Statistical Analysis Plan

Title: A 6-Month Extension Study Following Protocol VMALS-002-2 (A Phase 2a, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety of Engensis in Participants with Amyotrophic Lateral Sclerosis)

Protocol Number: VMALS-002-2b

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[redacted]

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New Document

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale

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1 INTRODUCTION

This is a Phase 2, 6-month extension study, multicenter study designed to assess the long-term safety of Engensis (containing the active pharmaceutical ingredient VM202) in Participants with ALS.

This document details the planned statistical analyses for the Helixmith Co., Ltd VMALS-002-2b study titled "A 6-Month Extension Study Following Protocol VMALS-002-2 (A Phase 2a, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety of Engensis in Participants with Amyotrophic Lateral Sclerosis)". This document covers all statistical analyses planned in the study.

The proposed analyses are based on the contents of the final protocol, version 1.1 (dated 12-OCT-2021).

2 STUDY OBJECTIVES

Primary Objective:

- To evaluate the long-term safety of intramuscular (IM) injections of Engensis in Participants with Amyotrophic Lateral Sclerosis (ALS)

Exploratory Objectives:

- To evaluate changes in muscle function following Engensis injections in ALS Participants
- To evaluate muscle strength changes following Engensis injections in ALS Participants
- To determine whether IM administration of Engensis has effects on respiratory function in ALS Participants
- To determine whether IM administration of Engensis has positive effects on survival in ALS Participants
- To evaluate Quality of Life improvement following Engensis injections in ALS Participants compared to Placebo
- To evaluate Patient and Clinical Reported Outcome improvement following Engensis injections in ALS Participants compared to Placebo

3 ENDPOINTS

3.1 Primary Endpoints

- Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest (AESIs) for Engensis compared to Placebo
- Incidence of clinically significant laboratory values for Engensis compared to Placebo

3.2 Exploratory Endpoints

- Change from Baseline (Study VMALS-002-2 Day 0) in total mean Revised Amyotrophic Lateral Sclerosis Function Rating (ALSFRS-R) scores at Day 365 for Engensis compared to Placebo
- Change from Baseline (Study VMALS-002-2 Day 0) in ALSFRS-R subscores for Fine and Gross Motor Functions (sum of scores for items 4 to 9) and for Bulbar Function (sum of scores for items 1 to 3) at Day 365 for Engensis compared to Placebo
- Changes in the slope of the total ALSFRS-R score over time for Engensis compared to Placebo
- Change from Baseline (Study VMALS-002-2 Day 0) in muscle strength assessed bilaterally by Handheld Dynamometry (HHD) in muscles in the upper and lower extremities at Day 365 for Engensis compared to Placebo
- Change from Baseline (Study VMALS-002-2 Day 0) in Quality of Life (QoL) using the ALS Assessment Questionnaire (ALSAQ; with 40 items, ALSAQ 40) on Day 365 for Engensis compared to Placebo
- Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) at Day 365 for Engensis compared to Placebo
- Change from Baseline (Study VMALS-002-2 Day 0) in Slow Vital Capacity (SVC) at Day 365 for Engensis compared to Placebo
- Time to tracheostomy for Engensis
- Time to all-cause mortality compared to Placebo

4 SAMPLE SIZE

The number of Participants in this study will be determined by the number who complete the Day 180 Visit in VMALS-002-2. The maximum potential Participants in VMALS-002-2b is 18, based on enrollment in VMALS-002-2.

5 RANDOMIZATION

Not applicable in this SAP.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the efficacy and safety data results. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Sets

6.1.1 Safety Analysis Population

The safety analysis population will contain all Participants who sign the Informed Consent of the VMALS-002-2b study. Participants will be grouped according to their actual treatment received in VMALS-002-2 study.

6.2 Derived Data

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives first Study Injection in the Study VMALS-002-2.

