visit (original values, and change from baseline).

Slope of decline will be estimated for both treatment groups, using a random slope model for change from baseline. To facilitate comparison with the main study, the model will be adjusted for REFALS randomization strata, and include the baseline measurement as a covariate.

Further, time to decline from baseline in an ALSFRS-R respiratory domain score (items 10–12) will be described (see 7.5.2.2).

To describe the study population, two additional variables will be derived from the ALSFRS-R:

King's clinical stage is a staging system used to measure the clinical progression of the ALS disease across body system regions. Staging is not directly collected as part of the study. Instead, King's clinical stage will be estimated from the ALSFRS-R as follows (Balendra, 2014):

1. Respiratory failure (Item 10 = 0 or Item 12 < 4) ⇒ Stage 4b
2. Nutritional failure (answered item 5b) ⇒ Stage 4a
3. For lower stages, count the number of regions involved:
    a. Bulbar (any of items 1–3 < 4)
    b. Upper limbs (either of items 4 and 5a < 4)
    c. Lower limbs (item 8 < 4)

King's stage is used to describe disease progression status at baseline.

ALS progression rate at baseline will be calculated as the number of points missing from a full ALSFRS-R score (48) at baseline divided by the time (in months) between symptom onset and the baseline ALSFRS-R measurement.

#### 7.5.2.2 Time-to-event endpoints

The following time-to-event secondary efficacy variables will be evaluated:

1. Time to NIV or death (NIVDEATH)
2. Time to decline from baseline in any ALSFRS-R respiratory domain score (FRSBR1D)

The data for the time-to-event variables will be stored in the ADTTE dataset with parameter names corresponding to those in parentheses above.

Premature discontinuations will be treated as right-censored in the analyses. Censoring rules for different scenarios are described in Table 1. For the purpose of determining the end date, survival and ventilation status are considered to be assessed daily; ALSFRS-R and SVC measurements are assessed only on study visits.

For descriptive purposes, Kaplan-Meier survival curves will be plotted.

#### 7.5.2.3 Borg Category Ratio 10 Scale

The Borg Category Ratio 10 (CR10) scale will be used in the assessment of dyspnoea (Borg GA, 1982). The subjects will be asked to point out a score quantifying their perception on the intensity of dyspnoea on the CR10 scale at rest in sitting and supine positions (immediately before SVC measurements). Orthostatic changes between sitting and supine positions will be calculated.

Descriptive statistics for all Borg CR10 variables (original values, and change from baseline) will be reported by treatment group for each study visit.

Table 1. Censoring rules for time-to-event analyses.

| *Scenario* | *Censored* | *End date* |
|---|---|---|
| Event criteria fulfilled | No | Date of endpoint assessment |
| Event criteria fulfilled at baseline | Yes | Date of baseline visit |
| Event criteria never assessed | Yes | Date of baseline visit |
| Discontinued study | Yes | Date of last endpoint assessment |
| Discontinued study treatment (1 day after*) | Yes | Date of last endpoint assessment |
| Died, when death not part of event criteria | Yes | Date of last endpoint assessment |
| Died, when death is part of event criteria | No | Date of death |

*) to account for potential events following immediately after the study treatment discontinuation.

### 7.5.3 Additional variables

#### 7.5.3.1 Health care and home care resource use

The subjects will be given a home diary for recording their use of health and home care resources. The diary will be filled in on a weekly basis. Any hospital inpatient days, other institutional care, any additional hospital emergency unit visits, days in other institutional care, and any outpatient visits to physicians or other relevant service providers will be recorded. In addition, all non-medical assistive devices that the subjects have in use at baseline are recorded, and thereafter all new devices that they start using due to ALS will be recorded in the diary each week. Regarding home care, the diary will contain information of the number of formal (paid/public services) and informal (unpaid e.g. by spouse, other family members, friends or other volunteers) home care hours received. Additionally, information will be collected about the number of times such home care has been received during the nighttime. Details of the home diary will be described in a separate document.

Health and home care resource use data will be aggregated over the course of the study for each subject, and summarised using descriptive statistics. Any further analysis for potential pharmacoeconomic purposes will be reported separately.

### 7.5.4 Sensitivity analyses

None planned.

## 7.6 Pharmacokinetics and pharmacodynamics

None planned. Blood samples were not collected.

## 7.7 Pharmacogenomics

Acetylation status was determined by bioanalytics in the main study, and categorized into four and two levels for reporting. Descriptive statistics for both will be reported by treatment group.

