

Statistical Analysis Plan

Phase 2a Study of the Effect of Serine Supplementation and Fenofibrate Treatment

on Serum Deoxysphinganine Levels in Patients with Macular Telangiectasia (MacTel) Type 2

(SAFE Study)

ClinicalTrials.gov Identifier: NCT04907084

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Indication	Macular Telangiectasia Type 2 (MacTel)
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Statistical Software	R version 4.3.2

TRANSPARENCY STATEMENT: POST-HOC PREPARATION OF THIS STATISTICAL ANALYSIS PLAN

This Statistical Analysis Plan (SAP) was prepared after the completion of data collection for the MacTel SAFE Study (NCT04907084) and after the study team had access to the accumulated data. It was not finalized prior to database lock or unblinding. This document is being submitted to ClinicalTrials.gov in accordance with 42 CFR 11.48(a)(5), which requires submission of the protocol and SAP (if not included in the protocol) at the time of results reporting.

The analytical approach described herein — descriptive statistics of within-arm percent change from baseline in serum deoxysphingolipid levels — is consistent with and derived directly from the statistical considerations pre-specified in the study protocol (Version 1.2, 10 June 2022, Section 16.3), which stated: “Due to the exploratory nature of the study and the small number of participants per treatment group enrolled in this study, the data will be analysed by descriptive statistics.” This

SAP does not introduce new hypotheses, new comparisons, or new primary or secondary outcomes beyond those specified in the original protocol.

Because this is an exploratory Phase 2a study using descriptive statistics only, with no pre-specified hypothesis tests or primary p-values, the post-hoc nature of this SAP does not introduce meaningful risk of outcome-driven analytical decisions or inflated Type I error. No formal hypothesis testing is performed in this study. All analyses described herein are pre-specified in the sense that they reflect the intent documented in the protocol prior to study initiation.

Any analyses performed that deviate from or extend beyond what is described in this SAP will be clearly identified as post-hoc or exploratory in the final clinical study report and any resulting publications. The date on this document reflects the actual date of preparation and has not been backdated.

1. Introduction and Background

This Statistical Analysis Plan (SAP) describes the statistical methods to be used for analysis of data from the MacTel SAFE Study (Phase 2a Study of the Effect of Serine Supplementation and Fenofibrate Treatment on Serum Deoxysphinganine Levels in Patients with Macular Telangiectasia Type 2), registered on ClinicalTrials.gov as NCT04907084.

This SAP is a stand-alone document that supplements the study protocol (Version 1.2, 10 June 2022). It provides detailed specifications for all statistical analyses to be performed, including primary, secondary, and safety analyses.

Macular telangiectasia type 2 (MacTel) is an age-related bilateral degenerative condition of the macula that may cause progressive loss of vision. Research has determined that MacTel patients have lower serine levels compared to matched controls, and that low serine is correlated with elevated deoxysphingolipids, which are toxic to neurons. The purpose of this study is to determine whether serine supplementation and/or fenofibrate treatment reduces circulating levels of deoxysphingolipids in MacTel patient serum.

1.1 Revision History

Version	Date	Description of Changes
1.0	May 7 2026	Initial version

2. Study Design Overview

This is a prospective, multi-site, multi-arm, randomized, open-label Phase 2a study. The study involves six parallel treatment arms with participants randomized in a 1:1:1:1:1:1 ratio using a permuted block design. The study was conducted at up to 5 clinical sites, with a minimum of 2 sites.

2.1 Treatment Arms

Participants were randomly assigned to one of the following six treatment groups:

- Arm 1: Serine 200 mg/kg/day (low-dose serine)

- Arm 2: Serine 400 mg/kg/day (high-dose serine)
- Arm 3: Fenofibrate 160 mg/day
- Arm 4: Serine 200 mg/kg/day AND fenofibrate 160 mg/day
- Arm 5: Serine 400 mg/kg/day AND fenofibrate 160 mg/day
- Arm 6: No treatment (control group)

All active treatments were administered once daily for 6 weeks, followed by a 4-week washout period.

