Official title: Multi-center, randomized, double-blinded assessment of Tecfidera® in extending the time to a first attack in radiologically isolated syndrome (RIS) (ARISE)

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Title of the study: Multi-center, randomized, double-blinded assessment of Tecfidera® in extending the time to a first attack in radiologically isolated syndrome (RIS)

Protocol Code: ARISE

STATISTICAL ANALYSIS PLAN (SAP)

Authors

Version and date Version 01 – 09 July 2021

SUMMARY

LIST OF ABBREVIATIONS

9-HPT	9-Hole Peg Test
CNS	Central Nervous System
EDC	Electronic Data Capture
EOS	End of Study
EDSS	Expanded Disability Status Score
ITT	Intent-To-Treat
ICH	International Council for Harmonisation
MS	Multiple Sclerosis
Neuro-QOL	Neuro Quality of Life Questionnaire
OCT	Ocular Coherence Tomography
PASAT	Paced Auditory Serial Addition Test
PRO	Patient Reported Outcome
PPS	Per Protocol Set
RIS	Radiologically Isolated Syndrome
RS	Randomized Set
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
T25-FW	Timed 25-FT Walk

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the relevant sections of the study protocol ARISE, Version 8 - November 5, 2018.

Following International Council for Harmonisation (ICH) Guidelines E3 and E9, its purpose is to describe in more detail how the analyses will be performed and presented. All definitions, derivation rules and handling of missing data procedure are reported.

Some relevant statements are directly quoted from the protocol, without however a full description of study design.

This document is finalized before the data is unblinded.

2. STUDY DOCUMENTS, DATA SOURCE AND SOFTWARE

2.1. Study documents

The following study documents are referred for the preparation of this SAP:

- Study protocol - Multi-center, randomized, double-blinded assessment of Tecfidera® in extending the time to a first attack in radiologically isolated syndrome (RIS) (ARISE) (Version 8 - November 5, 2018)
- SAS Listing Specifications for UT Southwestern - ARISE_109MS001 (Version: Final V4.0 - Version Date: 11Apr2019)
- CRF (Version e date).
- Sample size calculation document (Version Final, V1.1, Date 06Aug2018)

2.2. Data source

The following study databases are used in the study:

- SAS database
- MRI database
- Randomization list (PDF file)

Data will be captured via electronic data capture (EDC).

- Demographic and clinical Data: Comprehensive demographic data (i.e. date of birth, sex, race and ethnicity, etc.) and clinical data (i.e. date of first clinical visit, reason for the initial MRI scan, findings from the patient's clinical examination (to include vital signs), Visual Systems Tests (low vision contrast charts, ocular coherence tomography (OCT)) CMP and CBC results, cerebrospinal fluid test results, new onset clinical attacks, extent of recovery, etc. will be obtained from face-to-face clinical visits and existing medical records.
- Cognitive/Functional assessments (EDSS, expanded MSFC) Timed 25-FT Walk (T25-FW), 9-Hole Peg Test (9-HPT), Paced Auditory Serial Addition Test (PASAT-3 (3-second interval pause)), Symbol Digit Modalities Test (SDMT), will also be performed.
- Patient Reported Surveys: Surveys containing questions related to demographics, family history, lifestyle, environment and environmental exposure, and the Neuro Quality of Life Questionnaire (Neuro-QOL data), will be completed by each study participant.

- Adverse events, as well as concomitant medications, will be collected and reported. At the time of any patient withdrawing from the trial, an attempt will be made to determine the reason for discontinuation.
- Radiological Data: Comprehensive radiological data will be collected from RIS subjects. Data to be incorporated into the study database include the date of the first MRI scan demonstrating anomalies within the brain that are suggestive of MS, number of lesions, lesion location, the presence of contrast enhancing lesions, the number of contrast enhancing lesions, changes observed between MRI studies, etc.
  In addition, data from the clinical MRI study of the cervical spine obtained at screening or Month 0 and at EOS will be incorporated if completed.

