STATISTICAL ANALYSIS PLAN

(Short) study title:	ADOREXT (ALS trial with Daily ORal Edaravone EXTension) study
Name of the sponsor:	Ferrer Internacional, S.A.
Protocol identification:	FAB 122-CT-2201
Version and date of SAP:	Final v1.0, 19APR2024

VERSION HISTORY

Version	Date	History list
1.0	19 Apr 2024	Final version

APPROVAL PAGE

I hereby declare that I have read and reviewed this document. To the best of my knowledge, the content accurately states the intended analyses and output to be provided. This document is intended for an agreement on analysis and reporting details between the sponsor and Author! et al B.V.

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LIST OF ABBREVIATIONS

8-OHdG	8-hydroxyguanosine
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Score – revised
ALSAQ-40	ALS Assessment Questionnaire-40-Item
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case report form
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
EQ-5D-5L	EuroQoL – 5 Dimensions – 5 Levels
GCP	Good Clinical Practice
ICH	Internation Conference on Harmonisation
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NFL	Neurofilament light
OLE	Open label extension
P75ECD	Neurotrophin receptor p75
PDF	Portable Document Format
PEG	Percutaneous Endoscopic Gastrostomy
PNG	Portable Network Graphics
PT	Preferred Term
Q1	Lower quartile
Q3	Upper quartile
QoL	Quality of life
RMST	Restricted Mean Survival Time
RTF	Rich Text Format
SAE	Serious Adverse Event

SAF	Safety analysis population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
SVC	Slow Vital Capacity
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WHO	World Health Organisation

1 GENERAL

This Statistical Analysis Plan (SAP) describes in detail the methods and presentation of the data analyses which will be conducted for study FAB 122-CT-2201 by Certara.

This plan is written in agreement with protocol versions (see table), and case report form (CRF) version 3.0, dated 28 Nov 2023.

Version*	Date
V2.0 ITA & NL	24/01/2023
V1.1 FRA	03/04/2023
V2.1 RUS	11/05/2023
V1.1 ESP	01/06/2023
V1.1 POL	01/06/2023
V1.1 POR	07/06/2023
V1.1 GBR	06/07/2023
V1.1 BEL	06/07/2023
V1.3 IRL	06/07/2023
V1.1 GER	10/07/2023
V1.1 SWE	10/07/2023

*see Protocol versions tracker for more details

The protocol and the (annotated) CRF are the primary source for this document, together with the relevant Good Clinical Practice (GCP) and International Council on Harmonization (ICH) guidelines. Furthermore, sponsor requirements for reporting will be considered.

Additional changes or updates of those documents or requirements may result in a new version of the reporting/statistical analysis plan. This study-SAP is to be finalized prior to database lock for study FAB 122-CT-2201.

The statistical analysis and summary tabulations described in this SAP will provide the basis of the results sections of the clinical study report (CSR) for this trial.

2 STUDY INFORMATION

2.1 Study Objective(s)

The primary objective of this study is to evaluate the long-term safety of FAB122 in patients with Amyotrophic Lateral Sclerosis (ALS).

The secondary objectives of this study are as follows:

- To evaluate the effect of treatment with FAB122 on overall survival

- To evaluate the effect of treatment with FAB122 on disease progression in patients with ALS
- To evaluate the effect of treatment with FAB122 on cognitive functioning
- To evaluate the effect of treatment with FAB122 on quality of life (QoL).

Due to study early termination, some analysis planned in the protocol will not be performed (see Section 6). This SAP focuses on a subset of analyses related to objectives of safety, overall survival, and disease progression.

2.2 Design of the Study

This is a multicenter open-label Phase III extension study to investigate the long-term safety of 100 mg FAB122 once daily as oral formulation in ALS patients.

All patients participating in the main study (ADORE) study will be invited to roll over to FAB122 and to participate in ADOREXT. Patients that discontinued treatment in the main ADORE study for other than safety reasons, will be also invited to re-start treatment with FAB122 in the open label extension (OLE) study. The duration of this OLE was planned to be until the product is commercially available at each participant country, provided good tolerance and safety is proven. The sponsor could also make the decision to terminate the study at any time in case the objectives of the ADORE study are not met.

Patients not willing to continue receiving active treatment in the extension study or that had already discontinued study treatment during the course of the ADORE study for safety reasons, will be asked to be contacted by phone and followed up for vital status.