6.2.3 Duration / Study Day / Time

Study day will be calculated as the number of days from first Study Injection in the Study VMALS-002-2:

- date of event – date of first Study Injection + 1, for events on or after first Study Injection in the Study VMALS-002-2
- date of event – date of first Study Injection, for events before first Study Injection in the Study VMALS-002-2

Duration of ALS diagnosis will be presented in months and calculated as (Date of Screening of the Study VMALS-002-2– Date of Onset of Symptoms +1) / 30.4375.

Time to tracheostomy will be calculated as time from date of first Study Injection in the VMALS-002-2 Study to date of first occurrence of ALSFRS-R questionnaire with answer **"0 - Invasive mechanical ventilation by intubation or tracheostomy"** to question **"12. Respiratory insufficiency" (**ASLFRS-R date – date of the first injection +1) presented in days.

Time to all-cause mortality will be calculated as the time period from date of first Study Drug Injection in the Study VMALS-002-2 to date of death within 365 days presented in days (death date – date of the first injection +1).

Both time-to-event endpoints will be censored by date of last visit.

6.2.4 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

6.2.5 Missing / Partial Start / Stop Date of Adverse Events (AE) and Concomitant Medications

Missing and partial start and stop dates will be imputed for analysis purposes as follows.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.

- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the subject's screening date or the stop date of the event / concomitant medication whichever is earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing, the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is the latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in the same month as the first dose of study drug in which case, the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

6.2.6 Missing Last Dates of Study Drug Dosing

Not applicable in this SAP.

6.2.7 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

6.2.8 Exposure to Study Drug

Not applicable in this SAP.

6.2.9 Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)

Subscore for Fine and Gross Motor Functions will be calculated as sum of scores for items 4 to 9; subscore for Bulbar Function will be calculated as sum of scores for items 1 to 3. Total score will be calculated as sum of scores for items 1 to 9.

6.2.10 Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40)

The questionnaire consists of 40 questions (Q1-Q40), which are converted to 5 subscales using the following rules (according to the ALSAQ User Manual):

PHYSICAL MOBILITY = ((Q1 + Q2 + Q3 + Q4 + Q5 + Q6 +Q7 + Q8 + Q9 + Q10)/40) x 100.

ACTIVITIES OF DAILY LIVING/INDEPENDENCE = ((Q11 + Q12 + Q13 + Q14 + Q15 + Q16 + Q17 + Q18 + Q19 + Q20)/40) x 100.

EATING AND DRINKING = ((Q21+Q22+Q23)/12) x 100.

COMMUNICATION = ((Q24 + Q25 + Q26 + Q27 + Q28 + Q29 + Q30) /28) x 100.

EMOTIONAL FUNCTIONING = ((Q31 + Q32 + Q33 + Q34 + Q35 + Q36 + Q37 + Q38 + Q39 + Q40)/40) x 100.

If a subscale of the questionnaire has less than 50% of the questions correctly answered, it should be considered as missing.

The following approaches will be used in case of missing or incorrectly answered questions:

- Worst values will be imputed
- Average value of correctly filled questions of the subscale

Results of both approaches will be presented in separate tables. Subscale values will be presented with 1 decimal place. Number of decimal places for descriptive statistics will be presented using rules in Section 6.3.1.

6.2.11 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.12 Vital Signs

Body Mass Index (BMI) will be calculated as [weight in °KG] ÷ ([height in °CM] ÷ 100)^2.

6.2.13 Unscheduled Visits

Only scheduled post-baseline values will be tabulated. Post-baseline repeat / unscheduled assessments will not be tabulated, although these post-baseline assessments will be listed in the relevant appendices to the CSR. In all tables, excepting the table for participant visits (Table 14.1.1.2) data of the Early Termination visit will be combined with data of Day 365 visit.

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[1] unless otherwise noted.