2.2 Visit Schedule

Participants attended study visits at the following timepoints:

Visit	Timepoint	Key Assessments
Visit 1 (Screening)	Week -1	Fasting blood metabolites, chemistry/lipid panel, BMI, eligibility review, consent
Visit 2 (Baseline)	Week 0	Fasting blood metabolites, randomization, treatment initiation, ophthalmic imaging
Visit 3	Week 3	Fasting blood metabolites, chemistry/lipid panel, AE assessment
Visit 4 (End of Treatment)	Week 6	Fasting blood metabolites, chemistry/lipid panel, AE assessment, end of treatment
Visit 5 (End of Washout)	Week 10	Fasting blood metabolites, chemistry/lipid panel, AE assessment

2.3 Sample Size

The study planned to enroll between 60 and 120 participants (10-20 participants per treatment group). Given the exploratory, proof-of-concept nature of this Phase 2a study, no formal power calculation was performed. The sample size was determined based on feasibility and the ability to generate preliminary estimates of within-arm changes in deoxysphingolipid levels.

Enrollment Table:

control	fenofibrate	serine 200 mg/kg	serine 400 mg/kg	serine 200 mg/kg + fenofibrate	serine 400 mg/kg + fenofibrate
15	15	16	14	13	15

3. Study Objectives and Endpoints

3.1 Primary Objective

To evaluate within-arm changes in serum deoxysphingolipid levels from baseline following treatment with serine 200 mg/kg/day, serine 400 mg/kg/day, fenofibrate 160 mg/day, serine 200 mg/kg/day plus fenofibrate 160 mg/day, serine 400 mg/kg/day plus fenofibrate 160 mg/day, or no treatment (control).

3.2 Primary Endpoints

The primary endpoint is the percent change from baseline in serum deoxysphingolipid levels at Week 6 (end of treatment), as represented by deoxy-dihydroceramides (doxDHCer), the species found to be the most toxic. Serum doxDHCer species to be analyzed include:

doxDHCer m18:0/16:0
doxDHCer m18:0/18:0
doxDHCer m18:0/20:0
doxDHCer m18:0/22:0
doxDHCer m18:0/23:0
doxDHCer m18:0/24:0
doxDHCer m18:0/24:1

Each metabolite was looked at individually and as the sum of all 7 species. We also evaluated other sphingolipid species including deoxy-ceramides (doxCer) and deoxysphinganine (doxSA).

3.3 Secondary Objective

To evaluate within-arm changes in serum amino acid and lipid levels following treatment, and to assess safety of the treatments.

3.4 Secondary Endpoints

Secondary endpoints include:

- Percent change from baseline in serum amino acid levels (including serine, glycine, and other relevant amino acids) at Weeks 3, 6, and 10
- Percent change from baseline in serum lipid levels (including total cholesterol, LDL, HDL, vLDL, triglycerides, and ceramide species) at Weeks 3, 6, and 10
- Change from baseline in blood chemistry values (ALT, AST, alkaline phosphatase, albumin, creatinine, eGFR, electrolytes) at Weeks 3, 6, and 10
- Change from baseline in complete blood count with differential at Weeks 3, 6, and 10
- Change from baseline in creatine phosphokinase (CPK) and lipase at Weeks 3, 6, and 10
- Incidence and nature of adverse events (AEs) and serious adverse events (SAEs)

4. Analysis Populations

4.1 Enrolled Population

All participants who signed informed consent and underwent the screening visit (Visit 1).

4.2 Randomized Population

All participants who were randomized to a treatment arm at the Baseline visit (Week 0). This is the primary population for reporting baseline characteristics and treatment exposure.

4.3 As-Treated Population

All participants who completed the Week 3 visit within the protocol-specified window and who were at least 50% compliant with their assigned treatment regimen as recorded on medication compliance forms. Participants were reclassified based on compliance, being moved to the appropriate group if they took less than 3 days of their assigned treatment (i.e. taking product one day and then stopping but continuing to come to visits were reclassified to controls).

