



Statistical Analysis Plan

Open-label Extension part of AP101-02

A Phase 2a, multicenter, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacodynamic markers, and pharmacokinetics of AP-101 in patients with familial amyotrophic lateral sclerosis (fALS) and sporadic amyotrophic lateral sclerosis (sALS)

Addendum 1 draft

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A Phase 2a, multicenter, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacodynamic markers, and pharmacokinetics of AP-101 in patients with familial amyotrophic lateral sclerosis (fALS) and sporadic amyotrophic lateral sclerosis (sALS)

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1. INTRODUCTION AND OBJECTIVES

1.1. Introduction

AP101-02 is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy safety, tolerability, PK, and PD of AP-101 in patients with amyotrophic lateral sclerosis (ALS); specifically for patients with familial ALS (fALS) and sporadic ALS (sALS).

The original statistical analysis plan (SAP) version 1.0 was finalized 11Dec2024. The primary focus of that plan was on the open-label extension (OLE), with limited attention given patient experience during the double-blind period. During the interim analysis of the sALS OLE, decisions were made to focus more on the complete patient experience from the start of the double-blind through the OLE. Therefore, this document has been written to implement the renewed focus, and since it was written after unblinded data analyses were examined, it is considered an addendum to, rather than an updated version of, the SAP.

1.2. Study Objectives and Endpoints – Open-label Extension

Table 1 shows the objectives and endpoints of the open-label extension portion of the study.

Table 1. Objectives and Endpoints – Open-label Extension

Objectives	Endpoints
Primary	
To determine the safety and tolerability of AP-101 after multiple IV doses	- Incidence of AEs and SAEs including immunogenicity - Incidence of abnormalities in vital signs, clinical laboratory assessments, physical and neurological examinations, electrocardiograms and changes in weight
Secondary	
To determine the PK profile of AP-101 after multiple IV dose administrations	The primary PK parameters are AUC, and concentration at end of infusion.
To determine effects of AP-101 on pNfH and NfL levels in CSF and plasma after multiple IV doses of AP-101	Measurement of pNfH and NfL levels in CSF and plasma after multiple IV doses of AP-101
Exploratory	

Objectives	Endpoints
To determine the effect of AP-101 on disease progression after multiple IV doses at the end of the open label period	- Measurement of the clinical effect of AP-101 on the rate of functional decline as measured by the ALSFRS-R, its subdomains, and adjusted ALSFRS-R which removes questions 2, 9-12. - Time to a decline of 6 points in the ALSFRS-R over questions 1 – 9 only - Time to a decline of 9 points in the ALSFRS-R over questions 1 – 9 only
To determine effects on alternate measures of disease progression after multiple IV doses of AP-101	Measurement of the clinical effect of AP-101 on lung function (SVC) and pulse oximetry and disease staging (King's staging tool)
To determine effects on AP-101 on overall patient survival and additional measures of outcome for AP-101 after multiple IV dosing	- Composite time to event measurement comprising time to death or non-invasive ventilation use for 22 to 24 hours per day - Difference in mean rank between treatment arm and control arm in the Combined Assessment of Function and Survival (CAFS), a joint model of survival and ALSFRS-
Effects on quality of life after multiple IV dosing of AP-101 at the end of the open label period	Quality of life by ALSSQOL-SF
Identify non-clinical and exploratory biomarkers of disease activity that change over time	Measurement of other biological markers of disease activity including creatinine and transcriptional markers
To determine CSF penetration of AP-101 after multiple IV dosing	AP-101 levels in the CSF

Abbreviations: AE = adverse event; ALSFRS R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ALSSQOL-SF = Amyotrophic Lateral Sclerosis Specific Quality of Life Instrument-Short Form; AUC = area under the concentration versus time curve; CAFS = combined assessment of function and survival; CSF = cerebrospinal fluid; IV = intravenous; NfL = neurofilament light chain; PK = pharmacokinetic; pNfH = phospho-neurofilament heavy chain; SAE = serious adverse event; SVC = slow vital capacity; $t_{1/2}$ = elimination half-life; TEAE = treatment emergent adverse event.

1.3. Statistical Hypotheses

The OLE portion of the study is open-label with a single arm of 2500 mg AP-101, therefore no formal statistical hypotheses are to be tested using data collected during the OLE. The focus will be on estimation of trends after long-term exposure to AP-101. In some cases, comparisons between participants receiving placebo and participants receiving AP-101 during the double-blind portion will be made, to assess the impact of the length of AP-101 treatment.

Descriptive statistics will be used for statistical evaluation of efficacy, safety, and tolerability, including the use of graphical displays of trends following the first dose of AP-101.

1.4. Sample Size Determination

The double-blind portion of the study was planned to enroll a maximum of 63 participants (21 with fALS and 42 with sALS), randomly assigned in a 2:1 randomization ratio. Not all participants are expected to continue into the OLE, and therefore the sample size available during the OLE is unknown.

2. GENERAL STATISTICAL METHODOLOGY AND CONVENTIONS

2.1. General Considerations

All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

Unless denoted otherwise, data for sALS participants and fALS participants will be analyzed separately.

Data listings will be sorted by treatment received during the double-blind period, investigative site, and patient identification number, and patients will be identified in the listings by the investigator number concatenated with the patient number.