Subjects rolling over the active treatment will visit the clinic at Baseline (whenever possible, visit 6 or 8 of the main study + 6 weeks in case the OLE is not fully set up) and every 3 months thereafter.

2.3 Study medication

Patients will receive 100 mg FAB122 granules for oral solution in single sachets, which has to be dissolved in 100 mL water prior to administration.

2.4 Sample size

No formal size calculation has been done for the extension study. The main study plans to include approximately 300 patients. It is anticipated that 200-225 patients might be included in this extension study.

All subjects who completed the full study period in the main ADORE study and providing informed consent to comply with extension trial procedures are eligible to participate in this extension study.

2.5 Study assessments

The schedule of assessments is available in Table 1 of the study protocol.

3 SUBJECTS FOR ANALYSIS

3.1 Analysis populations

3.1.1 Modified Intent-to-treat (mITT and mITTe) Analysis Sets

The mITT analysis set includes all patients who were randomized in the ADORE study and received at least 1 dose of investigational product regardless of any protocol deviation (see Section 6). The mITT population will be used for the analysis of efficacy variables, and statistical analysis will be done "as randomized" in ADORE study. The mITT is considered the primary analysis population for efficacy.
The mITTe analysis set refers to the subset of patients of mITT who enrolled in ADOREXT.

3.1.2 Safety Analysis Set Extension (SAFe)

The SAFe population includes all patients enrolled in ADOREXT who have received at least one dose of the investigational drug during the extension study, irrespective of satisfying other criteria. This population will be used for the analysis of safety and tolerability, and statistical analysis will be done "as treated". Although all patients will be treated with FAB122 in ADOREXT, data will be presented also using the randomization groups of ADORE study.

3.2 Protocol deviations

Following Sponsor review of the protocol deviations, none was found as impacting safety and no formal analysis of protocol deviations was found as required following early termination of the study.

3.3 Data Review Meeting

Not applicable / not in the scope of this SAP following early termination of the study.

4 STUDY ENDPOINTS

The primary, secondary and safety endpoints of this study are reported in the sections below. Due to study early termination, some analysis planned in the protocol will not be performed (see Section 6). Focus of this SAP are the primary endpoint, the overall survival and survival time. The ALSFRS-R score will also be described.

4.1 Primary endpoint

The primary endpoint is the nature, frequency and severity of Treatment Emergent Adverse Events (TEAEs).

4.2 Secondary endpoint(s)

- ALSFRS-R and mortality-adjusted change from baseline in ALSFRS-R total score until the end of the study
- Overall Survival, defined as time from study treatment start in ADORE study to death from any cause
- Survival time, defined as time from study treatment start in ADORE study to the occurrence of respiratory insufficiency (insufficiency defined as tracheostomy or the use

of non-invasive ventilation for ≥20 h per day for ≥10 consecutive days) or death from any cause
- Change from baseline in SVC until the end of the study
- Mean change in norm standardized ECAS total score
- Change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) until the end of the study
- Change from baseline in EuroQoL – 5 Dimensions – 5 Levels (EQ-5D-5L) until the end of the study
- Change from baseline in Health related QoL Visual Analogue Scale (VAS) score until the end of the study
- Change from baseline in the prognostic ALS biomarker neurofilament light (NFL)
- Change from baseline in the ALS biomarkers creatinine and creatinine kinase
- Change from baseline in the ALS biomarker Urinary extracellular domain of neurotrophin receptor p75 (Urinary P75ECD)
- Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG)
- Cost-Utility analysis of treatment with FAB122

4.3 Safety endpoint(s)

- Parameters derived from in vital signs and 12-lead electrocardiogram (ECG)
- Parameters derived from laboratory tests (hematology, biochemistry, urinalysis)
- Proportion of subjects that drop out due to adverse events.

5 STATISTICAL ANALYSIS

5.1 General considerations

Appropriate rounding will be performed for the summary statistics: arithmetic mean, median, SD (standard deviation) and confidence limits will be presented with one more decimal than the original data; minimum and maximum values will be presented with the same precision as the original data. In frequency tables, percentages will be presented with 1 decimal. P-values will be presented with 3 decimals, and those smaller than 0.001 will be replaced by <0.001.

