STATISTICAL ANALYSIS PLAN

(Short) study title:	ADORE (ALS Daily ORal Edaravone) study
Name of the sponsor:	Ferrer Internacional, S.A.
Protocol identification:	FAB 122-CT-2001
Version and date of SAP:	Updated final 4.0, 07 December 2023

VERSION HISTORY

Version	Date	History list
0.1	15 Nov 2021	Draft version for sponsor review.
0.2	22 Feb 2022	2nd draft version for review
0.3	13 May 2022	Pre-final version
0.4	09 Dec 2022	Updated pre-final version
1.0	19 Dec 2022	Final, including changes in updated protocol version
1.1	01 Jun 2023	Updated version for review. Due to update protocol, updated CRF, additional derivations, and additional analyses.
2.0	22 Jun 2023	Final for signature
2.1	11 Sept 2023	Updated version for review. Use of new SAP template. Derivations added for NCS, added handling of mis-randomized patients not being treated (for ITT), removal of CTC-AE summaries, adding mapping of unscheduled visits.
3.0	14 Sept 2023	Final for signature
4.0	07 Dec 2023	Final for signature, changes for primary endpoint analysis and some additional clarification for the PP/ITT sensitivity analysis.

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.

Lead Statistician:

Name, title, company: [redacted]

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Signature Date

Sponsor contact:

Name, title, company: [redacted]

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Signature Date

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LIST OF ABBREVIATIONS

8-OHdG	8-hydroxyguanosine
ADaM	Analysis Data Model
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
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
AR(1)	First order Autoregression
AST	Aspartate transaminase
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BUN	Blood urea nitrogen
CAFS	Combined Assessment of Function and Survival
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CK	Creatinine kinase
CS	Compound Symmetry
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Lead
DM	Data Manager
DSMB	Data Safety Monitoring Board
ECAS	Edinburgh Cognitive and behavioural ALS Screen
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQoL – 5 Dimensions – 5 Levels
FCS	Fully Conditional Specification
GGT	Gamma-glutamyl transpeptidase
GLM	Generalized Linear Model

HCT	Haematocrit
HGB	Haemoglobin
HHD	Hand-held dynamometer
HR	Heart Rate
ICE	Intercurrent Event
ICH	Internation Conference on Harmonisation
LDH	Lactate dehydrogenase
ITT	Intent-To-Treat
MAR	Missing At Random
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
MiToS	Milano-Torino staging system
mITT	Modified Intent-To-Treat
MMRM	Mixed Model for Repeated Measures
NCS	Nerve Conduction Study
NFL	Neurofilament Light
$P75^{ECD}$	Extracellular domain of neurotrophin receptor p75
PDF	Portable Document Format
PEG	Percutaneous Endoscopic Gastrostomy
PK	Pharmacokinetic(s)
PM	Project Manager
pMI	Placebo Multiple Imputation
PNG	Portable Network Graphics
PP	Per Protocol
PT	Preferred Term
PTT	Prothrombin Time
QoL	Quality of Life
Q1	Lower quartile
Q3	Upper quartile
RBC	Red Blood Cells
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
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SVC	Slow Vital Capacity
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WBC	White blood cell
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-2001 by Certara. Any references to PK analyses in this SAP are under responsibility of the involved PK scientist from the client, and analysis details are therefore not specified in this SAP. This plan is written in agreement with protocol version 4.0, dated 24 May 2023, and blank CRF version 3.0, dated 21 June 2023, the relevant GCP-ICH guidelines and sponsor requirements.

Since a separate DSMB-SAP will be developed for the DSMB analyses, this full study-SAP is to be finalized prior to database lock and unblinding for study FAB 122-CT-2001.

The protocol and the (annotated) CRF are the primary source for this document, together with the relevant GCP-ICH guidelines. Furthermore, sponsor requirements for reporting will be taken into account. Additional changes or updates of those documents or requirements may result in a new version of the reporting/statistical analysis plan.

2 STUDY INFORMATION

2.1 Study Objective(s)

The primary objective of this study is to assess the effect of treatment with 100 mg of FAB122 on disease progression in patients with ALS.

The secondary objectives of this study are as follows:

- To evaluate the effect of treatment with FAB122 on survival
- To evaluate the safety and tolerability of FAB122
- To evaluate the effect of treatment with FAB122 on quality of life (QoL)
- To evaluate the effect of treatment with FAB122 on cognitive functioning
- To evaluate the pharmacokinetics (PK) of FAB122.

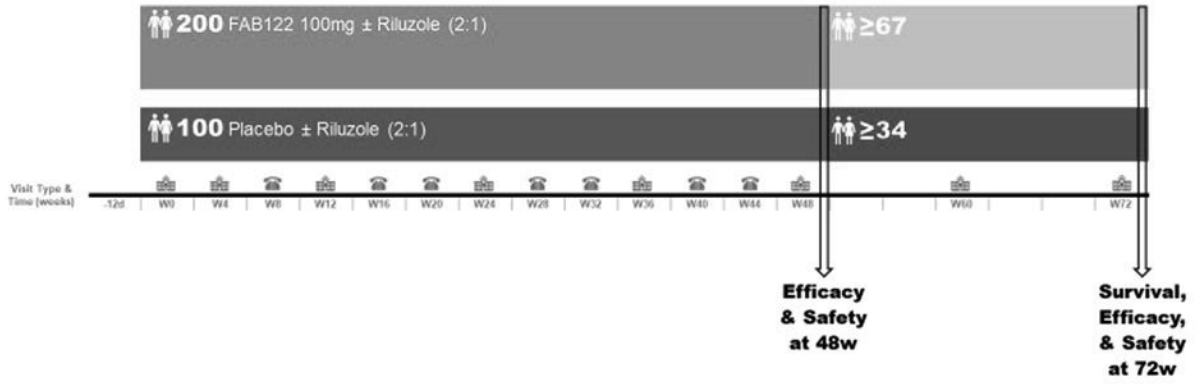
The exploratory objectives of this study are as follows:

- To evaluate the PK interaction of FAB122 and riluzole
- To explore and identify biomarkers that inform the statistical understanding of ALS and/or their therapeutic treatments.

2.2 Design of the Study

This is a multicenter, multinational, double-blind, randomized (2:1), placebo-controlled Phase III study to investigate the efficacy and safety of 100 mg FAB122 (former TW001) once daily as oral formulation in approximately 300 ALS patients (200 FAB122, 100 Placebo).

Patients will receive double-blind treatment up to a maximum of 72 weeks. The study is planned to continue until the last randomized patient has reached 48 weeks of follow-up (or has reached an intercurrent event) AND the first one third (100) of the randomized patients has reached 72 weeks of follow-up (or has reached an intercurrent event).



2.3 Study medication

Patients will receive 100 mg FAB122 or matched placebo for 48 or 72 weeks. Riluzole (100 mg/day or less) may be used as background (add-on) therapy, where patients should be on stable doses at the start of the study and for at least 30 days before the initiation of study drug.

2.4 Sample size

The sample size estimation is based on the primary endpoint: the change from baseline in ALSFRS-R score after 48 weeks. A difference of 3.0 points between FAB122 treatment arm and placebo is assumed with a (pooled) standard deviation of 7.5 and an allocation ratio of 2:1 (FAB122:Placebo). With these assumptions, a total sample size of 300 (200 patients on FAB122 and 100 on placebo) is needed to achieve 90% power to detect the difference of 3.0 points between the two treatment groups at a 5% (2-sided) level of significance.

For further details on the background of these assumptions, refer to the protocol.

2.5 Study assessments

	Screening	Baseline	Treatment period													
	(-12/-2 days)	V1 D1 W0	V2 D28 W4 ±3D	T1 D56 W8 ±4D	V3 D84 W12 ±3D	T2 D112 W16 ±4D	T3 D140 W20 ±4D	V4 D168 W24 ±7D	T4 D196 W28 ±7D	T5 D224 W32 ±7D	V5 D252 W36 ±7D	T6 D280 W40 ±7D	T7 D308 W44 ± 7D	V6/EoT D336 W48 ±7D	V7 D420 W60 ±7D	V8[1] D504 W72 OR EoT[2]
Administrative procedures																
ICF	X															
ICF for PK	X															
In/exclusion criteria	X	X[3]														
Medical history	X															
Prior/Concomitant medication	x----------													----------x		
Randomization		X														
Dispensing study medication/Compliance check		X*			X			X			X			X	X	
Clinical Procedures																
Physical examination	X	X						X						X		X
Weight	X	X						X						X		X
Height	X															
Vital Signs	X	X	X		X			X			X			X	X	X
12-lead ECG	X	X						X						X		X
Neurological examination[4]	X	X	X		X			X			X			X	X	X
NCS[5]	X*		X		X			X								
(S)AE monitoring	x----------													----------x		
Laboratory procedures																