Summaries will be presented by treatment group. Treatment group labels will be displayed as follows:

Engensis (N=XX)	Placebo (N=XX)	Overall (N=XX)

Listings will be sorted in the following order treatment group, Participant, parameter unless otherwise stated. All data will be listed.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments will be given.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the participant population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Decimal places for derived data described in section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the

interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where the result is known in advance will be an integer; for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

Rounding will be carried out according to the following rules: if the digits on the right start with 0, 1, 2, 3 or 4, then the rounding digit will remain unchanged, if the digits on the right begin with 5, 6, 7, 8 or 9, then the rounding digit will be increased by 1.

6.4 Subject Disposition

The following data will be tabulated: subjects completed the study, cases of withdrawal/discontinuation by primary reason will be tabulated for the Safety Analysis Population (Table 14.1.1.1). Participant visits will be presented in a separate table (Table 14.1.1.2).

The following data will be presented in a listing (Listing 16.2.1.1):

- Date of Informed Consent
- Original Consented Protocol Version
- Date of Discontinuation
- Primary reason for discontinuation
- Study completion (Yes/No)
- Date of last dose (from VMALS-002-2)
- Date of last visit

6.5 Protocol Deviations

A listing of protocol deviations will be provided. The listing will include participant number, protocol deviation description and deviation comments (Listing 16.2.1.2).

6.6 Baseline Comparability

Demographics and baseline characteristics will be presented for the Safety Analysis Population.

The comparability of treatment groups with respect to participant demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by randomized treatment group for the following variables:

- Demographic and Baseline Characteristics collected at screening visit (Table 14.1.2.1)
  - Age
  - Gender
  - Child-bearing potential
  - Race
  - Ethnicity

Weight, height and BMI and their changes from baseline will be presented in a separate table (Table 14.1.2.2).

All demographic and baseline characteristics will be presented in a listing (Listing 16.2.4.1).

6.7 Medical History

Not applicable in this SAP.

6.8 Concomitant Medications

All collected medications will be considered as concomitant medications.

Concomitant medications will be presented for the Safety Analysis Population.

Concomitant medications will be coded using WHO Drug dictionary version March 2020 (or later) and summarized using Anatomic Therapeutic Chemical (ATC) Level 3.

Concomitant medications will be presented in a table by randomized treatment group (Table 14.3.8.1) and in a listing (Listing 16.2.4.2).

6.9 Exposure to Study Drug

Not applicable for this SAP.

6.10 Treatment Compliance

Not applicable for this SAP.

6.11 Efficacy Analyses

Not applicable for this SAP.

6.12 Pharmacokinetic Analyses

Not applicable for this SAP.

6.13 Pharmacodynamic Analyses

Not applicable for this SAP.

6.14 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Analysis Set.

6.14.1 Adverse Events

All study-related Adverse Events (AEs) will be collected starting after completion of the IC process at Screening to Day 0/randomization of the VMALS-002-2 study. Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) will be collected after first injections of VMALS-002-2 study until the time that the Participant withdraws the IC of this study. All Serious Adverse Events (SAEs) will be collected from the completion of the IC process until the time that the Participant withdraws the IC of this study. Any SAE occurring after IC of VMALS-002-2 study and before the first injection should be recorded and reported only if associated with a VMALS-002-2 protocol-specified procedure. Any AEs reported during Screening of VMALS-002-2 study after completion of IC of VMALS-002-2 study will be collected and recorded separately from TEAEs reported on Day 0 and through the end of the study.

Medical occurrences that begin before the start of study intervention and not related to required study procedures, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not as AEs.

Adverse events with relationship equal to “Possibly related”, “Probably related” and “Definitely related” will be considered as adverse events related to study medication. If an AE has missing relationship it is assumed to be possibly related to the study drug for analysis purposes.

Adverse events with fatal outcome will be considered as fatal events. Maximum severity will be assumed for an AE with missing severity.

AEs will be coded using Medical Dictionary of Regulated Activities (MedDRA, version 23.0, or later) by System Organ Class (SOC) and preferred term (PT).