Descriptive statistics presented in general summary tables will be the number of non-missing observations (n), mean, SD, minimum, median and maximum for quantitative data. For categorical data, frequency counts and percentages will be determined. The denominator when calculating percentages will be the number of patients in the applicable analysis population. Descriptive statistics will be displayed for all visits that a measurement is collected on, even if the endpoint is only referring to limited visits for the analysis.

Baseline is defined as the last value measured prior to first study treatment administration in ADOREXT study, unless otherwise specified. Typically, baseline data are collected at Visit 6 or 8 of the ADORE study. In case this value is missing for a specific patient in ADOREXT CRF data, but an earlier measurement is collected in ADORE study data, this value will be used as baseline instead. Unscheduled measurements are excluded as baseline value.

5.2 Missing or excluded data

For presentation of descriptive statistics of efficacy data, no imputation or sensitivity analysis will be included, and data will be presented 'as is'. All these analyses will be done on data available at the visit considered. In summary tables, the number of patients without missing data will be presented (per visit, if applicable) unless otherwise specified. In calculations of percentages, the denominator will be the number of patients in the applicable analysis population.

Data of patients from site 5806 will not be included in the ADOREXT analysis, following GCP findings, in accordance with the analysis performed in ADORE study.

Using the most conservative approach, missing/incomplete information related to AEs will be handled as listed below, to indicate an AE as being treatment emergent or presented having a certain intensity/causality. Note that imputed dates/times or intensity/causality will not appear in data listings, but only in descriptive statistics tables (where applicable).

- In case of (partially) missing onset dates, the AE will be handled as follows:
  - If full start date is available, and on or after first dosing date, the AE is considered treatment emergent.
  - In case full stop date is available and prior to first dosing date, the AE is considered prior.
  - If the day part of the start date is missing:
    - The AE is considered treatment emergent if the month and year of the start date are the same or after the month and the year of the first dosing date.
  - If the day and month part of the start date are missing:
    - The AE is considered treatment emergent if the year of the start date is the same or after the year of the first dosing date.
  - In case the start date is completely missing:
    - If stop date is fully available and on/after the first dosing date, the AE is considered treatment emergent.
    - If the stop date is partially missing, but the month and year (or year alone in case of missing month) are after the month and year (or year alone) of the first dosing date, the AE is considered treatment emergent.
  - In case full start date and full stop date are missing, the AE is considered treatment emergent.

- In case intensity is missing for a certain TEAE, it will be regarded as severe.
- In case causality is missing for a certain TEAE, it will be regarded as related.
- In case seriousness is missing for a certain AE, then this is discussed and addressed prior to database lock and unblinding in agreement with the sponsor and the Data Management vendor.

ALS history and randomization data will be inherited from ADORE analysis datasets.

Mapping of unscheduled or early termination visits

When visit assessments are missing, repeat assessments may be mapped to the appropriate visit in the database by the DM vendor, when appropriate. For these unscheduled assessments following a missing protocol visit or assessment, mapping will be done to the (closest) protocol visit at which the applicable assessment should have been performed before the date of unscheduled visit.

In case of a repeated or additional assessments for non-missing assessments, mapping will only be done for replacement if this is clearly agreed (at patient and visit level) with the client and specified by DM vendor (e.g. because it replaces an erroneous measure collected at the actual visit), and as such will be used in statistical data presentations. These agreements will be documented by the Sponsor as appropriate.

The data of early withdrawal may be mapped to the most appropriate scheduled post-baseline visit as applicable per assessment, to be agreed together with the DM vendor and the client on occurrence. The documentation of these agreements is to be finalized by the Sponsor as appropriate. For early termination visits in general mapping will be done to the closest protocol visit at which the applicable assessment should be performed after the date of early termination.

5.3 Interim analysis

Not applicable.

5.4 Baseline characteristics

5.4.1 Inclusion/exclusion criteria

Not applicable / not in the scope of this SAP following early termination of the study.

5.4.2 Demographics

Descriptive tabulations of the data for demographics and ADORE baseline characteristics will be made for the SAFe. Demographic data (including weight and height measurements) per treatment group and overall will be presented. Appropriate descriptive statistics for age, height, weight, BMI, race, ethnicity and gender will be given, including ALS history data, using data from ADORE baseline. Descriptive statistics will be n, arithmetic mean, SD, median, minimum and maximum for quantitative data. For qualitative data, frequency counts and percentages will be determined.