The two-level categorization of acetylation status will be used to stratify the reporting of safety.

## 7.8 Exploratory biomarkers

None pre-planned for the clinical study report.

## 7.9 Safety

The analyses presented in this section will be reported for the Safety population, including all subjects having received any study treatment.

### 7.9.1 Deaths

The number of deaths will be reported with descriptive statistics by treatment group and relation to study treatment: before, during treatment or within 25 days of stopping, or later.

### 7.9.2 Adverse events

Adverse events (AEs) will be classified by system organ classes (SOC) and preferred terms (PTs) using the MedDRA dictionary version 23.1.

A treatment-emergent AE (TEAE) is defined as any event arising or worsening after the start of study drug administration until 25 days after the last study medication intake.

A summary of TEAEs and non-TEAEs will be presented, showing total numbers of events and subjects having events:

1. Fatal outcome
2. SAE status
3. Other significant AEs
4. AESI status
5. Causality
6. Severity
7. Actions taken

The number of TEAEs, and number and proportion (%) of subjects having TEAEs by SOC and PT will be given by treatment group. The number of events will also be broken down by:

1. Severity (mild, moderate, severe)
2. Causality (related, not related)
3. Timing with respect to starting treatment (disjoint union of: ≤ 2 weeks, ≤ 4 weeks, ≤ 8 weeks, ≤ 12 weeks, ≤ 24 weeks, ≤ 48 weeks)
4. Dose change groups (see 7.4)

Incidence rates for subjects' first events adjusted for exposure time will also be reported. They are calculated by dividing the number of subjects ever experiencing the event while on treatment by the number of days subjects were exposed to the study treatment.

All serious adverse events (SAEs) and other significant AEs will be evaluated case by case. Narrative descriptions will be included in the study report for all AEs leading to death, other SAEs, AEs leading to study treatment withdrawal, and certain other significant AEs (OSAEs).

Groups of treatment emergent AEs of special interest (AESIs) are defined by Standardized MedDRA Queries (SMQs) where noted, and by in-house search categories (IHSCs) defined as lists of preferred terms, otherwise. Statistics for the following AESIs will be reported:

1. Asthenia or fatigue
2. Decrease in red cell parameters
3. Drug related hepatic disorders - comprehensive search (SMQ)
4. Haemorrhages (SMQ)
5. Headache
6. Hypokalaemia (SMQ)
7. Hypotension
8. Increased heart rate
9. Ischaemic heart disease (SMQ)
10. Neurocognitive disorder
11. Palpitations
12. Suicide/self-injury (SMQ)
13. Supraventricular tachyarrhythmias (SMQ)
14. Ventricular tachyarrhythmias (SMQ)

See Appendix 10.2 for the queries used to create the groups. If an SMQ has both a broad and a narrow definition, the narrow search will be used.

In addition to standard AE reporting, detailed characteristics will be reported for AESIs:

1. SAE status
2. Need for concomitant medications
3. Severity
4. Changes in dosage
5. Outcome
6. Timing with respect to starting treatment
7. Duration of event
8. Safety subgroups (listed in 6.2.14)

Further, for AESIs, 95% confidence intervals (CIs) will be reported for incidence proportions and incidence rates, and risk ratios and incidence rate ratios (with 95% CIs) between the treatment groups will be estimated.

### 7.9.3 Laboratory values

Laboratory variables are not collected as part of the regular study visits. However, baseline values from the REFALS end-of-study visit will be summarised with descriptive statistics. See REFALS SAP for further definitions.

### 7.9.4 12-lead ECG

Descriptive statistics of standard 12-lead ECG variables and abnormal ECG findings will be tabulated by treatment group for each study visit.

Disjoint comparisons of heart rate changes from baseline to the thresholds of > 20 bpm and > 30 bpm will be summarised by treatment group at each study visit.

### 7.9.5 Vitals signs

Descriptive statistics of subject weight, BMI, vital signs (i.e. pulse rate and both systolic and diastolic blood pressure in supine position) will be tabulated by treatment group for each study visit.