For continuous variables, summary statistics will include number of participants, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of participants, frequency, and percentages.

For endpoints where comparisons between the previous treatments received (during double-blind portion), differences between treatment arms (and their associated confidence interval if applicable) will be calculated as [Placebo – {AP-101}].

The 21-day follow-up visit during the double-blind portion is set to occur 3 weeks after the last dose of study drug (scheduled for the Week 24 visit). For participants joining the OLE, the participant will complete the scheduled 21 day follow up visit of the double-blind phase at Week 3 of the OLE.

2.2. Reporting Conventions

The following conventions will be applied to all data presentations and analyses:

- Continuous variables will generally be summarized by the number of patients, mean, standard deviation, median, minimum, and maximum.
- Categorical variables will be summarized by the number and percentage of patients within each category.
- Confidence intervals will be reported as two sided at the 90% level.
- All mean and median values will be formatted to one more decimal place than the measured value.
- Standard deviation values will be formatted to two more decimal places than the measured value.
- Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percent of responses will be presented in the form XX (XX %), where the percentage is in parentheses. Percentages will be rounded to the nearest percent. In the case of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%).
- Date variables will be formatted as DDMMYYYY for presentation.

2.3. Randomization and Blinding

The OLE portion of the study is open-label. However, to protect the blinding of the double-blind phase, participant's prior treatment information will remain blinded; therefore, after entry into the OLE, all participants who received placebo in the double-blind phase will receive blinded 500 mg of AP-101 on Day 22 and 2500 mg of AP-101 on Day 23. After entry into the OLE, all participants who received active treatment in the double-blind phase of the study will receive placebo (same infusion volume of 500 mg AP-101) on Day 22 and 2500 mg of AP-101 on Day 23. Thereafter, dosing with open-label **AP-101** 2500 mg will take place every 3 weeks for 6 months as specified in the OLE SoA.

2.4. Analysis Populations

The OLE population was the only population defined for the OLE in SAP v1.0. With the renewed focus on the complete patient experience, the Double-blind Intent-to-treat (DB ITT) population has been added:

Population	Description
OLE Population	All participants who complete the double-blind phase of the study and receive at least one dose in the OLE period of the study, which begins at the double-blind period 21-Day follow-up visit as Day 1 of the OLE. For safety analyses, participants will now be analyzed according to the intervention they were assigned to within the double-blind phase, and as a single comprehensive group.
DB ITT Population	All participants who were included in the ITT population for the analyses of the double-blind period data, regardless of participation in the OLE.

The designation “DB ITT and OLE Population” will be used for analyses that include both periods, and all participants during each period, regardless of OLE participation. For analyses that include visits that occurred during the double-blind period, but only include participants who entered the OLE period, the OLE Population will be used.

2.5. Treatment Groups

All participants in the OLE will be in the AP-101 treatment group. The treatment received during the double-blind phase will also be reported in most data summaries.

2.6. Definition of Baseline Assessments

For the double-blind period, the last assessment made before the first dose of study drug was defined as the Baseline assessment. This included all pre-dose assessments made on or before Day 1. For analysis of the OLE period, a second baseline will be defined as the assessments made at Week 24 of the double-blind period. The day of these assessments will also be referred to as Day 1 of the OLE. Analyses of OLE data will primarily utilize the baseline from the double-blind period but may also utilize the OLE baseline for some analyses.

2.7. Definition of Study Visit

Patient data will be analyzed according to the nominal visit collected in the eCRF. Unscheduled visits at which safety data is collected (e.g. labs and ECGs) may result in clinically significant findings or withdrawal, which will be included in adverse event and/or disposition summaries.

2.8. Handling of Dropouts and Missing Data

Both efficacy and non-efficacy summaries and analyses will use observed cases only. No imputation of missing values will be done. The number of missing observations will be reported.

Some patients enrolled before protocol amendment 2 may have a Day 28 follow-up visit rather than a Day 21 follow-up visit. The number of such patients will be reported, and their Day 21 visit results will be imputed using the observed Day 28 visit results (e.g. the Day 28 visit results will be treated as Day 21 visit results).

Any measurements such as labs, SOD1, mSOD1, neurofilaments, etc., which are either above or below the limit of quantification will be imputed using said limit.

2.9. Adjustment for Multiplicity

Since no formal statistical hypothesis testing using OLE data will be conducted, other than for exploratory purposes, no adjustment for multiplicity will be performed.

2.10. Adjustment for Multiple Centers

Differences between study centers will not be incorporated into the statistical analyses for this study. There are no plans to analyze data within centers.

2.11. Subgroup Analyses

Subgroup analyses will be performed for various endpoints, including neurofilaments (NfL and pNfH) and measures of mSOD1 and SOD1.

The following subgroups will be analyzed:

- fALS cohort.
- sALS cohort in participants who exhibit positive (e.g., detectable) mSOD1 (referred to as the mSOD1 cohort)
- fALS and mSOD1 cohort.
- fALS and sALS cohorts.
- sALS cohort.