5.4.3 Disposition

To present disposition, summaries will be provided for all randomized, enrolled in extension, treated in extension, and completed extensions along with reasons for early discontinuation. Completion status will be derived from CRF form “Study Completion”. Additionally, the number/percentage of patients in the mITT and SAFe will be presented. The patient disposition will be presented per treatment group and overall.

5.4.4 Medical history and Concomitant Medication

Not applicable / not in the scope of this SAP following early termination of the study.

5.4.5 Other screening data

Not applicable following early termination of the study.

5.5 Statistical analysis primary and secondary efficacy endpoints

All efficacy analysis will be conducted on the mITT set, unless otherwise specified.

5.5.1 Primary analysis

Not applicable, no primary endpoint for efficacy is included in this study.

5.5.2 Secondary analysis

5.5.2.1 Overall Survival and 'Survival Time'

Time to event endpoints for overall survival and survival time definitions are reported in Section 4.2. Patients who early terminated the ADOREXT study for reasons different from death will be considered as still alive and with no respiratory insufficiency event at the time of study discontinuation, unless otherwise specified in the survival follow-up CRF form. Endpoints will be derived by combining the survival data from ADORE and ADOREXT.

Descriptive statistics including median, Q1/Q3 quartiles with 95% confidence intervals will be tabulated. Endpoints will be also summarized with the use of the Kaplan-Meier method.

The difference between the groups randomized in ADORE to FAB122 and placebo will be evaluated descriptively by means of a stratified log rank test. Hazard ratios and 95% confidence intervals will be estimated with the use of a stratified Cox proportional-hazards regression model with treatment group as the sole explanatory variable.

The difference between the groups will also be assessed using restricted mean survival time (RMST) analysis. Considering the duration of the ADOREXT study, the RMST will be performed up to the largest observation time from the pooled ADORE and ADOREXT data, adjusting for the stratification variables.

Randomization strata from ADORE study will be used for the stratified analysis. No adjustment will be performed for the treatment cross over following enrollment in ADOREXT study.

5.5.2.2 ALSFRS-R questionnaire

Descriptive statistics for absolute and change from extension baseline in total ALSFRS-R score will be presented by treatment group in summary tables.

Results will also be presented for the following subscales:

- Bulbar function (questions 1-3 of the ALSFRS-R)
- Fine motor function (questions 4-6 of the ALSFRS-R)

- Gross motor function (questions 7-9 of the ALSFRS-R)
- Respiratory function (questions 10-12 of the ALSFRS-R)

Only patients included in the mITTe will be included in the summaries.

5.5.3 Other efficacy endpoints and examinations

Not applicable / not in the scope of this SAP following early termination of the study.

5.6 Safety and tolerability evaluation

All safety presentations will be created using the SAFe population.

5.6.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as an adverse event that appears at or after first dosing of extension. In case of (partially) missing start/stop dates, refer to Section 5.2.

An AE overview table will be created displaying the number of patients (and percentage) experiencing a treatment-emergent adverse event (TEAE) and the number of TEAEs for: any TEAE, any mild/moderate/severe TEAE, any unrelated/related TEAE, any serious AE, any serious TEAE, and any TEAE leading to study treatment discontinuation, any AE leading to death.

All TEAEs and those leading to death will be tabulated. SUSARs will be reported by the pharmacovigilance vendor.

All TEAEs are tabulated by System Organ Class (SOC) and Preferred Terms (PTs) within each SOC according to the MedDRA terminology list. TEAEs will be tabulated busing frequency counts (number of patients with at least one event, and number of events) and percentage of patients with the event. Similar tables will be created for TEAEs leading to premature treatment discontinuation and Serious TEAEs. These summary tables will be presented by decreasing frequency of occurrence based on SOC and PT.

For summary tables, an AE is considered related if the causality to the study medication is classified as either ‘‘Probably Related’ or ‘Possibly Related’, where a missing relationship is also considered related. Otherwise, it will be considered unrelated for summary tables.

5.6.2 Other safety endpoints and examinations

Not applicable / not in the scope of this SAP following early termination of the study.

5.7 Scheduled visits, dosing and treatment compliance

Not applicable / not in the scope of this SAP following early termination of the study.