In this study the adverse events (AEs) will be presented from collected since Screening visit of VMALS-002-2 study. AEs that registered as not treatment emergent (not TEAEs) will be presented in a separate listing and will not be tabulated. TEAEs will be tabulated in similar manner as two sets: TEAEs started at date of signing of IC for this study or later and all TEAEs collected during both studies. All AEs from both studies will be united for presenting in listings.

6.14.1.1 Treatment Emergent Adverse Event (TEAE) Definition

- A TEAE is any untoward medical occurrence associated with the use of an investigational product or study procedure in a clinical study Participant, whether or not considered related to the study intervention.
- NOTE: A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention or procedure.
- An event that emerges during treatment, having been absent at pretreatment, or worsens relative to the pretreatment state, as defined in the E9 Guidance.
- The TEAE is not related to causality / drug relatedness. It may or may not be related to the drug but is considered a TEAE due to its appearance at or after the treatment has been administered.

Events Meeting the TEAE Definition

- Any abnormal laboratory test results (hematology, or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an TEAE/TESAE unless

it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the TEAE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the Participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the TEAE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

6.14.1.2 Treatment Emergent Serious Adverse Event (TESAE) Definition:

Any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the Participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - In general, hospitalization signifies that the Participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the TEAE should be considered serious.
   - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an SAE.

d. Results in persistent disability/incapacity
   - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the Participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

6.14.1.3 Adverse Events of Special Interests (AESI)

There are 3 main categories of AESIs as presented below:

a) considered to be related to the angiogenesis potential of Engensis
b) other medical problems in this patient population
c) COVID-19 infections occurring in Participants during the study

AESI Considered Related to Angiogenesis

Atherosclerosis

Hyperplasia of the vasa vasorum in the early stages of atherosclerosis is independent of angiogenesis, but the intimal neovascularization that follows the hyperplasia of the vasa vasorum is angiogenesis-dependent. Angiogenesis increases oxygen and nutrients to the artery wall and supports initial plaque growth. Once the atherosclerotic plaque develops, intimal angiogenesis is thought to contribute to characteristics of an unstable plaque, plaque hemorrhage, and plaque rupture. Therefore, diagnoses suggestive of recent coronary artery disease since Baseline will be evaluated as AESIs.

Cancer

Angiogenesis plays an important role in the proliferation and metastatic spread of cancer as these processes are dependent on an adequate supply of oxygen and nutrients and removal of waste products. All types of cancer reported during the study will be deemed to be AESIs.

Other Medical Problems in ALS Patients

- Pulmonary Medical Problems: Because patients with ALS are at an increased risk to develop pulmonary medial problems such as aspiration of food or liquids. pneumonia, and respiratory arrest, all events of this type that occur during the study will be considered AESIs.
- Progressive Muscle Weakness: Because some patients with ALS may develop rapidly progressive muscle weakness that results in loss of ability to care for self, decubitus ulcers, or weight loss due to impaired deglutition, all events of this type that occur during the study will be considered AESIs.
- Bulbar Disease: Participants may develop bulbar disease or worsening on bulbar disease during the study, manifested as challenges with dysarthria, facial weakness, impaired tongue pulsion or palate elevation, and impaired mastication and swallowing; all of these types of events that occur during the study will be considered AESIs.

COVID-19 Infections

A diagnosis of COVID-19 infection occurring in participants will be recorded as an AESI and their disposition during the trial following the diagnosis of the COVID-19 infection will be tracked.

6.14.1.4 Outputs planned for Adverse Events

TEAEs with start date and time before date and time of the Informed Consent for VMALS002-2B will be presented in a separate listing and will not be tabulated.