Beyond the above, subgroup analyses may also include:

- mSOD+ (meaning the group of subjects with detectable levels of mSOD1).
 - Note mSOD+ in the sALS cohort is equivalent to the mSOD1 cohort.
- By mutation (if sufficient available data – specifically dichotomized as “any mutation”, among FUS, C9orf72, SOD1 or TARDBP, vs. “no mutation”).
- Baseline ALSFRS-R score (dichotomized at median: baseline ALSFRS-R < median vs. $\geq$ median.)
- Baseline NfL levels (dichotomized at median: baseline NfL < median vs. $\geq$ median.)

Additionally, any of the above subgroup analyses may be further grouped by baseline total ALSFRS-R score and/or subdomain score.

2.12. Pooled Analyses

Data will be summarized separately for fALS and sALS patients. Once sufficient data is collected, some analyses may include pooling of fALS and sALS data for various endpoints, including neurofilaments (NfL and pNfH) and measures of mSOD1 and SOD1. These analyses, if done, will be considered exploratory and will be similar to the standard analyses.

These pooled analyses may also include subgroups as defined in section “Subgroup Analyses”, including but not limited to mSOD+, mutation status, and baseline ALSFRS-R score.

2.13. Coding of Concomitant Medications and Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). The versions of the dictionaries used for reporting will be provided in the CSR.

3. INTERIM ANALYSES

Safety data will be reviewed on an ongoing basis by the Safety Review Committee (SRC)/TLSR. The SRC will remain blinded throughout the double-blind portion of the study. For the planned interim safety review, SRC may be unblinded to study treatment if deemed necessary. The SRC will be unblinded following the lock and unblinding of the double-blind portion database, and will no longer hold regular meetings but will be available for consultation as needed. The TLSR will continue to meet quarterly during the OLE.

Once all sALS participants have completed the 6- month OLE period, an interim analysis will be performed on sALS participant data, including descriptive statistics and graphical summaries as

appropriate. The fALS participants will continue in the study and an additional database lock and analysis will be performed once all fALS patients complete the 6-month OLE treatment period. This will include any pooling of fALS and sALS data deemed appropriate (see section “2.12 Pooled Analyses”).

3.1. Safety Data Monitoring:

AL-S Pharma has created a Safety Review Committee (SRC) and Trial Level Safety Review plan with independent physician experts in ALS to objectively evaluate and monitor participants during the trial, as described above in Section 3. For additional information on the remit and operations of the SRC, refer to the Safety Review Committee Charter and TLSR plan.

4. STATISTICAL ANALYSES AND REPORTING

4.1. Patient Characteristics

4.1.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study. A summary of disposition will be provided for all patients enrolled in the OLE portion of the study. All patients who discontinued from the OLE portion of the study (or treatment) will be identified, and the extent of their participation in the study will be summarized. If known, a reason for their discontinuation will be provided.

A patient who completes the OLE is defined as completing Week 24 dosing and the 21-day follow-up visit of the OLE portion of the study. When a patient joins the OLE, they will complete the scheduled 21-day follow up visit of the double-blind phase at Week 3 of the OLE. A patient who never discontinues treatment before completing the study is said to have completed the treatment.

Summaries of the disposition of OLE participants will be based on the OLE Population and include a breakdown by randomized double-blind treatment.

4.1.2. Protocol Violations

A list of protocol violations that could potentially impact the analysis of the study will be determined by the study team during the conduct of the study. These violations will be presented in a listing only, which will include violations from the double-blind period and the OLE.

4.1.3. Demographics and Baseline Assessments

Participant demographics (age at start of double-blind period, age group (≤ 55 vs. >55), gender/sex, race, ethnicity, height, weight, and body mass index [BMI]), and baseline ALS measures (type of ALS, months since ALS diagnosis to start of double-blind period, mutation

status/ type, baseline ALSFRS-R total, plasma NfL, and riluzole/edaravone/other relevant drug use) will be summarized by treatment.

4.1.4. ALS and Medical History

Medical history will be collected prior to the double-blind portion of the study and coded according to MedDRA. Patients reporting medical history will be summarized by relatedness to ALS, system organ class (SOC), and Preferred Term (PT) for the OLE Population.

In addition, information on patients' symptom onset was collected and will be summarized separately from other medical history. The summary will include months since symptom onset, the baseline disease progression rate, location of onset (bulbar, thoracic, or spinal), and motor neuron phenotypes.

Disease progression rate is defined as the ALSFRS-R Total Score at baseline of the double-blind period minus 48, the assumed value at symptom onset, divided by months since symptom onset (negative values indicate a decline). The rate will be categorized into the following three categories:

1. Slow progressors: A rate greater than or equal to -0.3 (i.e. a decline of no more than 0.3 per month),
2. Normal progressors: A rate less than -0.3 and greater than or equal to -1.03,
3. Fast progressors: A rate of less than -1.03.

4.1.5. Prior and Concomitant Medications

Concomitant medications will be defined as medications taken on or after the date of the first dose of study treatment in the OLE period. This includes all medications initially taken prior to the date of first dose of study treatment but with a stop date that is either missing or after the date of first dose of study treatment. At the start of the OLE period, patients were allowed to add standard of care medications, other than tofersen.

Those medications where the stop date is documented as prior to the date of first dose of study treatment in the double-blind period will be classified as prior medications. The prior medications will not be included in any summary reports or listings for the OLE study, to avoid redundancy with the double-blind study report.