	Screening	Baseline	Treatment period													
	(-12/-2 days)	V1 D1 W0	V2 D28 W4 ±3D	T1 D56 W8 ±4D	V3 D84 W12 ±3D	T2 D112 W16 ±4D	T3 D140 W20 ±4D	V4 D168 W24 ±7D	T4 D196 W28 ±7D	T5 D224 W32 ±7D	V5 D252 W36 ±7D	T6 D280 W40 ±7D	T7 D308 W44 ± 7D	V6/EoT D336 W48 ±7D	V7 D420 W60 ±7D	V8[1] D504 W72 OR EoT[2]
Chemistry/ Haematology[6]	X	X[15]	X		X			X			X			X	X	X
Vitamin B6 monitoring[7]	X	X	X		X			X			X			X	X	X
Urinalysis[8]	X	X	X		X			X			X			X	X	X
β-hCG[3]	X															
Urine Pregnancy Test[3]	X	X	X		X			X			X			X	X	X
HIV/Hepatitis B,C	X															
ALS evaluation procedures																
ALSFRS-R	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SVC	X	X			X			X			X			X	X	X
HHD		X			X			X			X			X	X	X
ALSAQ-40		X						X						X		X
ECAS		X						X						X		X
EQ-5D-5L		X			X			X			X			X	X	X
VAS		X			X			X			X			X	X	X
Cost questionnaire		X			X			X			X			X	X	X
King's staging system and MiToS		X			X			X			X			X	X	X
PK																
Blood sampling for FAB122[9]		X[9]	X[9]											X[9]		X[11]
Blood sampling for riluzole[10]		X	X													
ALS biomarkers																
Blood sampling for biomarkers[12]		X	X		X			X			X			X	X	X
Urine collection for biomarkers[13]		X	X		X			X			X			X	X	X
Future Biomedical Research																

	Screening	Baseline	Treatment period													
	(-12/-2 days)	V1 D1 W0	V2 D28 W4 ±3D	T1 D56 W8 ±4D	V3 D84 W12 ±3D	T2 D112 W16 ±4D	T3 D140 W20 ±4D	V4 D168 W24 ±7D	T4 D196 W28 ±7D	T5 D224 W32 ±7D	V5 D252 W36 ±7D	T6 D280 W40 ±7D	T7 D308 W44 ± 7D	V6/EoT D336 W48 ±7D	V7 D420 W60 ±7D	V8[1] D504 W72 OR EoT[2]
Blood sampling for genotyping for FBR (if consented)		X														
Blood sampling for RNA and serum collection for FBR (if consented)		X			X			X			X			X	X	X
CSF sampling for FBR (if consented)[14]		X			X			X								

V=visit; T= telephone call; EoT = End of Trial; W=Week, D=Day
*First dosing

1. If a patient is withdrawn from the study or discontinues study treatment, will be asked to return to the clinic and the procedures as depicted for the End-of-Trial visit will need to be done. The first 100 patients (1/3 of the total study population) will continue study participation until week 72 (Visit 8), or until reaching an intercurrent event. For all other patients (2/3 of the study population) the end of the study will be the week 48 (visit 6) of each patient (or an intercurrent event.
2. If a patient does not participate in the extended follow-up study the End of Trial (EoT) visit will take place between 1 and 14 days after treatment cessation. If a subject roll over to the extended treatment study, treatment is to be continued until the EoT visit. The EoT visit should also be performed 7-14 days after study termination in case of withdrawal or early termination of the study.
3. β-hCG in plasma and urine pregnancy test should only be performed in women of childbearing potential.
4. Possible peripheral nerve dysfunction (= sensory or motor symptoms), diminished or absent reflexes (compared with baseline examination), sensory abnormalities (e.g. numbness or tingling) or weakness on neurological examination) will be monitored during the study. In case a subject experiences clinical signs or symptoms at home, subjects will be asked to contact the clinic.
5. The DSMB will assess the results of the NCS for the first enrolled 60 patients (about 40 active and 20 placebo). The NCS will be conducted for the first enrolled 60 patients at screening , and on weeks 4, 12, and 24. Then according to the evaluation by the DSMB, one of the following options will be performed: 1) If no neurological concerns are observed, the study will continue with one additional NCS at week 48 for the first 60 patients. Then for the next enrolled patients, one NCS will be performed at Screening and another one at week 48. Additional NCS(s) could be performed between Screening and week 48 if any abnormality is detected by the neurological examination or any suggesting symptoms of neuropathy are reported by the patient. 2) If NCS show signs of neurological damage, intensive NCS monitoring will continue for all patients at Screening and on weeks 4, 12, 24, 36, 48, 60, and 72.
6. Hematology: hematocrit, hemoglobin, RBC (red blood cell count & parameters), WBC (white blood cell count inclusive differential count), platelet count. Biochemistry: total protein, alkaline phosphatase, AST (aspartate transaminase), ALT (alanine transaminase), GGT (Gamma-glutamyl transpeptidase), direct and total bilirubin, blood urea nitrogen (BUN), creatinine (serum), sodium, potassium, chloride, calcium, bicarbonate, LDH (lactate dehydrogenase), CK (creatinine kinase), eGFR (estimated glomular filtration rate), uric acid, aPTT, PTT, fibrinogen and fasting glucose. Cystacin C
7. Vitamin B6 levels will be monitored and, if necessary, supplementation of vitamin B6 (pyridoxine (100 mg/day)) will be prescribed.
8. Urinalysis: Blood, Glucose, Protein, Specific gravity, Ketone, pH, Nitrite, Leukocytes, Bilirubin, Urobilinogen, Microscopic exam, if abnormal results are noted.
9. Blood sampling for FAB122 PK analysis will be done in ~90 subjects in selected sites. Of those ~30 subjects will participate in a PK profiling sampling schedule and the additional ~60 subjects will participate in a population PK sampling schedule. Sampling schedule for PK profiling: pre-dose and 15 min, 30 min, 1, 1.,5, 2, 4 hrs., and 6hrs. after the FAB122 morning dose. The pre-dose sample may be collected within 30 minutes prior to dosing, the samples taken 15 and, 30 min post dosing samples should be taken within ±2 minutes of the scheduled time, the 1 hr. post dosing sample within ±5 minutes, the 2-hour sample within ±10 minutes and the 4 hr. and 6hr. sample within ±20 minutes of the scheduled time. The time of sampling will be accurately recorded. Sampling schedule for population PK: (1) pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, (3) 1 hour and (4) 1.5 hour after the second PK sample was taken.
10. Blood sampling for the determination of riluzole concentration will be done in the subjects included in FAB122 population PK sampling in baseline and week 4 (~90 subjects) at (1) pre-dose (within 1 hour prior to dosing).(2) within 5- and 30-minutes post dosing, (3) 1 hour and (4) 1.5 hour after the second PK sample was taken. In case of discontinuation of a subject, due to safety reasons or early termination of the study, a PK sample for determination of the FAB122 concentration is to be taken in those sites where FAB122 sampling is operational. The clock time and time after last dosing is to be noted in the CRF.
11. Blood biomarkers: neurofilament light chain (NfL). Serum creatinine and serum creatine kinasa will be measured in biochemistry lab testing.
12. Urine biomarkers: 8-hydroxy-2 '-deoxyguanosine (8-OhdG), extracellular domain of neurotrophin receptor p75 (p75ECD).
13. Optional CSF sampling will be performed (if consented) in about 30 patients at baseline, week 12, and week 24. Lumbar Puncture for CSF sampling is an aseptic procedure which needs standard bedside aseptic procedures with no-touch technique, sterile drapes and use of chlorhexidine or an equivalent antiseptic. Local anaesthesia with small amount of lidocaine can be infiltrated. A right-handed practitioner should position the patient in the left lateral decubitus position, with the vertebrae in line with the horizontal plane and the head in a neutral position and the knees flexed, also setting position could be applied if seemed by the practitioner. The bony landmark is the L4 spinous process and the L3/L4 interspace is recommended. Atraumatic 22-gauge needle could be used, however smallest diameter needle with which the practitioner can confidently perform the procedure avoiding an increased number of attempts should be chosen. 10 ml CSF sample will be drawn at each time point. After the procedure, a small sterile dressing is placed on the site and the patient can mobilise as soon as it is comfortable to do so. Regular analgesics such as paracetamol could be prescribed.
14. Only labs parameters that are abnormal in the screening visit will be re-evaluated in baseline visit.

* In case it's necessary, NCS assessment can be performed during the baseline visit, provided the approval from the central reader are available prior to randomization.

3 SUBJECTS FOR ANALYSIS

3.1 Analysis populations

3.1.1 Intent-to-treat (ITT) Analysis Set

The ITT analysis set consists of all randomized patients. The ITT population will be used for the analysis of efficacy variables, and statistical analysis will be done “as randomized”.

3.1.2 Modified Intent-to-treat (mITT) Analysis Set

The mITT analysis set includes all patients who were randomized for this study and received at least 1 dose of investigational product regardless of any protocol deviation. The mITT population will be used for the analysis of efficacy variables, and statistical analysis will be done “as randomized”. The mITT is considered the primary analysis population.

3.1.3 Per protocol (PP) Analysis Set

The PP population includes a subset of the mITT population. Patients with major protocol deviations that might impact the primary endpoint will be excluded from this population. These deviations will be determined before database lock and unblinding. The PP population will be used in the analysis of efficacy variables.

3.1.4 Safety (SAF) population

The SAF population includes all randomized patients who have received at least one dose of the investigational drug, 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”.

3.1.5 Pharmacokinetics (PK) population

The PK population includes all patients who received the investigational drug and provided evaluable PK data. The PK population will be used for the analysis of the PK assessments only.

3.2 Protocol deviations

Major protocol deviators will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. In the course of the study, all protocol deviations will be collected, and during the Blind Data Review Meeting (see section 3.3) the major and minor deviations and the consequences regarding the analysis populations/statistical analysis will be assessed. Any patients or data values excluded from analysis will be identified, along with their reason for exclusion. In general, outlier data will not be excluded. A dataset will be created and used for tabular/listing presentations.