Descriptive statistics will also be reported for the following categorised measurements:

- systolic blood pressure:
  - < 90 mmHg and a decrease of ≥ 20 mmHg
  - > 140–160 mmHg and an increase of ≥ 20 mmHg
  - > 160 mmHg and an increase of ≥ 20 mmHg
- diastolic blood pressure:
  - < 60 mmHg and a decrease of ≥ 20 mmHg
  - > 90–100 mmHg and an increase of ≥ 20 mmHg
  - > 100 mmHg and an increase of ≥ 20 mmHg
- pulse rate:
  - < 60 bpm and a decrease of ≥ 15 bpm
  - > 100 bpm and an increase of ≥ 15 bpm
- change from baseline body weight:
  - a decrease of:
    - > 7–10%
    - > 10–20%
    - > 20%
  - an increase of:
    - > 7–10%
    - > 10–20%
    - > 20%

### 7.9.6 Physical findings and other observations

Special situations and physical examination findings will be summarised by treatment group using descriptive statistics.

## 7.10 Additional analyses

### 7.10.1 Prior and concomitant treatments

Prior and concomitant treatments will be coded using the anatomical therapeutic chemical (ATC) classification system, WhoDrug version V201909. The number and percentage of subjects using prior (started before baseline) and concomitant (ongoing at end of follow-up, or stopped after baseline) treatments will be summarised by pharmacological subgroup and chemical substance.

### 7.10.2 Suicidality

Suicidality will be summarised at each visit by treatment group using descriptive statistics. Additionally, suicidality at any point over the course of the study will be described.

### 7.10.3 COVID-19

The number of subjects affected with any changes to study visit procedures, the number of protocol deviations, and study visits performed as a telephone contact rather than a protocol-specified on-site visit due to COVID-19 will be summarized by treatment group with descriptive statistics.

Both confirmed and suspected infections of COVID-19 will be reported as adverse events. The number of affected subjects will then be found as part of regular AE reporting (see 7.9.2).

In addition to appearing in standard reporting, protocol deviations and AEs related to COVID-19 will also be summarised in a dedicated section.

### 7.10.4 Combined analyses with the main study

Additional analyses combining the data collected in REFALS with the data collected in REFALS-ES will be performed outside the scope of the clinical study report. This section outlines the currently planned analyses.

The primary population used for combined reporting will be the REFALS safety population.

REFALS study baseline characteristics will be reported for the REFALS-ES safety population.

Descriptive statistics for change from REFALS baseline will be reported for supine SVC, ALFSFR-R and Borg endpoints, as well as vital signs (pulse rate, systolic and diastolic blood pressure).

Descriptive statistics for supine SVC and ALSFRS-R endpoints over the course of both studies will be reported in relevant efficacy subgroups identified in the REFALS study.

Random slope models will be fitted using data from both studies to estimate the rate of decline in supine SVC and ALSFSR-R endpoints over an extended follow-up period. A time-by-study-by-arm interaction will be investigated to potentially identify a change in slopes for the placebo arm transitioning over to active treatment for REFALS-ES.

Kaplan-Meier curves will be estimated for the time-to-event endpoints described in 7.5.2.2, and additionally time to invasive ventilation (tracheostomy or intubation) or death, and time to death. Estimation will start from the REFALS baseline and continue until the end of the extension study.

Adverse events and the number of deaths over the course of both studies will be summarised.

## 7.11 Changes from the clinical study protocol

Due to the results of the main study, and the consequent early termination of this extension study, the scope of reporting has been narrowed.

Most statistical analyses have been removed; instead, we report only descriptive statistics.

The analysis population is referred to as “safety population” rather than “full analysis set” for clarity, as the definition completely aligns with the safety population concept.

Protocol-defined reporting of REFALS baseline characteristics has been moved to additional analyses. Baseline characteristic reporting now reflects status at REFALS-ES baseline.

## 7.12 Execution of statistical analyses

Statistical analyses will be performed by or under the supervision of Data Science at Orion Pharma.

## 7.13 Software

Statistical analyses, tables and subject data listings will be performed with SAS® for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA).

# 8. REFERENCES

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Cedarbaum JM et al. (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 169 (1-2): 13-21.

Quanjer PH et al. (2012) Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 40 (6): 1324-43.

# 9. REVISION HISTORY

| Version | Date | Summary |
|---|---|---|
| **0.19** | 2020-12-16 | Cleaned up version for approval. No content changes. |
| **0.18** | 2020-12-16 | Revised based on comments reviewers. Primary change was to add additional combined analyses separately. |
| **0.1** | 2020-12-04 | Initial draft based on REFALS SAP. |

# 10. APPENDICES

## 10.1 Medical history groups of interest

https://pallas.orion.fi/webtop/urn.htm?id=090017ff8243e30b&version=0.1

## 10.2 Adverse events of special interest

https://pallas.orion.fi/webtop/urn.htm?id=090017ff8243e35a&version=0.2