The percent of patients who receive each concomitant medication, based on the WHODD preferred drug name, will be tabulated. ALS standard of care medications added during the OLE will be designated in tabulations. By-patient listings of all concomitant medications that includes WHODD preferred drug names will be prepared.

4.2. Efficacy Endpoints

Unless otherwise specified, efficacy endpoints will include the value at each visit as well as the change from baseline. The analysis population for efficacy endpoints will be the DB ITT Population, unless otherwise indicated.

4.2.1. Time to Death or Permanent Ventilator

Survival data may be confounded by the use of ventilation strategies. Therefore, a composite measurement of time to death or permanent ventilator use will be used. Patients who neither die nor are put on permanent ventilation will be censored at the last visit that has confirmed them as being alive and not on permanent ventilation. Permanent ventilation is defined as non-invasive ventilation that is used for at least 22 hours per day. From here forward this will be referred to simply as “non-invasive ventilation.” since the data collection tools were designed so that patients were only flagged as receiving non-invasive ventilation if it was for at least 22 hours per day. Therefore, in this study, the terms permanent and non-invasive are synonymous.

The analysis of survival data during the OLE phase is complicated by the fact that the time since the start of active AP-101 will be quite different for patients randomized to placebo during the double-blind phase compared to those randomized to active AP-101. In the original SAP v1.0, the analysis of time to death or permanent ventilator use was to be performed in three distinct ways. During the sALS OLE interim analysis, the decision was made to focus only on the 3rd approach. All three approaches are included here for completeness, but the first two will no longer be performed.

1. As the time from the start of treatment in the OLE period to the event. Only patients enrolled in the OLE will be included.
2. As the time from the start of active AP-101 treatment to the event. For patients in the AP-101 group during the double-blind period, the time will start at the beginning of that period. For patients who were in the placebo group during the double-blind period, the time will start at the beginning of active treatment in the OLE period. This analysis will include all double-blind AP-101 patients, but only include the placebo patients that subsequently entered the OLE.
3. Finally, the third approach will compare the two treatment groups from the double-blind period, with the time starting at the beginning of the double-blind period. The analysis will include all patients, regardless of whether they enrolled in the OLE period. Patients in the AP-101 group during the double-blind period will be designated as “AP-101 – AP-101.” Placebo patients that subsequently entered the OLE period will have crossed over to active treatment, and this group will be designated as “Placebo – AP-101.” As such, this is a comparison between patients who receive AP-101 on day 1, versus those that

wait 6 months before receiving AP-101. No conclusions can be drawn from this analysis regarding AP-101 versus Placebo.

A summary of the number of events, number of censored patients, and time-to-event will be provided for the composite endpoint as well as time to death (ignoring non-invasive ventilation), time to non-invasive ventilation (where death events are censored), and time to tracheostomy (where death events are censored). These summaries will be provided by treatment received in the double-blind period and for all treated patients overall.

Censoring rules for the individual component of time to death are as follows: For patients who do not die, censor at last visit confirmed as alive, regardless of ventilation status.

Time-to-event summaries will be performed via a Kaplan-Meier analysis. The 25th, 50th (median), and 75th quartiles will be presented along with their 90% confidence intervals, as well as a plot of survival curves. For the third (and now only) approach, comparing “AP-101 – AP-101” versus “Placebo – AP-101,” these estimates and plots will be provided for each group.

4.2.2. ALS Functional Rating Scale – Revised (ALSFRS-R)

The ALSFRS-R will be assessed at the visits and times specified in the SoA.

The ALSFRS-R measures 4 functional domains, including respiratory, bulbar function, gross motor skills, and fine motor skills. There are 12 questions, each scored 0 to 4 for a possible total score of 48 with higher score denoting better function (Cedarbaum et al. 1999).

ALSFRS-R scores will be provided as listings, and total ALSFRS-R scores will be summarized at each visit in the double-blind and OLE periods, by treatment received in the double-blind period and overall for all treated patients. The summary of total ALSFRS-R scores will include change from double-blind baseline, as well as change from OLE baseline for OLE visits. For the 21-day follow up visit for both the double-blind and OLE periods, the change from baseline for each treatment group, as well as the difference between groups, will be estimated with 90% confidence intervals.

4.2.2.1. Additional ALSFRS-R Endpoints

Similar analysis as described for the ALSFRS-R above (e.g. summaries at each visit and change from baseline) will be performed for the following:

- ALSFRS-R Subdomains and Sub-scores
 - Bulbar: questions 1-3
 - Fine motor: questions 4-6

- Gross motor: questions 7-9
- Overall motor: questions 4-9
- Non-Respiratory: questions 1-9
- Non-Respiratory non-drooling: questions 1, 3-9
- Respiratory: questions 10-12

Additionally, two time-to-event endpoints will be constructed via the ALSFRS-R using the “Non-Respiratory” sub-score (e.g. the sum of questions 1-9):

- The time to decline of 6 points on non-respiratory items
- The time to decline of 9 points on non-respiratory items

Time-to-event summaries will be performed via a Kaplan-Meier analysis. The 25th, 50th (median), and 75th quartiles will be presented along with their 90% confidence intervals, as well as a plot of survival curves. Subjects who die before declining enough to reach this endpoint will be considered to have reached the endpoint at the time of death. Subjects who do not decline sufficiently to reach the endpoint, or whose decline cannot be determined (e.g. due to withdrawal), will be censored at the last available ALSFRS-R score.