The following tables will be presented:

- Summary of TEAEs (Table 14.3.1.1)
- TEAEs by System Organ Class and Preferred Term (Table 14.3.1.2)
- TESAEs by System Organ Class and Preferred Term (Table 14.3.1.3)
- TEAEs by System Organ Class and Preferred Term and Maximum Severity (Table 14.3.1.4)

- TEAEs by System Organ Class and Preferred Term and Maximum Relationship (Table 14.3.1.5)
- TESAEs by System Organ Class and Preferred Term and Maximum Severity (Table 14.3.1.6)
- TESAEs by System Organ Class and Preferred Term and Maximum Relationship (Table 14.3.1.7)
- Incidence of Clinically Significant Laboratory Values (Table 14.3.1.8)
- AESIs by System Organ Class and Preferred Term (Table 14.3.1.9)

The following listings will be provided:

- All TEAEs (Listing 16.2.7.1)
- AESIs (Listing 16.2.7.2)
- TESAEs (Listing 16.2.7.3)
- TEAEs leading to study discontinuation (Listing 16.2.7.4)
- TEAEs related to study medication (Listing 16.2.7.5)
- TESAEs leading to death (Listing 16.2.7.6)
- AEs that registered as not TEAEs (Listing 16.2.7.7)

6.14.2 Laboratory Data

Laboratory data consists of results of following examinations: serum chemistry, hematology and urine pregnancy test.

Serum chemistry will include the following variables:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Calcium
- Inorganic Phosphate
- Magnesium
- Glucose
- Amylase
- Lipase
- Lactate Dehydrogenase

- Blood Urea Nitrogen (BUN)
- Creatine Kinase (CK)
- Creatinine
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Alkaline Phosphatase
- Gamma-Glutamyl Transpeptidase (GGT)
- Total Bilirubin
- Total Protein
- Albumin

Hematology will include the following variables:

- White Blood Cells Count
- Hemoglobin
- Hematocrit
- Platelet Count
- Neutrophils Count

Serum chemistry and hematology analyses will be performed at Day 240 and Day 365. Measured values of serum chemistry and hematology analyses and their changes from baseline, will be presented with descriptive statistics at each visit by treatment group (Tables 14.3.4.1 and 14.3.4.3). Incidence of clinically significant values will be tabulated (Table 14.3.1.8), shift tables for abnormal values will be presented for each parameter (Tables 14.3.4.2, 14.3.4.4). Percentages for each parameter will be based on the number of participants who have at least one measurement for at baseline and at corresponding post-baseline visit.

Result of urine pregnancy test is variable with two possible values: positive / negative. The test should be performed only for women with childbearing potential at Day 365.

Results of serum chemistry, hematology and urine pregnancy tests will be listed (Listings 16.2.8.1 – 16.2.8.3).

6.14.3 Vital Signs

The following vital signs will be measured at Day 240, Day 300 and Day 365/ET visits:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath / min)
- Body temperature (degrees Celsius)
- Body weight (kg)
- Body height (cm)
- Pulse oximetry (%)

Descriptive statistics for observed values and changes from baseline for vital signs including height, weight and BMI will be presented by treatment group and visit (Table 14.3.6.1). Also frequency table by the clinical significance will be presented for each vital sign (Table 14.3.6.2).

All results of vital signs measurements will be listed (Listing 16.2.8.4).

6.14.4 Electrocardiogram Data

Electrocardiograms will be performed at Day 240 and Day 365. Descriptive statistics for electrocardiogram results: general interpretation, abnormal findings and clinical significance will be presented by treatment groups (Tables 14.3.7.1 and 14.3.7.2).

All electrocardiogram results will be listed (Listing 16.2.8.5).

6.14.5 Physical Examination

Complete physical examination will be performed at Day 240 and Day 365.

The following body systems will be examined:

- HEENT (Head, Eye, Ear, Nose, Throat)
- Heart
- Lungs
- Abdomen
- Extremities
- Lymph Nodes
- Neurological
- Musculoskeletal System
- Skin/Integumentary Systems

Each parameter will be presented with frequencies and percentages of values (Normal, Abnormal not Clinically Significant, Abnormal Clinically Significant) in shift tables based on baseline for each treatment group (Table 14.3.6.3). Percentages will be based on the number of participants who have measurement at baseline and at corresponding post-baseline visit.

A listing of physical examination results will be presented (Listing 16.2.8.6).