3.3 Blind Data Review Meeting

The patients will be classified during the (Blinded) Data Review Meeting (BDRM) to the analysis populations using the protocol deviations. Invitees to this meeting are the Sponsor Medical Representative (CTL or delegate), the Sponsor Project Manager (PM), the Sponsor PK scientist, Julius Clinical PM, Julius Clinical Data Manager (DM) and the Certara lead statistician, but more roles can be invited if considered necessary. Input to this meeting will be supplied by the involved Data Management Department or the responsible PM at least one week in advance of the meeting: a blinded list of all protocol deviations (including missing and outlier data), with specific detailing and description regarding the deviation, preferably in excel.

This meeting will be held in a blinded manner. The goal of this meeting is to reach consensus on minor and major protocol deviations. In case of a major deviation impacting the primary or secondary endpoints, the specific patient will be excluded from the PP population, either completely or from a specific time point onwards. The meeting must be held prior to database lock and unblinding.

The decisions taken during this meeting will be documented by the PM (or a delegate as agreed) and sent for review to all parties involved as soon as possible after the meeting, but before database lock. If all parties involved agree, then the document is finalized, signed and stored before database lock by the PM.

4 STUDY ENDPOINTS

4.1 Hierarchical multiple testing

A hierarchical multiple testing procedure will be used to evaluate superiority of the primary endpoint, followed by the evaluation of superiority of the key secondary endpoints. A fixed sequence stepwise multiple testing procedure at the 0.05 level will be performed in the following pre-specified hierarchical order:

I. Primary endpoint: change from baseline ALSFRS-R score after 48 weeks.
II. Key secondary endpoint: CAFS at 48 weeks
III. Key secondary endpoint: Survival time (death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days) over 72 weeks

Each step will be considered confirmatory if all previous steps were successful (i.e. if superiority was achieved). If any of the previous steps were unsuccessful, the subsequent steps are regarded as exploratory.

4.2 Primary endpoint

The primary endpoint is the change from baseline in Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) score after 48 weeks.

4.3 Secondary endpoint(s)

All secondary endpoints will be analyzed at 48 weeks including all patients, and additionally at 72 weeks for the subset of patients who reach 72 weeks (or ICE) as a subgroup analysis. The exception will be the planned main analysis for the key secondary endpoint of survival time (see below). This analysis will include data up to 48 weeks for all patients and up to 72 weeks for the subgroup of patients with planned extended follow-up. Analyses conducted at earlier time-points are informative but of lower relevance.

<u>Key secondary endpoints</u>

- Combined assessment of function and survival (CAFS) at 48 and 72 weeks;
- Survival time, i.e. time to death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days, over 72 weeks.

<u>Efficacy</u>

- Change from baseline in ALSFRS-R score after 24, and 72 weeks;
- The slope of the decrease in ALSFRS-R score over time at 24, 48 and 72 weeks;
- Change from baseline in ALSFRS-R score after 24, 48 and 72 weeks on:
    - Bulbar function (question 1-3 of the ALSFRS-R);
    - Fine motor function (question 4-6 of the ALSFRS-R)
    - Gross motor function (question 7-9 of the ALSFRS-R)
    - Respiratory function (question 10-12 of the ALSFRS-R)
- Time to a 3, 6, 9 and 12 points change from baseline in ALSFRS-R score;
- Proportion of subjects with change from baseline in ALSFRS-R score at 24, 48 and 72 weeks in categories: categories will include change ≥0, change between <0 and ≥-1, change between <-1 and ≥-2 etc.;
- Time to change in staging of disease progression (King's staging system and MiToS) or death over 72 weeks;
- Overall survival: Proportion of subjects alive (survival rate) after 24, 48 and 72 weeks;
- Proportion of subjects alive and no tracheostomy[1], or no initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days after 24, 48, and 72 weeks;
- Change from baseline in slow vital capacity (SVC, liters) at 24, 48 and 72 weeks;
- Change from baseline in the overall mega score for the hand-held dynamometer (HHD) at 24, 48 and 72 weeks.

QoL

- Change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) Form at 24, 48 and 72 weeks;
- Change from baseline in EuroQoL – 5 Dimensions-5 Levels (EQ-5D-5L) questionnaire score at 24, 48 and 72 weeks.
- Change from baseline in Health related QoL Visual Analogue Scale (VAS) score at 24, 48 and 72 weeks.

Cognition

- Proportion of subjects with a change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS (Edinburgh Cognitive and behavioural ALS Screen) total score;
- Change from baseline for ALS Specific, ALS Non-Specific, and ECAS total score at 24, 48 and 72 weeks;
- Time to a mean change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS total score.

Pharmacokinetics

(Population) PK parameters of FAB122 and riluzole

4.4 Exploratory endpoint(s)

Pharmacokinetics

PK interaction between FAB122 and riluzole

[1] Defined as tracheostomy due to trouble breathing as per item 12 of the ALSFRS-R.

Biomarkers

- Change from baseline in the prognostic ALS biomarkers neurofilament light (NFL) and heavy chain (NFH)
- Change from baseline in the surrogate ALS biomarkers creatinine and creatine kinase
- Change from baseline in the surrogate ALS biomarker Urinary extracellular domain of neurotrophin receptor p75 (Urinary $P75^{ECD}$)
- Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG)

Health economics

Cost-Utility analysis of treatment with FAB122.

4.5 Safety endpoint(s)

- Nature, frequency and severity of Treatment Emergent Adverse Events;
- 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

Raw data (in listings) will be presented in the same precision as received. 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, unless otherwise specified. In case this value is missing for a specific patient, but an earlier measurement (e.g. screening) is present, this value will be used as baseline instead. Unscheduled measurements are excluded as baseline value.

If available in the database, data for screening failures will not be presented in summary tables, except for disposition and end-of-study displays. Data for screening failures will be listed as available.

For patients that are unable to attend the clinic on a study visit due to ALS progression, at least ALSFRS score, AEs and concomitant medication data are collected. These data may be collected by telephone and are considered of the same quality as performed during live visits.

If a patient is not able to attend the site for two consecutive visits, then IMP will be discontinued at the 2nd missed visit, but participation in the trial and data collection can continue via telephonic visits to collect ALSFRS-R, AE and concomitant medication. It is assumed that data collected via telephone visits is of same quality as the data collected via site visits.

For QoL questionnaires: in case of technical issues with the ePRO device, these can be completed on a paper version as a backup. The data collected per paper are considered of the same quality as collected with the ePRO device.

5.2 Missing or excluded data or intercurrent events

Efficacy data – intercurrent events

The intercurrent events during the study can be broadly classified as terminal and non-terminal intercurrent events. Death or "real" loss to follow-up are considered terminal intercurrent events, wherein there is absolutely no data available for these patients after the occurrence of the event. The other intercurrent events are non-terminal, where there is a possibility of collecting data from these patients after the occurrence of the intercurrent event (ICE).

Note that per design of the study, only 100 patients will be followed until week 72. The non-available data for the ~200 patients between week 48 and 72 will not be considered as ICE.

Regarding intercurrent events, following ICH E9 (R1), two types of strategies will be applied for the primary statistical analysis performed for the primary endpoint and utilizing the primary analysis population (mITT).

The "Treatment Policy" strategy will be applied to the following intercurrent events:

- Treatment discontinuation due to adverse events.
- Treatment discontinuation due to lack of efficacy.
- Other unforeseen treatment related reasons (i.e. due to efficacy or safety issues).
- Rescue medication.
- Non-treatment-related reasons, other than those already specified earlier. This includes situations like patients moving to another location for treatment unrelated reasons. Note that the "Treatment Policy" strategy might not be applicable if there are real lost-to-follow-up cases after doing all efforts to retrieve the data.

For deaths, the Treatment Policy cannot be applied, and missing data imputation will be used for the statistical analyses.

The "Treatment Policy" strategy implies that the efficacy observed assessment (including those collected after the occurrence of the intercurrent event) will be used regardless of the occurrence of an intercurrent event.

The "Composite" strategy will be applied to the following intercurrent events.

- Related[2] death (or death with unknown reasons). It is expected that the rate of death at 52 weeks will be lower than that observed in the trial (<17%). A non-substantial but lower rate is expected in the experimental arm.
- "Real" lost to follow-up. These are cases where there is lost to follow-up after reasonable attempts to contact the patient have been made and all efforts to retrieve the data have failed.

The "Composite" strategy for handling these events will be applying a conservative scenario using the 95% worst percentile combined with multiple imputation (the intercurrent event is explicitly taken into account and made part of the outcome by this imputation, conditioned on timepoint). This method uses the imputation of a conservative value representing the 95th worst percentile.

Efficacy data – missing

To evaluate the impact of missing data and of the earlier handling methods, a number of sensitivity analyses will be performed for the primary endpoint utilizing the primary analysis population (mITT).