6 CHANGES FROM PROTOCOL AND OTHER RELEVANT REMARKS

Due to study early termination, some analysis planned in the protocol will not be performed. This SAP focuses on a subset of analyses related to objectives of safety, overall survival, and

disease progression. In particular, analysis will be performed for the primary endpoint, the overall survival and survival time. The ALSFRS-R score will also be described.

Overall survival and survival time endpoints definition will be updated to align with ADORE study. ALSFRS-R is also added to the secondary endpoints as it will be analyzed without mortality adjustment.

The mITT analysis set was not originally planned in the study protocol and included in the SAP to perform survival analysis combining ADORE and ADOREXT data.

7 DATA RECEIPT

All data will be received per transfer agreements. The received files will be imported into SAS and will be programmed into analysis datasets, before programming of the tables, listings and figures is done. The analysis datasets will not be checked against CDISC standards.

8 TECHNICAL DETAILS

8.1 Programming conventions

8.2 Coding

Coding of adverse events will be performed by the Data Management provider. Adverse events are coded with the MedDRA coding system. The DM vendor will use the latest versions available at time of database lock, as per DM documentation. Coding will be supplied as part of the data transfer. Concomitant medications and medical history are not in the scope of this SAP.

8.3 Analysis software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4. SAS tabular output (tables and listings) will be saved in RTF format. SAS graphs will be saved in PNG format. Both will be imported into Word® and supplied to the Medical Writer for use in the clinical study report. When the sponsor wants to receive the output before the study report, then the Word® document is transferred to PDF and supplied.

8.4 Presentation of tables, listings, graphs

All output will be generated as SAS tables, graphs and listings.

All tables and listings will be created such that they fit landscape pages, following the page format and margins of the CSR template to be used. The tables for the end-of-text and listings for the appendix will be created using SAS with an RTF output, and font Times New Roman size 9 will be used.

For graphs, in general Swiss font will be used, and output will be as created as PNG plot. Graphs are preferably created using black, grey and white color, to facilitate black-and-white printing. Different line patterns and symbols will be used to differentiate between classification or treatment levels. Only if it enhances clarity of the plot, distinct colors can be used instead. Graphs will be created such (i.e. taking into account line thickness and font size) that they can be presented as two (2) per page in the clinical study report.

9 TABLES, LISTINGS, GRAPHS

9.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 9.2, 9.3 and 9.4. Template tables and listings as well as *example* plots (as received from client or extracted from a relevant paper) will be used as a reference for creation of all output, and a separate document will be created for this. Table/graph/listing numbering will be followed, however, if the data give cause for combining or splitting tables or listings, numbering may be adapted as necessary.

9.2 In-text tables and graphs

In-text tables and graphs will be designed or extracted by the Medical Writer during creation of the Clinical Study Report, based on the tables and graphs created for section 14 of the CSR. Upon request of the Medical Writer or the client, in-text tables may be programmed, and details will be agreed in advance. These in-text tables will also use font Times New Roman.

9.3 End-of-text tables and graphs

Following ICH E3 guidelines, all tables and graphs mentioned here will be presented in Section 14 of the CSR, and tables will be prepared in the order and with section number as stated.

Table /graph number	**Contents of table/graph**
14.1 Demographic Data Summary figures and tables	
14.1.1	Demographics
14.1.2	Baseline Characteristics
14.1.3	ALS-specific history
14.1.4	Disposition
14.2 Efficacy Data Summary Figures and Tables	
14.2.1.1	Survival time: descriptive statistics
14.2.1.2	Survival time: Kaplan-Meier curves
14.2.1.3	Survival time: statistical analysis results (RMST)
14.2.2.1	Overall survival: descriptive statistics
14.2.2.2	Overall survival: Kaplan-Meier curves

14.2.2.3	Overall survival: statistical analysis results (RMST)
14.2.3.1	Descriptive statistics for absolute values and change from baseline ALSFRS-R total score and function domains
14.3 Safety Data Summary figures and tables – 14.3.1 Displays of Adverse Events	
14.3.1.1	Overview adverse events
14.3.1.2	Treatment emergent adverse events by SOC and PT
14.3.1.3	Treatment emergent serious adverse events by SOC and PT
14.3.1.4	Treatment emergent adverse events leading to treatment discontinuation by SOC and PT
14.3 Safety Data Summary figures and tables – 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events	
14.3.2.1	Deaths
14.3.2.2	TEAEs

9.4 Listings

Listings are not in the scope of this SAP.