Following the approach used for survival endpoints, these analyses will begin the time at the start of the double-blind period and include a comparison of the treatment groups in the analysis (two treatment arms). This analysis will ignore the cross-over of treatment in the placebo group and utilize time in the OLE period as necessary to reach the specified decline. All DB ITT patients will be used, regardless of enrollment in the OLE.

4.2.3. Slow Vital Capacity (SVC)

Upright SVC will be determined by performing 3-5 measures at the visits and times specified in the SoA, in accordance with criteria established by the American Thoracic Society and the European Respiratory Society (Goncalves de Barros et al. 2013).

SVC will be provided as listings and summarized at each visit in the double-blind and OLE periods, including the change from double-blind baseline, as well as change from OLE baseline for OLE visits. For the 21-day follow up visit for both the double-blind and OLE periods, the change from baseline for each treatment group, as well as the difference between groups, will be estimated with 90% confidence intervals.

4.2.4. Pulse Oximetry

SpO₂ stands for peripheral capillary oxygen saturation, an estimate of the amount of oxygen in the blood. Low SPO₂ is associated with worsening respiratory function. SpO₂ measurements will be performed as according to the SoA.

SpO₂ measurements will be provided as listings, and summarized in the same way as planned for slow vital capacity.

4.2.5. Hand-Held Dynamometry

Muscle strength will be assessed through the use of HHD instruments during the OLE period only through the Week 3 visit. This is the 21-day follow-up visit for the double-blind period and will be included in the double-blind analyses. Since no new data will be collected, HHD will not be summarized for the OLE period.

4.2.6. King's Staging Tool

Participants' ALS will be staged according to the King's staging tool, measured at the visits and times specified in the SoA (Roche et al. 2012). This tool uses the following classifications of ALS development:

- Stage 1: symptom onset (involvement of first region)
- Stage 2A: diagnosis
- Stage 2B: involvement of second region
- Stage 3: involvement of third region
- Stage 4A: need for gastrostomy
- Stage 4B: need for non-invasive ventilation

This functional staging system ranks patients based upon their level of independence (Stages 1 and 2) and the need for significant interventions (feeding tube, respiratory support).

The stage of each patient as per the King's staging tool will be provided as listings and summarized by double-blind treatment arm and overall, for all treated patients. The summary will include the number of stages changed from double-blind baseline at each visit, and change from the OLE baseline for OLE visits. After the finalization of the double-blind SAP, a change was made to the way the number of stages changed would be computed. For purposes of calculating the number of stages changed, the A and B designations accompanying stages 2 and 4 will be considered as supplemental information, rather than additional stages. Therefore, only the number will be used when determining the number of stages changed. For example, a

change from Stage 2A to Stage 4B would be a change of 2 stages (2 to 4), rather than 4 stages as originally planned.

For the 21-day follow up visit, the number of stages changed from baseline of the double-blind period and from baseline of the OLE will be summarized by double-blind treatment, and will include the median and a 90% confidence interval for the median.

In addition, a Kaplan-Meier analysis of the time to progression of one King's stage, subgrouped by starting stage (1 – 4), will be presented. The 25th, 50th (median), and 75th quartiles will be presented by double-blind treatment, along with their 90% confidence intervals, as well a plot of the Kaplan-Meier curves. As described in Section 4.2.1, the groups being compared are “AP-101 – AP-101” versus “Placebo – AP-101.”

4.2.7. The Combined Assessment of Function and Survival (CAFS)

The CAFS ranks participants' clinical outcomes based on survival time and change in the ALSFRS-R score. Each participant's survival and ALSFRS-R outcomes are compared to every other participant's outcomes, assigned a CAFS score, and then the summed scores are ranked. Ranks and scores will be computed using only the subjects in the cohort being analyzed. For example, the analysis of sALS will include only those subjects, while the analysis of pooled sALS and fALS subjects will include both types, when assigning ranks and scores.

Summary statistics for rank scores are not meaningful for a single treatment group, since the results (such as the mean) are predetermined from the sample size. Therefore, this endpoint will be computed for the purpose of comparing the treatment groups as assigned during the double-blind phase. This analysis will utilize the survival time and ALSFRS-R outcomes from the start of the double-blind period through the OLE period if available, and include all subjects in the DB ITT population.

The algorithm for generating CAFS scores is as follows [*Berry et al.*]:

1. Initially, all subjects start with a score of 0
2. Then for each subject i , compare that subject i individually to all *other* subjects in the trial exactly once.
3. When comparing subject i to some other subject j , the subject who performs better (see below) gains a point and the subject who performs worse loses a point. In the case of a tie, where neither subject outperformed the other, no points are added or subtracted.

For example, if subject i outperforms subject j , the CAFS for subject i increases by 1 and the CAFS for subject j decreases by 1. Note that a trial with N subjects will have $N-1$ comparisons per subject, and so the best and worst scores possible are $N-1$ and $-(N-1)$,

respectively (although these may be smaller in the case of ties).

To determine which subject fares better for each pairwise comparison:

- a. If both subjects die, the one with longer survival fared better
- b. If one subject dies, the one who survived fared better
- c. If both subjects survive, the subject with smaller decline in ALSFRS-R from baseline to the 21-day follow up visit (of the OLE period if available, of the double-blind period if not) fared better.