2.3. Software for statistical analysis

All statistical analyses will be performed with the use of SAS software, version 9.4 (SAS Institute), or R, version 3.5.1 and SPSS (IBM) version 24.0.

3. STUDY DESIGN AND FLOW

3.1. Study design

This is a multi-center, randomized, double-blinded study in which subjects will be treated with either Tecfidera or placebo (1:1 randomization) for 3 years or until End of Study (EOS) date.

Central Clinical and Imaging Units will screen all potential study subjects for inclusion/exclusion criteria.

Study participants, along with the treating and examining physicians, will be blinded to treatment assignment. Following informed consent and verification of entry criteria, study participants will be randomized 1:1 to either Tecfidera (120mg by mouth twice daily for 7 days with dose escalation to 240mg by mouth twice daily) or placebo.

Clinical follow-up will occur at weeks 0, 48, 96, 144 and/or EOS and during or immediately following clinical exacerbations.

During clinical visits comprehensive medical history data, safety labs, and optional biological samples will be obtained by the treating physician.

Patients will be scheduled for safety screenings at weeks 12, 24, 72, 120.

In addition, to the face-to-face visits, study participants will be contacted over the telephone at weeks 4, 8, 36, 60, 84, 108, and 132 to assess for medical or treatment difficulties in addition to study medication compliance.

Standardized MRI studies of the brain will be performed at weeks 0, 96, 144 or EOS; an additional MRI will be obtained at week 46 for those patients enrolled at the UTSW site only.

Clinical imaging studies of the brain and/or spinal cord performed during or immediately following the onset of a clinical exacerbation will be performed at the discretion of the Site.

A clinical MRI of the cervical spinal cord with and without contrast will be recommended to study participants at week 0 and week 144 as medical standard of care.

All reported acute or progressive clinical events will be adjudicated by the Central Clinical Unit. A recommendation to re-evaluate the patient within 3 months following the clinical event to assess for extent of recovery will be made.

3.2. Study flow

SCHEDULE OF ASSESSMENT

	Screen	W0	W4	W8	W12	W24	W36	W48	W60	W72	W84	W96
INFORMED CONSENT	X											
REVIEW OF ELIGIBILITY	X											
EVALUATION BY CLINICAL CORE AND CENTRAL IMAGING	X											
RANDOMIZATION		X										
RECORD HISTORY AND DEMOGRAPHICS		X						X				X
VISUAL SYSTEMS TESTS		UTSW						UTSW				UTSW
PATIENT REPORTED SURVEYS		X						X				X
PHYSICAL EXAM (INCLUDING VITAL SIGNS)		X						X				X
COGNITIVE/FUNCTIONAL ASSESSMENTS		X						X				X
PREGNANCY TEST (URINE)		X										
BLOOD DRAW : CBC/CMP FOR SAFETY SCREENING (LOCAL LAB FOR PI REVIEW)		X			X	X		X		X		X
BIOLOGICAL SAMPLE FOR DNA/RNA: SERUM		X						X				X
CSF SAMPLES (OPTIONAL)		X						X				X
MEDICATION ASSESSMENT & DISPENSE RX VIA PT PICK UP OR MAIL		X			X	X	X	X	X	X	X	X
BRAIN MRI		X						UTSW				X
CERVICAL SPINE MRI (OPTIONAL – STANDARD OF CARE)		X										X
TELEPHONE CONVERSATION			X	X			X		X		X	
PATIENT COMPENSATION		X						X				X
REVIEW ADVERSE EVENTS & CHANGES IN MEDICATION		X	X	X	X	X	X	X	X	X	X	X
COLLECT REMAINING STUDY MEDICATION												

- Medication assessment & administration includes completion of 'drug accountability record'.

- For subjects consented for 96 weeks which choose not to extend their participation through week 114/or EOS, week 96 should be recorded as 'early withdrawal' visit.