- **As treatment multiple imputation**: For any patient with missing values, the estimates for the missing assessments will be based on the actual treatment group of that patient. One-hundred imputations will be performed. A predicted mean matching based on a monotone regression (in case the missing data pattern is monotone) or on a fully conditional specification regression (in case the missing data pattern is arbitrary and non-monotone) will be applied. The predicted mean matching method imputes an observed value which is closest to the predicted value from the simulated regression model for each missing value. It ensures that imputed values are plausible and might be more appropriate than the regression method if the normality assumption is violated. The regression model will condition on observed values of the primary outcome measured at other time points (including baseline measurements) and possible other covariates that are related to the missing data pattern and/or primary endpoint. The statistical model for the primary endpoint will then be applied to each imputed dataset separately. The estimated parameters will be pooled using Rubin's combining rules. This analysis will be applied under the assumption of data missing at random (MAR).
- **Tipping-point analysis**: The tipping point is defined as the difference in the change from baseline in ALSFRS-R score at week 48 between FAB122 and placebo at which the study conclusion (i.e. the statistical significance) changes. This analysis is done to explore the impact of MNAR data and is therefore a sensitivity analysis under the assumption of MNAR. Missing data are imputed over a range of possible scenarios for treatment effect, in order to identify the scenario (or tipping point) that reverses the study conclusion as obtained in the original MAR/MCAR analysis. To find this tipping point a systematic shift will be applied to the (as-treated) imputed values (i.e. a MNAR adjustments in the multiple imputation process) in the FAB122 treatment arm. These shifts will cover a large enough range, in steps of 0.2 to find the value for which the analysis shows a change in significance of the primary hypothesis test, the tipping point. For each shift the primary analysis method will be repeated on the 20 multiple imputed data sets. In case such a tipping point has an unrealistic value (as per clinical decision), this will support the treatment effect found in the primary analysis.

[2] All deaths (including unrelated) are meant here, as it is safe to assume all deaths are related to ALS. In case of unrelated deaths, this will be very small number.

- **Hybrid approach**: With the hybrid approach the missing weeks for patients who discontinued due to AE or lack of efficacy will be imputed using the placebo-based pattern imputation under the MNAR assumption and under the assumption of monotone missing data. All other discontinuation/missing will be imputed using multiple imputation by treatment group using a multivariate stepwise approach using a fully conditional specification (FCS) regression method (Rubin, 1987), assuming the missing data pattern is arbitrary and non-monotone. Missing baseline values, if any, will be imputed using age and time since diagnose. Subsequent visits will be imputed using data of all previous weeks in a stepwise fashion. Twenty imputations will be performed.
- **Completer analysis**: This analysis includes only patients who have completed the study up to week 48, and those patients who died prior to 48 weeks assuming they would otherwise have completed the study up to 48 weeks.
- **Per Protocol and ITT Analysis**: This analysis will include patients from the PP and the ITT analysis sets. The same missing data imputation and ICE strategy as for the mITT analysis will be applied to these sensitivity analyses.

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.

Safety data

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.

Regarding prior/concomitant medication, a similar approach will be followed for partially missing dates, as will be done for AEs as described above.

Using the most conservation approach, missing/incomplete information regarding medical history/ALS history will be handled as follows to calculate the duration of symptom onset:

- If only the day part of the date of diagnosis is missing, then the first of the month is imputed for the start date.
- If the day and month part of the date of diagnosis is missing, then 01 January is imputed for the start date.

If the complete date is missing, then no imputation can be performed, and this will need to be discussed and addressed prior to database lock and unblinding in agreement with the sponsor and the Data Management vendor.

Other

Based on the BDRM, certain values can be decided to be excluded from analyses. These values will be listed, but not included in descriptive statistics, plots or statistical analyses. This may be (outlier) data that are a result of unambiguous measurement errors.

5.3 Mapping of unscheduled or early termination visits

When visit assessments are missing, repeat assessments performed within the agreed time window of +/- 7 days will be mapped to the appropriate visit in the database by the DM vendor. Repeat assessments performed outside of these agreed time windows are collected in the database using an unscheduled visit. For these unscheduled assessments following a missing protocol visit, 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 during the BDRM.

For patients that withdraw early from the trial, an early termination visit is scheduled 7-14 days after withdrawal, for which the same procedures as for visit 8 will be performed. The data of this early withdrawal will 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 during the BDRM. 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.

5.4 Interim analysis

No formal interim analysis is planned, however interim safety and efficacy results will be shared with a DSMB following a specific DSMB SAP and DSMB charter.

5.5 Baseline characteristics

5.5.1 Inclusion/exclusion criteria

An individual patient listing of deviations from the inclusion and exclusion criteria will be presented.

5.5.2 Demographics

Descriptive tabulations of the screening data for demographics will be made. 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. 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. The summary will be created for each efficacy analysis population separately. Additionally, demographic data will be listed.

5.5.3 Baseline characteristics

The patient baseline characteristic "substance use" and the stratification groups (the slope ALSFS-R score from the time of first symptoms until screening, concomitant use of riluzole) will be summarized per treatment group and overall using the safety population. Baseline characteristics will also be listed.

5.5.4 Disposition

To present disposition, a summary of all included, randomised, treated and completed[3] patients will be created. Number/percentage screened will be included as well, if available in the database. Additionally, in the same summary, the number/percentage of patients in the ITT, mITT, PP, PK and SAF will be presented and the frequency/percentage per reason for non-completion will be added. The patient disposition will be presented per treatment group and overall.

Additionally, a listing displaying all disposition information (including reasons for withdrawal and reasons for exclusion from the PP population) on a per patient level will be created. This listing will include exposure time for each patient, calculated from date of first dose until end of treatment, and follow-up time for each patient, calculated from date of first dose until end of study.

5.5.5 Medical history

Medical history will be tabulated per System Organ Class (SOC) and Preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology list and presented as number/percentage of patients in each SOC and PT for the SAF. SOC and PT will be presented in descending order of frequency of occurrence based on SOC and PT. These data will also be listed on a per patient level.

[3] A patient is considered to complete the study if he/she completed the 72 week treatment period OR if she/he completed at least 48 week of treatment at study completion (i.e. after the last patients have completed the study up to at least 48 week). Note that this is a different selection of patients then for the 'Completer Analysis' as defined as one of the sensitivity analyses.

5.5.6 ALS history

Collected information on ALS history will be summarized as appropriate. ALS duration will be determined based on the baseline data and the date of onset. In case of (partially) missing onset date, the imputation rules per section 5.2 will be followed.

5.5.7 Other screening data

Not applicable.

5.6 Statistical analysis primary and secondary endpoints

The primary analysis population is the mITT for the primary and all secondary endpoints. Analyses of the primary endpoint based on the ITT and PP will also be undertaken to provide supplementary information on efficacy. Statistical analysis on secondary endpoints will be considered explorative in nature and will only be done for the mITT.

For each of the primary and secondary endpoints descriptive statistics will be presented for original values and change from baseline values on a per-visit basis, for each treatment arm and overall. All individual primary and secondary endpoint data will be listed as well.

No multiple corrections will be applied: a hierarchical approach is used as per section 4.1 and all other endpoints are considered strictly explorative.

5.6.1 Primary analysis

The primary endpoint is defined as the change from baseline in total ALSFRS-R score after 48 weeks (primary timepoint).

For the primary analyses, a placebo (reference) multiple imputation (pMI) will be applied to impute missing data for any patients (i.e. from both treatment arms) who discontinue treatment early, irrespective the reason for drop-out (only when due to intercurrent events with unknown cause), and for which no data was collected after treatment discontinuation. The pMI method assumes the statistical behavior of placebo- and drug-treated patients after dropout is the statistical behavior of placebo-treated patients. A total of 20 imputed data sets will be created.

Before applying the statistical model to the primary endpoint, intercurrent events will be handled following the rules specified in Section 5.2.

The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM), considering ALSFRS-R is assessed at multiple timepoints. The average treatment effect (lsmeans) and the treatment difference (estimand) of the change from baseline ALSFRS-R total score at 48 weeks will be extracted from the results from this model and presented together with the 95% confidence interval and p-value. Other timepoints will also be presented.

The model will include factors for treatment, time, treatment-by-time interaction, the stratification factor concomitant use of riluzole (yes/no), baseline ALSFRS-R score and the stratification factor slope of disease progression as fixed effects. An unstructured (UN) covariance matrix will be used in the model. If the model does not converge, the structure will be adapted to respectively AR(1), Toeplitz or Compound Symmetry (CS). The results of the 20 imputed data sets will be combined to obtain the final estimate of the treatment difference with 95% confidence interval and p-value.

An example SAS code which can be used as basis is as follows:

```
proc mixed data=<data>;
  class trt time riluse;
  model cfb=trt time trt*time riluse base disslope / ddfm=kr;
repeated time/ subject=patient type=un;
  lsmeans trt*time/cl;
run;
```

Sensitivity analyses using the mITT population will be performed for the primary endpoint as described in Section 5.2. The same model will be used to each of the imputed datasets separately after applying the imputation techniques. The estimated parameters of the imputed datasets will be pooled using Rubin's combining rules to obtain a final result of the treatment difference with a 95% confidence interval and p-value.

Descriptive statistics will be presented for ALSFRS-R total score, including change from baseline.

5.6.2 Secondary analysis

All secondary endpoints at 72 weeks will be analyzed for the subgroup of patients who reach 72 weeks (or ICE). Analysis will be done for the full patient group until week 48, and a separate analysis will be done for the subgroup until week 72.

Key secondary endpoints

No sensitivity analysis or intercurrent event correction will be applied for any of these key secondary endpoints.

Combined assessment of function and survival (CAFS) at week 48 and 72

CAFS is used to compare each study patient's outcome to others in the trial in a series of pairwise comparisons, based on function (i.e. ALSFRS-R score) and survival. See section 9.1 for relevant derivations. For each pairwise comparison, a study patient is assigned a score and then the summed scores are ranked for all patients.