The mean rank score for each treatment group can then be calculated. A higher mean CAFS score indicates a better group outcome. These scores are then sorted and each subject is assigned a CAFS rank (not equal to their CAFS score), where a higher rank is given to subjects with higher CAFS scores (e.g. subjects with better performance are assigned a higher rank). The ranks for each treatment group will then be summarized descriptively. The difference between treatment groups will be estimated with 90% confidence intervals. Subjects whose survival status cannot be determined (e.g. due to withdrawal of informed consent) will be assumed as surviving only up until their last confirmed survival time for this analysis.

4.3. Pharmacokinetic and Pharmacodynamic Endpoints

4.3.1. PK Profile

At the visits and times specified in the SoA for the OLE period, venous samples will be collected to determine the serum concentrations of AP-101. The sampling times may be modified at the discretion of the sponsor, based on review of interim PK data as they become available. Actual PK sample collection dates and times will be recorded.

PK parameters for the Safety Population will be analyzed by an external vendor who will provide data summaries to EMB. The PK analyses will only be performed for participants who received at least 1 full dose of study treatment during the OLE and have baseline PK samples and at least 3 postbaseline evaluable PK samples. All serum PK samples will be utilized in a compartmental model to describe the PK parameters for these patients.

PK parameters will be reported with descriptive statistics which include: arithmetic mean, geometric mean, standard deviation, coefficient of variation (CV)%, geometric CV%, median, minimum, and maximum:

Multiple-dose PK parameters	Definition
$C_{\max}$	maximum drug concentration
$T_{\max}$	time to maximum observed drug concentration, or first maximum observed drug concentration if this occurs at more than 1 time point
$AUC_{0-t_{\text{last}}}$	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
$AUC_{0-\tau}$	area under the plasma concentration-time curve from time 0 to time tau (dosing interval)
V	apparent central volume of distribution
CL	total body clearance
Q	intercompartmental clearance
V_2	peripheral compartment volume
$t_{1/2}$	elimination half-life

4.3.2. CSF Penetration of AP-101 (PK in CSF)

CSF sampling will be collected at baseline, Week 12, and Week 24 of the double-blind period, and at the Week 24 visit of the OLE study, according to the SoA. The level of AP-101 in the CSF will be summarized at each available treatment visit as well as the change from DB baseline and change from OLE baseline, using the DB ITT Population.

4.3.3. Neurofilament Levels

Assuming an available assay, levels of pNfH and NfL will be measured from both CSF and plasma (e.g. serum) at various timepoints during the 6-month OLE study. These endpoints will be used to determine the effects of AP-101 on pNfH and NfL levels (in CSF or plasma): pNfH and NfL (CSF or plasma) may also be examined for correlations with other exploratory biomarkers and endpoints.

Neurofilament levels will be provided as listings. A summary table of serum NfL and of CSF pNfH levels will be provided which will include (for each visit) the neurofilament value and the change from DB baseline as well as change from OLE baseline. While serum pNfH and CSF NfL will be collected, summary tables of these will not be produced.

For the 21-day follow up visit (or Week 24 for CSF measures), the change from baseline will be estimated along with 90% confidence intervals. These summaries will be generated for relevant subgroups and/or pooling of data for serum NfL only.

Figures depicting the mean CSF pNfH and Serum NfL values over time from the start of the double-blind period through the OLE, will be provided, by randomized treatment during the double-blind period.

An additional supplementary analysis (using observed cases only) of the geometric mean ratio (GMR) of log-scale CSF pNfH and Serum NfL comparing the double-blind baseline value to the 21-day follow up visit, will be performed, using an ANOVA model comparing the treatment group to the placebo group which adjusts for the following:

- Baseline natural log of the neurofilament value
- Edaravone use at any time during or before the trial (yes/no)

This additional supplementary analysis of GMR will report the estimated GMR (and associated 90% confidence interval) of the treatment group and the placebo group. Figures depicting GMR across visits will also be produced.

Subgroup Analyses

A similar summary will be performed as above using the following subgroups:

- By baseline mSOD1+ (mSOD1 above vs. below lower limit of detection)
- By mutation status (any mutation vs. no mutation).
- By baseline ALSFRS-R total (dichotomized at median baseline value in PP population).

These will also be repeated using the pooled fALS and sALS data.

4.3.4. Total SOD1 and Misfolded SOD1

Levels of total SOD1 and misfolded SOD1 will be measured retrospectively from the CSF of participants at baseline and after at least 1 timepoint after treatment with AP-101. The amount of total and misfolded SOD1 will be provided as listings and summarized by double-blind treatment arm and overall for all treated patients. The summary will be similar to the neurofilament summary, and will be based on the DB ITT population.

Subgroup Analyses

An additional summary of (m)SOD1 by visit and change from baseline will be provided. This summary will be similar to the neurofilament summary.

A similar summary will be performed as above using the following subgroups:

- By baseline mSOD1+ (mSOD1 above vs. below lower limit of detection).
- By mutation status (any mutation vs. no mutation).
- By baseline ALSFRS-R total (dichotomized at median baseline value).