ASSESSMENT	WEEK 108	WEEK 120	WEEK 132	WEEK 144	RELAPSE	EARLY WITHDRAWAL	UNSCHEDULED
INFORMED CONSENT							
REVIEW OF ELIGIBILITY							
EVALUATION BY CLINICAL CORE AND CENTRAL IMAGING							
RANDOMIZATION							
RECORD HISTORY AND DEMOGRAPHICS				X	X	X	X
VISUAL SYSTEMS TESTS				UTSW only		UTSW only	
PATIENT REPORTED SURVEYS				X	X	X	X
PHYSICAL EXAM (INCLUDING VITAL SIGNS)				X	X	X	X
COGNITIVE/FUNCTIONAL ASSESSMENTS				X	X	X	X
PREGNANCY TEST (URINE)							
BLOOD DRAW : CBC/CMP FOR SAFETY SCREENING (LOCAL LAB FOR PI REVIEW)		X		X	X	X	SOC
BIOLOGICAL SAMPLE FOR DNA/RNA: SERUM				X	X	X	
CSF SAMPLES (OPTIONAL)				X		X	
MEDICATION ASSESSMENT & DISPENSE RX VIA PT PICK UP OR MAIL	X	X	X	X			
BRAIN MRI				X	SOC	X	SOC
CERVICAL SPINE MRI (OPTIONAL – STANDARD OF CARE)				SOC		SOC	SOC
TELEPHONE CONVERSATION	X		X				
PATIENT COMPENSATION				X			
REVIEW ADVERSE EVENTS & CHANGES IN MEDICATION					X	X	X
COLLECT REMAINING STUDY MEDICATION				X		X	

4. STUDY POPULATION AND ANALYSIS SET

Study population: This study will include RIS subjects from the U.S. who fulfill 2009 RIS Criteria. Inclusion and exclusion criteria to be met are reported in the study protocol.

For this analysis all tables will be presented only by referring to the whole randomized sample according to the intent-to-treat principle (ITT). Otherwise, the Sponsor will provide a list of patients to be included in the primary analysis.

Per Protocol Set (PPS): A subject will be part of the PPS if she/he will receive any amount of study medication and have no major protocol deviations. This Set will be identified by the Sponsor prior unblinding.

5. OBJECTIVES

5.1. Primary objective

Assessment of the time from randomization to the first acute or initial neurological symptom resulting in a progressive clinical course related to CNS demyelination in those treated and untreated with Tecfidera.

Acute neurological event: The development of an acute neurological episode localized to the optic nerve, brainstem, cerebellum, spinal cord, or long sensory or motor tracts, lasting > 24 hours followed by a period of symptom improvement.

Progressive event: The onset of a clinical symptom (e.g. leg weakness) with the temporal profile revealing at least a 12-month progression of neurological deficits.

5.2. Secondary objectives

Evaluation of the change in the number of new or enlarging T2 lesions, contrast enhancing lesions, T2-lesion volumes, and brain atrophy at the End of Study.

6. SEQUENCE OF PLANNED ANALYSES

6.1. Interim analyses

No interim analysis is planned for this study.

6.2. Final analyses and reporting

Description of baseline characteristics and analyses of primary endpoint identified in this SAP will be performed only after the last patient has completed the study.

The randomization codes will not be unblinded until this SAP has been approved and database has been locked.

7. VARIABLES / ENDPOINTS AND PLANNED ANALYSIS

7.1. Subject characteristics at study entry

Demographics and clinical data at baseline (reasons for the initial MRI scan and neurostatus scales) will be summarized by presenting frequency distributions and/or basic summary statistics (mean, standard deviation, median, and range).

7.2. Primary endpoint

7.2.1. Primary analysis

To run the primary analysis a Multivariate Bayesian Cox regression model will be created with the time from randomization to the first demyelinating event (acute or development of an initial symptom resulting in a progressive clinical course) as the primary outcome and with treatment as a binary covariate. The following baseline variables will be used to adjust for their possible confounding effect:

- Sex (F/M)
- Age at the time of RIS diagnosis (Index MRI Scans)
- MS family history (Y/N/Ukn)
- EDSS
- Number of brain MRI T2 lesions
- Presence of gadolinium enhancing lesions (Y/N)
- Presence of spinal cord lesions (Y/N)
- CSF examination (OCB+/OCB-)

Four different scenarios will be used to create the parameters of the prior distribution to be used in the Bayesian analysis. These scenarios are detailed in the Sample size calculation document.