Descriptive statistics for CAFS ranks will be made but are difficult to interpret as mean values depend on the size of the study. Descriptive statistics will also include mean difference in ranks with a 95% CI.

The difference between treatments CAFS ranks will be assessed using the Gehan-Wilcoxon rank test (also known as the Generalized Wilcoxon test) or, in case of relevant differences in baseline characteristics (as per factors included in the ANCOVA model mentioned), by using an ANCOVA model.

Regarding the Gehan-Wilcoxon rank test: if the analysis indicates a statistically significant effect, then the separate analysis of function and survival (as described below in the other secondary endpoints section) can provide insight whether the improved outcome for the group was driven by prolonged survival, improved function, or both. In case of an ANCOVA model: a General Linear Model (GLM) will be utilized with treatment, baseline ALSFRS-R score and stratification factors (slope of disease progression, concomitant use of riluzole) as covariates.

ALSFRS-R score values for patients who survived but have a missing week 48 score will be imputed following to the imputation defined in section 5.6.1, before the CAFS score will be

determined. The GLM will omit any (other) patients with missing data from the analysis. The duration from symptom onset is calculated from the medical history data.

In case of GLM, subsequent component analyses of function and survival will be used to determine which parameter(s) drive the overall effect on the CAFS results. The direction and magnitude of the function and survival components of the CAFS will inform the interpretation of the results.

'Survival Time'

'Survival Time', i.e. time to death[4] or time to reaching the criteria for respiratory insufficiency is the other key secondary endpoint. The criteria for respiratory insufficiency are defined as tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days, over 48 weeks or 72 weeks, respectively. Descriptive statistics (median and Q1/Q3 quartiles with 95% confidence intervals) and Kaplan-Meier curves will be provided. The difference between oral FAB122 and placebo will be assessed using restricted mean survival time (RMST) analysis for the time point week 48 (and another one for week 72 for the subgroup of 100 patients), adjusting for the stratification variables. The RMST analysis provides robust estimates even when the proportional hazard function is violated.

SAS PROC LIFETEST with option RMST will be used for this analysis.

In addition, a Cox regression model and a stratified log-rank test will also be applied as supportive analysis, including factors for treatment and stratification variables. Patients that complete the study and those that discontinue due to reasons other than death or due to reaching the criteria for respiratory insufficiency will be considered censored.

Other secondary endpoints

The following secondary endpoints will also be presented, as applicable. No sensitivity analysis, intercurrent event correction or imputation methods will be applied for any of these endpoints.

ALSFRS-R score

Absolute and change from baseline in total ALSFRS-R score after 24 (full group and subgroup) and 72 weeks (subgroup only) will be presented by treatment group in summary tables. Note that results after 12, 48 and 60 weeks for full group/subgroup as available will also be presented by treatment group in the same summary table. The statistical analysis is as described in the section on the primary endpoint.

The proportion of patients with change from baseline in ALSFRS-R score at 24, 48 and 72 weeks will be presented in categories for each treatment group. Categories will include change ≥ 0, change between <0 and ≥ -1, change between <-1 and ≥ -2 etc. A Chi-squared test will be performed, and the p-value added to the table.

The slope of the decrease in ALSFRS-R total score over time at 24, 48 and 72 weeks will be calculated and presented in summary tables. Per treatment arm, slopes will be determined using an MRMM model on the change from baseline, with independent variables treatment group, baseline value, time and treatment*time interaction. Slopes for each treatment group and slope difference between treatments will be presented. No individual per-patient slopes will be presented.

[4] Where date of death is taken from the Survival follow-up form.

Change from baseline in ALSFRS-R subscale scores will also be calculated after 24, 48 and 72 weeks for the following subscales:

- Bulbar function (question 1-3 of the ALSFRS-R);
- Fine motor function (question 4-6 of the ALSFRS-R);
- Gross motor function (question 7-9 of the ALSFRS-R)
- Respiratory function (question 10-12 of the ALSFRS-R);

Summary statistics for the change from baseline in the above subscale scores will be presented by treatment group and overall, again separately for the full group and the subgroup.

In addition, a similar statistical model as for the primary endpoint will be utilized for analyzing the change from baseline for the subscale scores.

Time to event - change from baseline or death

Time to event, being a change from baseline of 3, 6, 9 and 12 points or death in ALSFRS-R score over 48 or 72 weeks, respectively, will be calculated and summarized by median values with 95% confidence intervals. In addition, the Hazard Ratio with 95% CI will be presented. Comparisons between treatment groups will be done using a Logrank test.

Overall Survival

Proportion of patients alive (survival rate) after 24, 48 and 72 weeks for full group and subgroup as available will be presented by treatment groups and overall. Kaplan-Meier plots will be presented, and treatment groups will be compared using a log-rank test.

Progression free survival

Proportion of patients alive and no tracheostomy, or no initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days after 24, 48 and 72 weeks will be presented by treatment group. Kaplan-Meier plots will be presented, and treatment groups will be compared using a log-rank test.

Staging of disease progression

Data from staging of disease progression (King's scaling system, MiToS) after 12, 24, 60, 72 weeks as compared to baseline will be presented per visit by treatment group and overall, in summary tables using frequency and percentages. Frequency and percentages of patients showing a decline of ≥ 1 stage from baseline will be presented as well.

Kaplan-Meier curves will be created to present time to decline of ≥ 1 stage from baseline in both staging systems over 48 weeks or 72 weeks, respectively. A log-rank test will be used to determine the difference between study arms. Patients lost to follow-up will be censored. Days of maintaining the baseline stages will be presented per treatment arm and group/subgroup, including differences between treatment groups.

See section 9.1 for relevant derivations for King's scaling system and MiToS.

Slow Vital Capacity (SVC)

Relevant derivations for the SVC are presented in section 9.1.

Descriptive statistics for absolute value and change from baseline in slow vital capacity (SVC, liters) at 24, 48 and 72 weeks will be presented in by treatment group and overall. A similar statistical model as for the primary endpoint will be utilized for analyzing the change from baseline.

Hand-held dynamometer

Derivations for the HDD megascore are presented in section 9.1.

Descriptive statistics for absolute value and change from baseline in the overall mega score for the hand-held dynamometer (HHD) at 24, 48 and 72 weeks will be presented by treatment group and overall. A similar statistical model as for the primary endpoint will be utilized for analyzing the change from baseline for the overall mega score. Subscores (per muscle and per muscle group) will only be included in the listings.

QoL

The following QoL parameters will be calculated and presented by treatment group and overall in summary tables.

- Absolute values and change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) and the five scale scores at 24, 48 and 72 weeks. Scale scores will also be presented based on range, using frequency and percentages. A similar statistical model as for the primary endpoint will be utilized for analyzing the change from baseline for the total score only. Derivations for the ALSAQ-40 are presented in section 9.1.

- EuroQoL – 5 Dimensions-5 Levels (EQ-5D-5L) questionnaire score 24, 48 and 72 weeks. Frequency and percentage of each level will be presented for each timepoint on each of the dimensions, per treatment. Relevant derivations for the EQ-5D-5L are presented in section 9.1. The per patient 5-digit number will only be presented in the listing.

- Absolute values and change from baseline Health related QoL Visual Analogue Scale (VAS) score at 24, 48 and 72 weeks. Data from all visits collected will be presented in the summary. A similar statistical model as for the primary endpoint will be utilized for analyzing the change from baseline.

Cognition

The following cognition parameters will be presented by treatment group in summary tables. Results on the cognitive subdomains will only be presented in listings.

- Proportion of patients with a change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS (Edinburgh Cognitive and behavioral ALS Screen) total score;

- Absolute values and change from baseline for ALS Specific, ALS Non-Specific, and ECAS total score at 24, 48 and 72 weeks.

- Time to a mean change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS total score.

Pharmacokinetics

The Population PK parameters of FAB122 and riluzole will be presented by the PK vendor, and analysis is specified in a separate PK analysis plan. A separate PK report may be created by the PK vendor and added to the Clinical Study Report.

5.6.3 Additional analysis

As an additional (supportive) analysis, the joint assessment of change in functional decline[5] and overall mortality using a joint modelling (i.e. shared-parameter) framework over 48 weeks (all patients) and 72 weeks (subgroup of 100 patients) will be determined. The statistical model will combine ALSFRS-R score and survival[6], using a linear mixed model and a Cox model, as submodels combined into a non-linear mixed model using the SAS procedure PROC NLMIXED. Parameter estimates and standard errors will be presented. Initial values for the parameters in the joint model may be based on the resulting parameter estimates of the two submodels, as described before for ALSFRS-R and survival. Example SAS code is available as reference in the publication of Vonesh e.a., 2006.

5.6.4 Exploratory analysis

PK analysis

All summary tables, plots, listings, and analyses of the PK concentration data and parameters will be done by the PK vendor. PK listings containing the dates and times of the sample collection will be created by Certara.

The data for the PK concentration and the calculated PK parameters received according to the agreed data transfer specifications may be converted to CDISC format by Certara (if not done by the PK vendor) and can be supplied back to the PK scientist for use in the PK analyses.

Biomarkers

The following biomarkers will be summarized by treatment group as exploratory endpoints:

- 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 $P75^{ECD}$)
- Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG)

For NFL also the geometric mean and geometric mean ratio will be presented, using log-transformed (based on natural logarithm) data. The geometric mean is calculated as the exponent of the mean of the log transformed data. The geometric mean ratio is the ratio of two geometric means.