4.5 Safety Population

All randomized participants who received at least one dose of assigned investigational product (Intent-to-Treat) were used to assess AEs. Control group participants were included in the safety population for comparison of AE rates. Additional safety analyses included both this Intent-to-Treat Population and the As-Treated Population.

5. General Statistical Principles

5.1 Analytical Approach

Given the exploratory nature of this Phase 2a study and the small number of participants per treatment group (10-20 per arm), the primary analytical approach is descriptive statistics. No pre-specified hypothesis tests were planned for the primary efficacy analysis, and no alpha level has been set for primary efficacy comparisons. Observed data are summarized to provide preliminary estimates of within-arm treatment effects to inform the design of a future, larger treatment efficacy study.

5.2 Descriptive Statistics

For continuous variables, the following descriptive statistics will be reported:

- N (number of non-missing observations)
- Mean
- Standard deviation (SD)
- Median
- Minimum and maximum (range)
- 25th and 75th percentiles (Q1, Q3)
- 95% confidence interval for the mean

For categorical variables, counts (n) and percentages (%) will be reported.

5.3 Primary Metric: Percent Change from Baseline

The primary metric for efficacy analyses is percent change from baseline, calculated as:

$$\text{Percent Change} = \frac{(\text{Post-baseline Value} - \text{Average Baseline Value})}{\text{Baseline Value}} \times 100$$

Baseline is defined as the average value from the fasting blood sample collected at the Baseline visit (Week 0) and Screening (Week -1).

Percent change from average baseline was calculated for each participant at each post-baseline timepoint (Weeks 3, 6, and 10).

Absolute change from baseline was calculated and reported as a supplementary measure.

5.4 Confidence Intervals

95% confidence intervals will be reported for mean percent change from baseline within each treatment arm at each timepoint. Confidence intervals will be computed using the t-distribution given the small sample sizes. No adjustments for multiple comparisons will be made.

5.5 Handling of Missing Data

Imputation of missing data will be performed for the primary or secondary efficacy analyses using multiple imputation by chained equations.

If a participant withdraws from the study, data collected up to the point of withdrawal will be included in analyses. The reason for withdrawal will be documented and summarized.

For safety analyses, only available data will be used.

5.6 Statistical Software

R studio version 4.3.2

6. Primary Efficacy Analysis

6.1 Primary Outcome and Timepoint

The primary efficacy analysis examines the within-arm percent change from baseline in serum deoxysphingolipid levels at Week 6 (end of treatment visit).

The primary timepoint is Week 6 (end of the 6-week treatment period). Changes at Weeks 3 and 10 are secondary timepoints and provide information on the time course of response during treatment and during the washout period, respectively.

6.2 Primary Analysis Method

Within each of the six treatment arms, the mean percent change from baseline in total deoxysphingolipid levels, with 95% CI will be reported

The analysis will be performed separately for each deoxysphingolipid species measured, as well as for total deoxysphingolipid levels (sum of species).

6.3 Time Course Analysis

To evaluate the time course of deoxysphingolipid changes, within-arm descriptive statistics for percent change from baseline will also be reported at Weeks 3 and 10.

6.4 Control Arm

The control arm (no treatment) provides data on the natural within-individual variability in deoxysphingolipid levels over the 10-week study period in MacTel patients. This is the first study to characterize this baseline variability. Descriptive statistics for the control arm will be reported alongside all active treatment arms, but no formal statistical comparisons between arms are planned.

7. Secondary Efficacy Analyses

7.1 Amino Acid Levels

Percent change from baseline in serum amino acid levels (including serine, glycine, and alanine) will be summarized descriptively within each arm at Weeks 3, 6, and 10, using the same methods as the primary analysis. Serine levels are of particular interest as the hypothesized mechanism by which elevated deoxysphingolipids arise in MacTel.

7.2 Lipid Levels

Percent change from baseline in lipid panel components (total cholesterol, LDL, HDL, vLDL, triglycerides, and ceramide species) will be summarized descriptively within each arm at Weeks 3, 6, and 10.