These will also be repeated using the pooled fALS and sALS data.

4.4. Biomarkers

Additional biomarkers may include transcriptional and microRNA profiles from biological fluids, CSF, and serum. These are exploratory biological markers of disease activity and will be examined at various timepoints during the study as displayed in the SoA.

- This study will analyze biomarkers relevant to the mechanism of action for AP-101. Samples collected for these analyses may also be used to develop related research methods or to validate diagnostic tools or assays.
- Additional samples may be collected during the study if warranted and agreed upon by the investigator and sponsor.

Additional biomarker results will be provided as listings and summarized for the DB ITT Population. The summary will include change from baseline (both DB and OLE) at each visit.

4.5. Safety Endpoints

Unless stated otherwise, safety endpoints will be summarized and/or listed for visits in the DB and OLE periods using the DB ITT and OLE Population.

4.5.1. Study Medication Exposure

Extent of exposure, including the total dose administered, the total duration of infusions, and the number of infusions started, completed, interrupted, and not completed, will be summarized and included in listings. The days on treatment (calculated as date of last dose – date of first dose + 1) will be included in the summary. Summaries will include double-blind + OLE period exposure. Subjects randomized to Placebo during the double-blind period will only contribute exposure during the OLE period.

If warranted, study medication exposure may also be examined for correlations with other exploratory biomarkers and clinical endpoints.

4.5.2. Adverse Events

The incidence of adverse events and serious adverse events, the study's primary endpoint, will be reported using descriptive statistics only. Summary tables will include columns for the DB treatment period by treatment group, the OLE period by DB treatment group as well as for all treated OLE patients, and overall for all patients treated with AP-101 in either the DB or OLE periods. The definitions of the following events can be found in Appendix 5 of the protocol:

- AEs

- SAEs
- Investigational Product complaints (IPCs)

No statistical testing will be performed for comparisons of AEs.

Summaries of AEs will include the number of patients with at least one AE. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC, and the PTs within the SOC, in decreasing frequency in the Overall AP-101 treated column. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

Intensity of AEs will be graded using a 3-grade scale outlined below as suggested in ICH E3:

- Mild
- Moderate
- Severe

An overall summary of AEs will be provided that provides the incidence (number of events and patients) of the following:

- Any AE
- Any treatment-emergent AE (TEAE)
- Any treatment-related TEAE
- Any treatment-related Severe TEAE
- Any serious AE (SAE)
- Any AE resulting in infusion interruption
- Any TEAE resulting in treatment discontinuation
- Any SAE resulting in treatment discontinuation
- Any TESAE
- Any treatment-related TESAE
- Any AE of special interest (AESI)
- Any non-serious TEAE
- Any AE resulting in death (only if deaths occur in the study)

Additionally, summaries will be provided for the following by SOC and PT:

Treatment-Emergent Adverse Events

TEAEs will be summarized by SOC and PT, and by PT in order of decreasing frequency of preferred term. TEAEs are AEs that emerge or worsen after first dose in each period. The Double-blind Treatment Period includes AEs that occur prior to first dose in OLE, if applicable. The OLE Period includes AEs reported after informed consent for OLE. All AEs in the study that occurred during AP-101 treatment will be included in the Overall column. AEs with missing time that are recorded on the day of first dose in OLE are counted as both TEAE for Double-blind treatment period and TEAE in the OLE period.

Treatment-Related Treatment-Emergent Adverse Events

Every AE will be assessed by the investigator for its relationship to the assigned study medication. The subset of TEAEs considered by the investigator as either possibly, probably, or definitely related to study treatment will be summarized as drug-related TEAEs by SOC and PT.

Treatment-Related Treatment-Emergent Adverse Events by Maximum Severity Grade

Related TEAEs will also be summarized by maximum severity as graded by the NCI-CTCAE Version 5.0.

Serious Adverse Events

Treatment-Emergent SAEs will be summarized by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.

Treatment-Related Serious Adverse Events

Treatment-Related SAEs will be summarized by SOC and PT.

Serious Adverse Events Resulting in Treatment Discontinuation

If sufficient SAEs that result in Treatment discontinuation occur, these will be summarized by SOC and PT.

Treatment-Emergent (Not Including Serious) Adverse Events

The most common non-serious TEAEs will be summarized by SOC and PT. These reports will also present the total number of TEAEs for each SOC and PT.

Adverse Events Resulting in Death

If sufficient AEs that result in death occur, these will be summarized by SOC and PT.

4.5.3. Adverse Events of Special Interest

AESIs, including hypersensitivity reactions, will be provided as listings.

4.5.4. Adverse Events Related to Lumbar Puncture

Lumbar puncture (LP) to obtain CSF will be performed at several timepoints during this study. AEs related to lumbar puncture will be provided as a listing.

4.5.5. Clinical Laboratory Analyses

For each patient, laboratory tests detailed in Protocol Appendix 2 should be conducted according to the SoA (See Protocol). Laboratory test results for this OLE analysis will not present visits from the DB period, other than DB baseline, which are reported in the DB analysis summaries.

Laboratory tests include hematology, clinical chemistry, urinalysis, coagulation, and pregnancy tests (urine and serum).

Sponsor or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor if a central vendor is used for the study.