Furthermore, a listing will be created presenting all data that are out of reference range on a per-patient level, including any available unscheduled measurements. The investigator has judged the out-of-range values on their clinical significance, and this information will be added as well. Information regarding age at screening and gender will be added to this listing.

[5] Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. Stat Med. 2006; 25: 143 – 63

[6] R.P.A. van Eijk et al. Joint modeling of endpoints can be used to answer various research questions in randomized clinical trials. Journal of Clinical Epidemiology 147 (2022): 32-39

Cost-utility analysis

In this study, an exploratory cost-utility analysis for treatment with FAB122 will be conducted based on the data from the cost questionnaire providing direct and indirect costs associated with the disease, and information from eCRF data existing of hospitalizations, concomitant medication and occurrence of AEs.

The following cost parameters are considered for the cost-utility analysis among study groups:

- Number of contacts classified per specialist and type of contact.
- Number of hospitalizations related to ALS classified per unit of stay and length of stay.
- Specialized equipment / Devices cost per type of Medical Aid.
- Paramedical treatment visits (i.e. physical therapy, rehabilitation, occupational therapist, speech and language therapist, or otherwise specified by the patient).
- Formal care (i.e. health professional) and informal care (i.e. familiar/friend): duration and cost per type of service and overall.
- Employment situation.
- Occurrence of AEs in each group (see section 5.7.1, note: no costs are collected for this).

Descriptive statistics will be displayed for each of the categories above as well as for the costs by category and over all categories for each patient, where costs will be presented in euros. As applicable, duration of a hospitalization (in days) will be presented as average over the patients as well as the total summed duration over all patients per treatment group. Adding of costs and calculation from local tariff to euro will be done via programming, using input from client and DM vendor on used currency and exchange rates to be used by time of Database lock.

It should be noted that most cost-utility analysis fields are free text (in local language), which may make it complicated to derive all the above directly from the data. Also, in the data collected, there is no clear indication whether or not hospitalizations are related to ALS and total costs collected are not consistently entered. Specific data handling strategies may be discussed with the client and the DM vendor, otherwise descriptive statistics will be limited to items as collected, where free text fields will only be listed (without translation).

5.7 Safety and tolerability evaluation

All safety presentations will be created using the SAF population.

5.7.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after first study treatment. 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 discontinuation.

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 also be tabulated by severity (mild/moderate/severe) and by relationship to study medication (related/unrelated), using 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 discontinuation, Serious TEAEs and TEAEs of special interest. These summary tables will be presented by decreasing frequency of occurrence based on SOC and PT.

The summary tables will be accompanied by individual patient listings of *all* AEs including information on AE number, actual AE description, date of start and end of AE (or ongoing), PT (MedDRA), SOC (MedDRA), severity, relationship, pre-existing (yes/no), seriousness, special interest, action taken and outcome. Pre-existing AEs are not considered to be treatment emergent. AEs starting prior to administration of the study drug will only be listed.

Separate listings will be created for AESIs, SAEs, and deaths.

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. The original description will be used in listings.

5.7.2 Clinical laboratory

The following laboratory safety data are collected for this study:

Hematology	Chemistry	Urinalysis	Other
Haematocrit (HCT)	Bilirubin (direct) and Bilirubin (total)	Blood	Serum β-human chorionic gonadotropin (β-hCG)
Haemoglobin (HGB)	Alkaline phosphatase	Glucose	Hepatitis B surface antigen (HBsAg)
RBC	Alanine aminotransferase (ALT)	Protein	Hepatitis C virus antibody (HCV-Ab)
Platelet count	Aspartate aminotransferase (AST)	Specific gravity	HIV antibody (HIV-Ab)
WBC	Bicarbonate	Microscopic exam, if abnormal results are noted	Plasma vitamin B6 levels
Differential count: - Basophils - Eosinophils - Lymphocytes - Monocytes - Neutrophils	Calcium	Ketone	Cystatin C
	Chloride	PH	
	Creatinine	Nitrite	
	GammaGT (GGT)	Leukocytes	
	Fasting Glucose	Bilirubin	
	Potassium	Urobilinogen	
	Sodium		
	Uric Acid		
	Total protein		
	Urea (BUN)		
	eGFR		
	Activated partial thromboplastin time (aPTT)		
	Protrombin Time (PTT)		
	Fibrinogen		
	Lactate dehyrdognease (LDH)		
	Creatinine kinase (CK)		

Laboratory safety data will be summarized using descriptive statistics over time, and listed per visit and treatment group, using protocol visits. Change from baseline will be calculated and

presented as well for quantitative data, using the same summary statistics. The categorical data of urinalysis will be summarized by treatment and time in frequency tables by variable. If applicable, laboratory safety data collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

For laboratory safety data, all recorded and determined laboratory safety data will be listed. Safety laboratory parameters will be presented in the tables and listings in the same (standardized) units as supplied. Since data will be provided in both conventional as SI units, SI units will be used for presentation purposes.

It should be noted that Creatinine and Creatinine Kinase are also part of the Biomarker analysis and will therefore be presented twice for different analysis populations.

5.7.3 Vital Signs

Vital sign data will present measurements for height, weight, BMI, systolic and diastolic blood pressure, pulse rate, respiratory rate, pulse oximetry and temperature. Vital signs (absolute values and change from baseline) will be summarized (n, mean, SD, median, minimum and maximum) and listed per visit, per treatment group and overall, using protocol visits. Mean (SD) of absolute values for vital signs data (blood pressure, pulse rate and respiratory rate) will also be presented graphically through time.

If applicable, vital sign measurements collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics or graphical presentations.

5.7.4 ECG

From the 12-lead ECG data, HR, PR interval, QRS interval, QT interval, RR interval and QTcF will be reported for each visit and summarized using descriptive statistics. Change from baseline will be calculated as well, using the same summary statistics. Mean (SD) temporal profiles for 12-lead ECG (QT, QTcF) will be presented graphically. Clinically significant findings will only be listed.

If applicable, ECG measurements collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

5.7.5 Prior and concomitant medication

The use of concomitant medication will be listed for all patients: included will be the medication generic name, WHO coding information, dose, route of administration, start and stop date, frequency and reason for administration, as well as information if given for an AE. Differentiation will be made between prior and concomitant medication, by creating two separate listings.

Separate frequency tables will be presented for prior and concomitant medication per Standardized Medication Name as provided.

If a medication is started and stopped prior to the first dosed of study medication, then it is considered prior medication. In other instances, it is considered concomitant. In case of (partially) missing start/stop dates, refer to Section 5.2.

5.7.6 Physical examination

All abnormalities reported by the physical examinations will be listed.

5.7.7 Nerve conduction study (NCS)

NCS consists of the following assessments: Hand Temperature (ºC), Foot Temperature (ºC), SRAR, SNAP (µV) and SCV (m/s). The latter two have been determined for locations Median Nerve, Ulnar Nerve, Radial Nerve, Sural Nerve. Descriptive statistics will be presented for all assessments, irrespective of being performed per NCS protocol or quality assessment result. The following descriptive displays will be presented:

- Descriptive statistics per visit and treatment arm, including change from baseline.
- Mean +/- SD plots versus time
- Shift from baseline categories (presenting frequencies and percentages per visit and treatment arm)
- Percentage drop >50% from baseline (presenting frequencies and percentages per visit and treatment arm)
- Normal/abnormal classification results (presenting frequencies and percentages per visit and treatment arm)

Information on high/low/normal categorization is presented in section 9.1.

In case of multiple measurements for a specific visit, repeats have occurred because of a measurement being not quality approved. In those instances, the last repeated value will be used for the descriptive statistics. All collected values will be listed.

5.7.8 Other examinations

Any other data collected will be presented in listings.

5.8 Scheduled visits, Dosing and Treatment Compliance

5.8.1 Visit dates

A listing with actual visit dates will be presented.

5.8.2 Dosing and treatment compliance

Relevant dosing information, scheduled and actual dosing dates, drug accountability and treatment compliance will be listed for each patient.

A frequency tabulation of compliance below 80%, 80-120% (inclusive), and above 120% will be presented. Compliance will be determined using the drug accountability information collected in the database. The total number of sachets dispensed minus the total number of full sachets returned is considered the actual amount of trial medication taken. This should automatically include the number of missed doses. Sachets not returned will be considered not taken, from conservative perspective, and will be subtracted from this total number. The duration between the first dose date and the last dose date is considered the period over which the study medication has been taken and is the theoretical amount of trial medication taken (based on intake of one sachet per day). Percentage compliance is then calculated as ((actual – not returned)/theoretical) *100%.

6 CHANGES FROM PROTOCOL AND OTHER RELEVANT REMARKS

The hybrid approach for missing data (Section 5.2) uses placebo-based pattern imputation under the MNAR assumption instead of last observation carried forward for patients who discontinued due to AE or lack of efficacy.

Several clarifications have been made to the sensitivity analyses.

A few minor typing errors have been corrected (e.g. creatine kinase instead of creatinine kinase)

For CAFS, the protocol states that "A rank-ANOVA will be used as a sensitivity analysis". However, the CAFS are already ranked data and already analyzed via ANCOVA, so this specific analysis has been removed. Furthermore, it has been added that either a Gehan-Wilcoxon rank test or an ANCOVA or will be performed, based on assessment of baseline differences, as per literature reference. Lastly, for the analysis it is mentioned in the protocol that "the same covariates as the primary efficacy analysis" will be included. This is not completely true, as the time and time*treatment interaction will not be included in the ANCOVA model, hence the variables are slightly different.