7.3 Blood Chemistry

Absolute change from baseline in safety-relevant blood chemistry values (ALT, AST, alkaline phosphatase, albumin, creatinine, eGFR, CPK, lipase, electrolytes) will be summarized descriptively within each arm at Weeks 3, 6, and 10.

7.4 Gut Microbiome

Gut microbiome samples were collected during the study. These have been banked for future analyses including shotgun metagenomics to assess changes in microbiome diversity as a result of treatment.

8. Safety Analyses

All safety analyses will be performed on the Safety Population (Section 4.5). Given the small sample size, safety analyses are descriptive only; no formal hypothesis testing will be performed.

8.1 Adverse Events

All adverse events from the date of first dose (or randomization for control) through 30 days after last study visit will be included. The following summaries will be presented:

- Number and percentage of participants with at least one AE, by treatment arm
- Number and percentage of participants with at least one treatment-related AE, by arm
- Number and percentage of participants with at least one serious adverse event (SAE), by arm
- Number and percentage of participants who discontinued treatment due to an AE, by arm
- AE summary table: MedDRA preferred term, severity grade, and relationship to study treatment, by arm

Adverse events will be classified by system organ class and preferred term.

9. Baseline Characteristics

Baseline characteristics will be summarized for the Randomized Population by treatment arm and overall. No formal statistical comparisons between arms will be made. The following variables will be included:

- Age (years): mean, SD, median, range
- Sex: n (%)
- BMI (kg/m²): mean, SD
- Baseline fasting deoxysphingolipid levels: mean, SD, median, range
- Baseline serine levels: mean, SD, median, range
- Baseline lipid panel values: mean, SD, median, range
- Baseline blood chemistry values: mean, SD, median, range

10. Participant Disposition

A participant disposition summary will be presented, including:

- Number of participants screened
- Number of participants who failed screening and primary reasons for screen failure
- Number of participants randomized, by treatment arm
- Number of participants who completed the Week 6 visit (end of treatment), by arm
- Number of participants who discontinued early, by arm and primary reason for discontinuation

12. Protocol Deviations

All protocol deviations will be documented and reviewed prior to database lock.

The impact of major protocol deviations on the primary analysis population will be assessed. Participants with major deviations affecting eligibility will be excluded from the primary analysis population. Deviations impacting treatment compliance will be assessed to ensure participants are accurately analyzed “as treated” for the primary analysis.

13. Additional Considerations and Notes

13.1 Interpretation Guidance

Given the small sample size (10-20 participants per arm) and the exploratory nature of this Phase 2a proof-of-concept study, results should be interpreted with caution. The primary purpose of this study is to generate preliminary estimates of the magnitude of within-arm changes in deoxysphingolipid levels and to assess safety, not to draw conclusions about therapeutic efficacy. All confidence intervals will be wide given the small sample sizes and should be interpreted as providing a plausible range of effect sizes rather than precise estimates.

The control arm data will provide the first characterization of natural variability in deoxysphingolipid levels over a 10-week period in MacTel patients, which will be essential for designing a future powered study.

13.2 Multiplicity

No formal multiplicity adjustment is planned, consistent with the descriptive analytical approach pre-specified in the protocol. Any p-values computed for exploratory purposes will be noted as unadjusted and interpreted in the context of multiple comparisons.

13.3 Unplanned Analyses

Any analyses not specified in this SAP that are performed will be identified as post-hoc or exploratory analyses in the clinical study publication and will be clearly distinguished from the pre-specified analyses herein.

13.4 Database Lock

Statistical analyses will be performed after database lock. The database lock date will be documented in the clinical study report.

Appendix A: Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CBC	Complete Blood Count
CI	Confidence Interval
CPK	Creatine Phosphokinase
eGFR	Estimated Glomerular Filtration Rate
HDL	High-Density Lipoprotein
IQR	Interquartile Range
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit of Quantification
LMRI	Lowy Medical Research Institute
MacTel	Macular Telangiectasia Type 2
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
vLDL	Very Low-Density Lipoprotein