Laboratory test results other than the pregnancy tests and urine drug screening will be provided as listings and summarized. The summaries will include the test result value at DB baseline, and each OLE visit as well as the change from DB baseline and change from OLE baseline.

Pregnancy test and urine drug screening results will be provided as listings.

4.5.6. Vital Signs

For each participant, vital signs, including blood pressure, pulse rate, and body temperature, measurements will be recorded. Vital sign results for this OLE analysis will not present visits from the DB period, other than DB baseline, which are reported in the DB analysis summaries.

Single measurements will be taken at screening and the baseline visit. Supine triplicate blood pressure and pulse rate will be collected at all other time points. Body temperature to be obtained as single measurement. Pre-dose vital signs should be taken approximately 1 hour prior to the scheduled dosing.

At time points when orthostatic measurements are obtained, participants should be supine for at least 5 minutes and stand for approximately 2 minutes. When triplicate blood pressure or pulse rate measurements precede the orthostatic measurement, the last supine blood pressure or pulse rate measurement will be used for orthostatic calculations. If the participant feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Vital signs will be provided as listings and summarized. The summaries will include each vital sign's average value at each visit as well as the change from DB baseline and change from OLE baseline, using the average of any triplicate values for that visit (for blood pressure, only supine values will be used to determine the average). A separate listing and summary will be provided for orthostatic blood pressure which includes measures of blood pressure and pulse at each position (laying down 5 minutes, standing 1 minute, standing 3 minutes) as well as change from laying down to standing.

4.5.7. Electrocardiograms

For each participant, a 12-lead digital ECG will be collected. Sites are recommended to conduct ECGs prior to any blood sample collection. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrolment, the investigator will assess the participant for symptoms (for example, palpitations, near syncope, syncope) to determine whether the participant can continue the study. The investigator or qualified designee is responsible for determining if any changes in participant management is needed and must document his/her review of the ECG printed at the time of evaluation form at least 1 of the replicate ECGs from each point.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

Electrocardiogram results will be provided as listings and summarized. ECG results for this OLE analysis will not present visits from the DB period, other than DB baseline, which are reported in the DB analysis summaries. The summary will include change from DB baseline and OLE baseline, at each OLE visit.

4.5.8. Immunogenicity Assessments

Antibodies to AP-101 will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to AP-101 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to AP-101 and/or further characterize the immunogenicity of AP-101.

The detection and characterization of antibodies to AP-101 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for AP-101 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 2 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to AP-101.

A summary of anti-drug antibodies (ADA) will be provided that will include the number of subjects evaluable for TE ADA (subjects with at least one non-missing test result for ADA at both (1) baseline of OLE and (2) post-baseline), number of subjects with ADA present at baseline of the OLE, subjects with postbaseline TE ADA+, and subjects with postbaseline TE ADA-. A subject is postbaseline TE ADA+ if they have a baseline of ADA not-present and at least one post-baseline result of ADA present with titer $\geq 2 \times \text{MRD}$, or has a baseline result of ADA present and postbaseline result of ADA present with a ≥ 4 -fold increase in titer over baseline. A subject is postbaseline TE ADA- if they have a baseline result of ADA present and postbaseline result of ADA not-present or postbaseline result of ADA present with a < 2 -fold increase in titer over baseline.

4.5.9. Other Safety Endpoints

A directed neurological examination will be performed by the investigator or designee. If abnormalities are noted at these time points, additional examinations should be performed until the participant has returned to baseline. The examiner should be familiar with the participant's baseline examination. Mandated elements of the examination include inspection for cranial nerves, tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign. Neurological exam results will be provided as listings only.

Physical examinations will be performed as per the SoA. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and

neurological systems. Height (screening only) and weight will also be measured and recorded. A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Physical exam results will be provided as listings only.

Suicidal ideation and behavior risk monitoring will be assessed using the C-SSRS, which is a semi-structured clinical interview that assess suicidal ideation severity, suicidal ideation intensity, and suicidal behavior. C-SSRS results will be provided as listings.

A summary of incidence of patients with any abnormalities during the OLE period in vital signs, clinical laboratory assessments, physical exams, neurological exams, and ECGs will be provided. The summary will include the incidence of abnormalities.

Quality of Life

Measurement of Health-Related Quality of Life is a valuable measure of therapeutic efficacy and will utilize the ALSSQOL-SF questionnaire. This assessment will be administered at timepoints displayed in the SoA. The ALSSQOL-SF is a 20-item instrument that measures overall quality of life (QOL) and 6 specific domains for individuals with ALS (Felgoise et al. 2011).

The ALSSQOL-SF will be provided as listings and summarized. The summary will include change from DB baseline and OLE baseline, at each OLE visit.

5. REFERENCES

James D. Berry, Robert Miller, Dan H. Moore, Merit E. Cudkowicz, Leonard H. Van Den Berg, Douglas A. Kerr, Yingwen Dong, Evan W. Ingersoll & Donald Archibald (2013) The Combined Assessment of Function and Survival (CAFS): A new endpoint for ALS clinical trials, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 14:3, 162-168, DOI:10.3109/21678421.2012.762930

No other additional references outside of those in the protocol.

AP-101-02 OLE Statistical Analysis Plan - Addendum 1 - 28Apr2025

Interim Agreement Report

2025-05-28

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Agreement History

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