There are a few patients (# 3) that have been mis-randomized in the study and, consequently, did not receive study treatment. According to the definition, these patients still belong to the ITT population, being a secondary analysis population in this study. In principle no imputation will be applied for these patients for the primary endpoint and missingness is assumed to be MAR (missing at random). If the number of mis-randomized patients is larger than anticipated, a pMI approach will be considered for imputation of the baseline values.

There are several patients for who the CTCAE toxicity grade has been collected. These data will only be present in the CDISC files and the relevant listings, and not used in any descriptive statistics tabulations.

7 COVID-19 DETAILS

This study is conducted during the COVID-19 pandemic. A number of data capture decisions may need to be taken due to national, local, or site-specific restrictions imposed, with the primary need to prioritize the safety of clinical study teams and patients, and to maintain the integrity of the study/data collection.

The details of potential COVID-19 impact on the study's procedures and activities will be provided in the Risk Management Plan of the study and other applicable study plans (i.e: monitoring plan).

Screening and Baseline assessment will always be done in clinic. Every effort should be made to perform these visits, depending on local regulations. The contingency would only be applicable for the randomized/ongoing patients. In case of sanitary restrictions, the following assessment might be performed at patient's home by the site study team personnel or by a validated Home Nursing services provider, provided by the sponsor.

Any impact on the data and the statistical analyses will be assessed during the trial.

8 DATA RECEIPT

All data will be received per transfer agreements. The received files will be imported into SAS and will be programmed to CDISC standards (SDTM and ADaM) using the latest FDA accepted versions, before programming of the tables, listings and figures is done.

9 TECHNICAL DETAILS

9.1 Programming conventions

CAFS

To calculate[7] a patient's CAFS, each patient is scored on their relative function and time of death as compared to other patients (irrespective of treatment arm) in the trial. The summary CAFS score for each patient is the sum of the comparisons (-1, 0, +1) against all other patients. For each pairwise comparison of patients, the patient who shows a better score receives a +1, and the one who shows a worse score receives a -1. In the case of a tie, no points are added or subtracted (scoring is 0). If both patients die, the one surviving longer fared better; if only one survives then that patient fared better; and if both patients survive, the one with the smaller decline in ALSFRS-R from baseline fared better. If a patient discontinues early (only after first applying the imputation rule to ALSFRS-R), comparison to each other patient uses time to death if the comparator died before the patient's discontinuation time; otherwise, the comparison is based on the last ALSFRS-R time-point available for both patients. This way, a higher CAFS score indicates a better outcome.

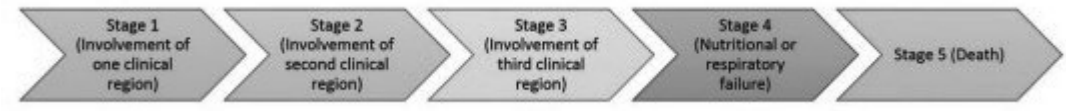
Next, each patients' summated score (the so-called function/survival score) is ranked, where ranking is done on week 48 (for all patients and the subgroup) and week 72 (for the subgroup of 100 patients) separately. In general, the ranking has the following characteristics: 1) the first patient who dies will have the lowest score and is ranked the lowest; 2) the last to die is ranked above all others who die; 3) among survivors, the patient with the greatest decline in ALSFRS-R is ranked just above the last patient who died; 4) the surviving patient with the least decline in ALSFRS-R is ranked highest; 5) when comparing ALSFRS-R decline among two survivors, the decline is measured at the longest time that both were followed. The average rank score is then calculated for each treatment group. A higher mean rank score indicates that patients in that treatment group, on average, have a better outcome.

Comparison should be done per patient based on their last observed follow-up time if lack of follow-up is due to logistic/administrative issues. This can only be assessed if the reason is clearly specified as being a logistic reason in the database.

King's scaling system

The King's system consists of five stages, ranging from 1 to 5, and is based on disease burden as measured by clinical involvement and significant feeding or respiratory failure, with stage 1 being symptom onset and stage 5 being death.
Based on the Kings Staging System data as collected in the CRF, the King's stage per visit can be determined as follows, where the highest stage is selected for each patient.

- If deceased, then Stage is 5
- If any nutritional (4a) or respiratory (4b) failure, then Stage is 4
- Count the number of regions (Bulbar, Upper limbs, Lower limbs) and this sum will be either Stage 1, 2 or 3.



[7] Berry, J. e.a. "The Combined Assessment of Function and Survival (CAFS): A new endpoint for ALS clinical trials", Amyotrophic lateral sclerosis and frontotemporal degeneration; Volume 12, 2013-issue 3, pages 162-168.

MiToS

MiToS is not collected per CRF but needs to be composed from the ALSFRS-R based on four key domains (walking/self-care, swallowing, communicating and breathing). Each domain has a threshold score reflecting the loss of function in the specific ALSFRS-R subscores as presented in the table below. Subscores of each item below the threshold are assigned a function score of 1 (meaning functional loss), while subscores above the threshold are assigned a function score of 0. MiToS stages are determined as the sum of those function score values across the four domains and includes 6 stages on functional ability. Where 2 items are used (with OR or AND), scoring is to be based on either one or both item scores as indicated. The sum illustrates how many functional domains are lost. The 6 MiToS stages are defined as: stage 0 presents no loss of function in any domain; stages 1–4 represent the loss of independence of function in 1, 2, 3 or 4 domains, respectively, and stage 5 is death.

Table: Thresholds scores

ALSFR-S domain	Item(s)	Threshold & functional score
Movement	(8) Walking	≥2: functional score=0 <2: functional score=1
	OR (6) Dressing and hygiene	≥2: functional score=0 <2: functional score=1
Swallowing	(3) Swallowing	≥2: functional score=0 <2: functional score=1
Communicating	(1) Speech	≥2: functional score=0 <2: functional score=1
	AND (4) Handwriting	≥2: functional score=0 <2: functional score=1
Breathing	(10) Dyspnea	≥2: functional score=0 <2: functional score=1
	OR (12) Respiratory insufficiency	≥3: functional score=0 <3: functional score=1

SVC

Values are determined for three trials; the highest value of the three trials will be used for the descriptive statistics and statistical analysis.

HDD megascore

Patients' muscle strength is measured bilaterally using HHD for two muscle groups: Elbow Flexion and Hip Flexion. Muscle strength is evaluated three times for each measured body location. For each, the highest value of the two most closely related values will be identified and presented. "Two most closely related" is defined as the two values closed to the mean of the three trials – from these two, the highest value will be selected for further use.

For calculation of individual muscle scores, the selected muscle strength is transformed as a percent change from baseline using the equation: [(post-baseline value – baseline value) / baseline value] x 100. The transformed muscle strength will be set to missing if the baseline value is zero.

The HDD mega-score is a composite score that averages strength across muscle groups. It is calculated as the mean of the non-missing transformed muscle strength scores among the four measured body locations, i.e., from the two muscle groups measured bilaterally. The overall HDD mega-score is calculated as follows. The maximum muscle strength will be standardized using a z-score transformation. For this standardization, data of a healthy population (N=228)[8] will be used. The table below provides the z-score transformations applicable, and those z-scores present the individual HDD mega-score per muscle. The HDD mega-score for each muscle group is determined by averaging the two z-scores within the muscle group. The overall HDD mega-score is the average of the four z-scores determined.

Muscle	Z-score transformation
Left Elbow Flexion	Z=(X-34.79)/11.51
Right Elbow Flexion	Z=(X-34.99)/11.77
Left Hip Flexion	Z=(X-43.88)/15.86
Right Hip Flexion	Z=(X-44.43)/15.61

ALSAQ-40

The ALSAQ-40 consists of 40 items/questions, referring to the patient's condition during the past 2 weeks and the answers are given on a five-point Likert scale (0=never, 1=rarely, 2=some-times, 3=often, 4=always or cannot do at all). These items are combined to provide 5 dimensions/scales - physical mobility (Q1-Q10), activities of daily living and independence (Q11-Q20), eating and drinking (Q21-Q23), communication (Q24-Q30), and emotional reactions (Q31-Q40). For each scale a summary score is calculated, ranging from zero (best health status) to 100 (worst health status) according to the formula[9]:

$$\text{Scale score} = \frac{\text{Total of raw scores of each scale item}}{\text{Maximum possible raw score of all scale items}} \times 100$$

Computations are therefore as follows for each scale for each patient, where a missing score will lead to a missing dimension for that specific patient.

[8] Table e-1 from Jeremy M. Shefner, e.a. *Quantitative strength testing in ALS clinical trials.* Neurology Aug 2016, 87 (6) 617-624.
[9] ALSAQ User Manual, August 2020

Scale	Computation
physical mobility	100 x ($\sum Q_i$ / 40)
activities of daily living and independence	100 x ($\sum Q_i$ / 40)
eating and drinking	100 x ($\sum Q_i$ / 12)
communication	100 x ($\sum Q_i$ / 28)
emotional reactions	100 x ($\sum Q_i$ / 40)

The interpretation of score ranges for the 5 scales are as follows:

Range	Interpretation
0-19	No problems
20-39	Problems rarely
40-59	Problems sometimes
60-79	Problems often
80-100	Problems always/ nearly always or unableto do at all

Although not specified in the scoring manual, a total score for the ALSAQ-40 will be derived as the mean of the 5 scales (yielding a range of possible scores of 0 to 100. The total score will be missing for a patient if one of the scales/dimensions is missing.