6.15 Exploratory Analyses

6.15.1 Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)

ALSFRS-R will be measured at Day 240, Day 300 and Day 365. Total score and subscores for Fine and Gross Motor Functions (sum of scores for items 4 to 9) and for Bulbar Function (sum of scores for items 1 to 3) their changes from baseline will be presented with descriptive statistics by visits and treatment group (Table 14.6.1, Listing 16.2.9.1).

Slope of the total score will be provided using graphical presentation of values by visit for both treatment group. The figures will be presented using time points from both VMALS-002-2 and VMALS-002-2b studies.

6.15.2 Handheld Dynamometry (HHD)

HHD will be measured at Day 240, Day 300 and Day 365. Maximal values of strength of each muscle group of 3 trials and their changes from baseline will be presented with descriptive statistics for each visit by treatment group (Table 14.6.2, Listing 16.2.9.2).

6.15.3 Amyotrophic Lateral Sclerosis Assessment Questionnaire, 40 questions (ALSAQ-40)

ALSAQ-40 will be measured at Day 240 and Day 365. Values of each question, subscales (Physical Mobility, Activities of Daily Living/Independence, Eating and Drinking, Communication and Emotional Functioning) with imputed values as described in section 6.2.10 and their changes from baseline will be presented with descriptive statistics for each visit by treatment group (Tables 14.3.6.4.1-14.3.6.4, Listing 16.2.9.4).

6.15.4 Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC)

CGIC and PGIC will be measured at Day 240 and Day 365. Global improvement, Efficacy index, Impression of change and Degree of Change will be presented with descriptive statistics for each visit by treatment group (Tables 14.6.5 and 14.6.6, Listings 16.2.9.5 and 16.2.9.6).

6.15.5 Slow vital capacity (SVC)

SVC will be measured at Day 240, Day 300 and Day 365. % predicted, best vital capacity, second best vital capacity and third best vital capacity and their changes from baseline will be presented with descriptive statistics by visits and treatment group (Table 14.6.7, Listing 16.2.9.7).

6.15.6 Time to tracheostomy

Time to tracheostomy will be presented with descriptive statistics and corresponding survival curves using Kaplan- Meier analysis (Table 14.6.8, Listing 16.2.9.8).

SAS code example for Kaplan-Meier analysis:

```
proc lifetest data=DATAIN method = km;
  time AVAL*CNSR(1);
  strata TRT01PN / test = logrank;
run;
```

DATAIN – source dataset

AVAL – time to event

CNSR – flag for censoring, if CNSR=1 then the corresponding value of AVAL is a censored value and not an observed event

TRT01PN – treatment group

Analysis will be performed on data combined for core study the Study VMALS-002-2 (Screening, Day 0 pre-dose, Day 30, Day 60 pre-dose, Day 84, Day 120 pre-dose, Day 144 and Day 180) and for this extension study the Study VMALS-002-2b (Day 240, Day 300, Day 365/ET4).

6.15.7 Time to all-cause mortality

Time to all-cause mortality will be presented with descriptive statistics and corresponding survival curves using Kaplan-Meier analysis (Table 14.6.9, Listing 16.2.9.8). Analysis will be performed on data combined for core study the Study VMALS-002-2 and for this extension study the Study VMALS-002-2b.

7 INTERIM ANALYSIS

No interim analyses are planned.

8 DATA SAFETY MONITORING BOARD ANALYSIS

Data safety monitoring board (DSMB) analyses are described in a separate DSMB Statistical Analysis Plan.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

There are no changes to the planned protocol analysis.

10 REFERENCES

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3. ICH Guidance E9: Statistical Principles for Clinical Trials
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5. Jeremy M. Shefner, PhD, Dawei Liu, PhD, Melanie L. Leitner, PhD, David Schoenfeld, PhD, Donald R. Johns, MD, PHD Toby Ferguson, MD, PhD, Merit Cudkowicz, MD, MSc (2016) "Quantitative Strength Testing In ALS Clinical Trials", Neurology 87 august 9

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