The association of each covariate with time to the first clinical symptom will be quantified by hazard ratios (HR) along with their 95% credible intervals (CI).

7.2.2. Secondary analysis

As a secondary analysis a classical survival analysis with the time from randomization to the first demyelinating event (acute or development of an initial symptom resulting in a progressive clinical

course) will be run. Kaplan-Meier survival analyses will be used to evaluate the outcome and Log-rank tests will be used to compare survival data between groups (treated vs non-treated) at univariate analysis. A multivariate Cox model adjusting for the above-mentioned covariates will be also run.

7.3. Secondary endpoints

Analyses of MRI outcomes will include participants who had at least one follow-up MRI.

- In the trial the mean T2 lesion volume derived from T2-weighted MRI over a 144-week period and the slope of change from baseline to week 96 and week 144 will be compared between treatment arms. Analyses will be based on a linear mixed effect model for repeated measures which will include a random intercept to account for the within-participant correlation and with treatment, visit, and treatment and visit interaction as fixed effects. T2 lesion volume will be log-transformed for the analysis. Adjusted analyses may include, if necessary, the number of enhancing lesions at baseline as covariate.

- The mean cumulative number of new enhancing lesions and the mean cumulative combined number of unique lesions (include new lesions enhanced on T1-weighted MRI plus new and newly enlarging lesions on T2-weighted MRI, without double-counting) over 144 weeks and the change from baseline to week 96 and week 144 will be compared between the two study groups. Means, differences, and P values will be calculated with the use of negative binomial regression models (with number of lesions enhanced on MRI at baseline as the covariate for the cumulative number of new lesions enhanced on MRI and the cumulative combined number of unique lesions).

- Whole brain atrophy using percent brain volume change (PBVC) derived from SIENA will be compared between treatment arms from baseline to week 96, week 96 to week 144, and baseline to week 144. Means, differences, and P values will be calculated with ….. Adjusted analyses may include, if necessary, baseline brain volumes, as measured by normalized brain parenchymal volumes (nBPV) derived from SIENAX.

For patients missing the 144 weeks MRI visit, the 96-week visit will be used, including an offset variable indicating the follow up duration. An additional analysis will be run using a Poisson mixed model, which included a random intercept to account for the within-participant correlation.

8. STUDY DEFINITIONS AND CONVENTIONS

8.1. Data handling

Continuous data will be summarized by using a descriptive statistics (n, mean, standard deviation, median, maximum, and minimum). Unless otherwise stated, mean and/or median will be displayed to one more decimal place than the original data; the standard deviation will be displayed to two decimal places more than the original data; minimum and maximum will be displayed to the same number of decimal places as the original data.

Categorical variables will be summarized using counts and percentages (displayed with one decimal place).

All p-values will be rounded to three decimal places, unless the true p-value is less than 0.001, and the notation "$p < 0.001$" will be used or if the true p-value is greater than 0.999, for which "$p > 0.999$" will be used.

All statistical hypotheses will be tested at the 0.05 significance level, and p-values reported will be based upon two-sided testing.

Confidence intervals, if needed, will be calculated at the 95% level.

8.2. Missing data

Missing dates will be imputed as follows:

- If only day is missing/unknown, then the 1st of the month will be imputed
- If day and month are missing/unknown, then the1st of January will be imputed
- When the whole date is missing, the date will be considered as missing.

No plan is foreseen for imputing missing data of other variables, therefore only the observed values up to study completion (or withdrawal time) will be used in the statistical analyses. Dropouts will be not replaced.

LIST OF SUMMARY TABLES (T) AND FIGURES (F)

Name	Description	Population	TYPE
DEMO	Demographic and clinical data at baseline	ITT	T
COX	Cox regression	ITT	T
KM	KM curves	ITT	F
MRI	Linear mixed regression and Poisson mixed regression	ITT	T