EQ-5D-5L

The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems) and is scored as a 1-digit number (ranging 1-5, respectively) expressing the level for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state (e.g. 1-1-3-4-5).

Nerve conduction study (NCS)

Normal ranges for NCS are defined as below. Values below the lower limit are considered LOW, values above the upper limit HIGH, and otherwise (if not missing) values are considered to be NORMAL.

Parameter	Age group	Lower limit	Upper limit
Hand Temperature (ºC)	-	30	37
Foot Temperature (ºC)	-	30	37
Median Nerve – SNAP Amp (µV)	< 60 yrs	11	-
	> 60 yrs	5	-
Median Nerve – SCV (m/s)	-	30	70
Ulnar Nerve – SNAP Amp (µV)	< 40 yrs	11	-
	40 - ≤ 60 yrs	7	-
	> 60 yrs	5	-
Ulnar Nerve – SCV (m/s)	-	30	70
Radial Nerve – SNAP Amp (µV)	< 40 yrs	11	-
	40 - ≤ 60 yrs	7	-
	> 60 yrs	5	-
Radial Nerve – SCV (m/s)	-	30	70
Sural Nerve – SNAP Amp (µV)	< 40 yrs	8	-
	40 - ≤ 60 yrs	5	-
	> 60 yrs	2	-

Sural Nerve – SCV (m/s)	-	30	70
Sural-Radial Amp Ratio (SRAR)	< 40 yrs	0.45	-
	40 - ≤ 60 yrs	0.32	-
	> 60 yrs	0.19	-

Percentage change from baseline will be calculated as (value – baseline)/baseline.

9.2 Coding

Coding of adverse events, concomitant medication and medical history will be performed by the Data Management (DM) provider. Adverse events and medical history are coded with the MedDRA coding system. Concomitant medication is coded according to the WHO drug code and the ATC class code. 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.

9.3 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.

9.4 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 Clinical Study Report (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.

10 TABLES, LISTINGS, GRAPHS

10.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 10.2, 10.3 and 10.4. 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.

10.2 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.

10.3 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. Where the column Topline is marked, the output will be part of the Topline results to be supplied shortly after Database lock and will include the results for the full set (until week 48) as well as the subgroup of 100 patients (until week 72) for the secondary analyses.

Table /graph number	Contents of table/graph	Topline
14.1 Demographic Data Summary figures and tables		
14.1.1	Demographics	X
14.1.2	Baseline characteristics	X
14.1.3	Disposition	X
14.1.4	Medical history	
14.1.5	ALS-specific history	X
14.1.6	Compliance	X
14.2 Efficacy Data Summary Figures and Tables		
14.2.1.1-14.2.1.x	Descriptive statistics for absolute values and change from baseline ALSFRS-R total score and function domains	X
14.2.1.x	Mean (SD) plot ALSFRS-R total score	
14.2.2.1	Statistical analysis results ALSFRS-R total score (including ICE approaches)	X
14.2.3.1-14.2.3.5	Sensitivity analyses for ALSFRS-R total score	
14.2.4	Statistical analysis results ALSFRS-R function domains	
14.2.5	Descriptive statistics for categorized change from baseline ALSFRS-R total score	
14.2.6	Descriptive statistics for slope of decrease of ALSFRS-R total score	
14.2.7	Descriptive statistics for time to change from baseline for ALSFRS-R total score, including HR (95% CI) and log-rank test	
14.2.8.1	Descriptive statistics for CAFS	X

14.2.8.2	Statistical analysis results CAFS	X
14.2.9.1	Survival time: descriptive statistics	X
14.2.9.2	Survival time: Kaplan-Meier curves	X
14.2.9.3	Survival time: statistical analysis results (RMST)	X
14.2.9.4 - 14.2.9.5	Survival time: supportive analyses (Cox and log-rank)	
14.2.10.1	Overall survival: population alive	
14.2.10.2	Overall survival: Kaplan-Meier curves	
14.2.11.1	Progression-free survival: descriptive statistics	
14.2.11.2	Progression-free survival: Kaplan-Meier curves	
14.2.12	Statistical analysis results joint model	
14.2.13.1-14.2.13.3	Descriptive statistics for King's staging system	X
14.2.13.4	Kaplan-Meier curves King's staging system	
14.2.14.1-14.2.14.3	Descriptive statistics for MiToS	X
14.2.14.4	Kaplan-Meier curves MiToS	
14.2.15.1	Descriptive statistics for SVC	
14.2.15.2	Statistical analysis results for SVC	
14.2.16.1	Descriptive statistics for HDD mega score	
14.2.16.2	Statistical analysis results for HDD mega score	
14.2.17.1-14.2.17.6	Descriptive statistics for Quality of Life: ALSAQ-40 (total score and 5 scales)	
14.2.17.7	Statistical analysis results for Quality of Life: ALSAQ-40 total score	
14.2.17.8	Descriptive statistics for Quality of Life: EQ-5D-5L	
14.2.17.9	Descriptive statistics for Quality of Life: VAS	
14.2.17.10	Statistical analysis results for Quality of Life: VAS	
14.2.18.1-14.2.18.x	Descriptive statistics for Cognition (ECAS)	
14.2.19.1-14.2.19.x	Descriptive statistics for Biomarkers	
14.2.19.5	Out of range Biomarkers	

14.2.20.1- 14.2.20.x	Descriptive statistics for Cost-Utility analysis	
14.3 Safety Data Summary figures and tables – 14.3.1 Displays of Adverse Events		
14.3.1.1	Overview adverse events	X
14.3.1.2	Treatment emergent adverse events	X
14.3.1.3- 14.3.1.5	Treatment emergent adverse events by severity	X
14.3.1.6- 14.3.1.7	Treatment emergent adverse events by relationship	X
14.3.1.8	Treatment emergent adverse events leading to premature discontinuation	X
14.3.1.9	AESIs	X
14.3.1.10	SAEs	X
14.3 Safety Data Summary figures and tables – 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events		
14.3.2.1	AESIs	
14.3.2.2	SAEs	
14.3.2.3	Deaths	
14.3 Safety Data Summary figures and tables – 14.3.4 Abnormal Laboratory Value Listing (each patient)		
14.3.4.1	Out of range clinical laboratory	
14.3.4.2- 14.3.4.7	Descriptive statistics Clinical laboratory – haematology, clinical chemistry, urinalysis, serology, vitamin B6	
14.3.4.8.1	Descriptive statistics Vital signs	
14.3.4.8.2	Mean (SD) plot Vital signs	
14.3.4.9.1	Descriptive statistics ECG	
14.3.4.9.2	Mean (SD) plot ECG	
14.3.4.10	Physical Examination	
14.3.4.11.1- 14.3.4.11.x	Nerve Conduction Study	
14.3.4.12- 14.3.4.13	Prior and concomitant medication	

10.4 Listings

Following ICH E3 guidelines, all listings mentioned here will be presented in Section 16.2 of the CSR, and listings will be prepared in the order and with section number as stated.

Individual listings will be prepared of all the data collected in the database, following SDTM data format. No combining of data other than mentioned in this paragraph will be performed. The key variables in the listings (except a few displaying screening data) will be patient number and treatment. If applicable, visit number will be listed additionally. Furthermore, a listing containing study visit dates will be presented.

Listing number	Contents of listing
16.2.1 Discontinued patients	
16.2.1.1	Inclusion/exclusion criteria – description
16.2.1.2	Inclusion/exclusion criteria – deviations
16.2.1.3	Patient disposition
16.2.2 Protocol deviations	
16.2.2	Protocol deviations
16.2.3 Demographic and baseline data	
16.2.3.1	Demographics
16.2.3.2	Randomization
16.2.3.3	Substance use
16.2.3.4	Medical history
16.2.3.5	ALS history
16.2.3.6	Pregnancy test
16.2.4 Compliance and/or treatment data	
16.2.4.1	Treatment exposure
16.2.4.2	Drug accountability and compliance
16.2.4.3	Study visits
16.2.5 Individual efficacy response data	
16.2.5.1	ALSFRS-R
16.2.5.2	CAFS

16.2.5.3	King's staging system
16.2.5.4	MiToS
16.2.5.5	SVC
16.2.5.6	HDD
16.2.5.7	QoL
16.2.5.8	Cognition (ECAS)
16.2.5.9	Biomarkers
16.2.5.10	Cost-utility
16.2.5.11	Survival
16.2.6 Adverse event listings	
16.2.6.1	Adverse events
16.2.6.2	AEs leading to discontinuation from the study
16.2.6.3	Vital signs
16.2.6.4	ECG
16.2.6.5	Physical Examination
16.2.6.6	Neurological examination
16.2.6.7	Nerve conduction study
16.2.6.8	Prior and concomitant medication
16.2.7 Listing of individual laboratory measurements by patient	
16.2.7.1	Laboratory safety data – haematology
16.2.7.2	Laboratory safety data – clinical chemistry
16.2.7.3	Laboratory safety data – urinalysis
16.2.7.4	Laboratory safety data – coagulation
16.2.7.5	Laboratory safety data – serology
16.2.7.6	Laboratory safety data – Vitamin B6
16.2.7.7	General comments