# STATISTICAL ANALYSIS PLAN

**A Placebo-Controlled, Randomized, Double-Blind Study to Assess the Safety, Tolerability and Efficacy of Folinic Acid Administered to Pediatric Subjects with Autism Spectrum Disorder (ASD)**

Protocol 0038-26-SZMC

**NCT Number:** NCT07642661

Folinic Acid in Autism Spectrum Disorder (ASD)

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# 1. Introduction

## 1.1 Background and rationale

Autism spectrum disorder (ASD) encompasses a heterogeneous group of neurodevelopmental disorders characterized by impairments in social communication and the presence of restricted and repetitive behaviors. Despite substantial advances in understanding the biological mechanisms underlying ASD, there are currently no approved pharmacological treatments targeting the core symptoms of the disorder. Existing medications are primarily directed at associated symptoms such as irritability and aggression and are often associated with significant adverse effects.

Accumulating evidence suggests that abnormalities in folate metabolism may contribute to the pathophysiology of ASD in a substantial subset of affected children. Folate is essential for numerous neurodevelopmental processes, including DNA synthesis, methylation, neurotransmitter production, mitochondrial function, and regulation of oxidative stress. Disruptions in folate transport and metabolism may therefore adversely affect brain development and function.

One of the most consistently reported biological findings in ASD is the presence of folate receptor alpha autoantibodies (FRAAs), which may interfere with folate transport across the blood-brain barrier and contribute to cerebral folate deficiency. Several studies have demonstrated a high prevalence of FRAAs among children with ASD, and emerging evidence suggests that treatment with folinic acid (leucovorin calcium), a reduced folate that can bypass impaired folate transport mechanisms, may improve language, communication, adaptive functioning, and behavioral symptoms in selected individuals with ASD.

In addition to its role in folate metabolism, folinic acid may influence multiple biological pathways implicated in ASD, including methylation processes, oxidative stress regulation, immune function, and mitochondrial metabolism. Recent studies further suggest that genetic variation in folate-related pathways may contribute to treatment response variability.

The present study is designed to assess the efficacy, safety, and tolerability of folinic acid administered as an add-on treatment in young children with ASD. In addition, the study will investigate whether biomarkers related to folate metabolism, including FRAA status, maternal FRAA status, oxidative stress markers, transcriptomic profiles, proteomic signatures, microbiome composition, and genetic variation in folate-related pathways, are associated with clinical response.

We hypothesize that treatment with folinic acid will result in significantly greater improvements in behavioral symptoms and adaptive functioning compared with placebo during the randomized placebo-controlled phase of the study.

## 1.2 Objectives

The primary aim of this study is to assess the effect of folinic acid compared to placebo on ASD-associated behavioral problems, using the Aberrant Behavior Checklist-Irritability Subscale (ABC-I) score, measured as change from baseline to Week 9.

The main secondary aims are to assess the effect of folinic acid compared to placebo on adaptive functioning and communication skills using the Vineland™ Adaptive Behavior Scales, Third Edition (VABS-3) Communication Domain and Socialization Domain scores, measured as change from baseline to Week 9.

Other secondary aims include:

(1) To assess the tolerability and safety of folinic acid compared to placebo using adverse event monitoring, physical examinations, laboratory assessments, and treatment compliance measures.

(2) To assess global improvement in ASD-associated symptoms using the Clinical Global Impression-Improvement (CGI-I) scale and the Caregiver Global Impression of Change (CGIC) assessment at Week 9.

(3) To assess the effect of folinic acid compared to placebo on core ASD symptoms, communication abilities, emotional and behavioral regulation, adaptive functioning, sleep, and caregiver-reported quality of life using the following outcome measures:

- Social Responsiveness Scale, Second Edition (SRS-2)
- MacArthur-Bates Communicative Development Inventories (MB-CDI)
- Aberrant Behavior Checklist-Community (ABC-C)
- Autism Impact Measure (AIM)
- Emotion Dysregulation Inventory (EDI)
- Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB)
- Children's Sleep Habits Questionnaire (CSHQ)
- Quality of Life in Autism Questionnaire (QOLA)
- Modified GISSI questionnaire

All efficacy outcomes will be evaluated as change from baseline to Week 9 unless otherwise specified.

(4) To assess the proportion of participants achieving clinically meaningful improvement, including predefined responder criteria based on ABC-I and CGI-I outcomes.

(5) To evaluate the association between treatment response and biomarkers related to folate metabolism and ASD pathophysiology, including:

- Folate receptor alpha autoantibodies (FRAAs)
- Maternal FRAA status
- Serum folate
- Vitamin B12
- Homocysteine
- Oxidative stress markers including reduced and oxidized glutathione
- Transcriptomic profiles
- Proteomic signatures
- Gut microbiome composition
- Genetic variation in folate-related metabolic pathways

(6) To identify baseline clinical, biochemical, immunological, and molecular predictors of treatment response that may support future precision-medicine approaches in ASD.

(7) To evaluate changes in biomarkers during treatment and explore their relationship with clinical improvement.

(8) To compare the efficacy, safety, and tolerability of two active folinic acid dose regimens during the second randomized treatment phase using the above efficacy and safety assessments, measured as change from Week 9 to Week 17.

(9) To generate preliminary data regarding biological mechanisms associated with folinic acid treatment in ASD, including pathways related to folate metabolism, oxidative stress regulation, immune function, mitochondrial function, and neurodevelopment.

# 2. Study Methods

## 2.1 Trial Design

This is a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy, safety, and tolerability of folinic acid in children with Autism Spectrum Disorder (ASD).

A total of 150 children with ASD, aged 3–6 years, will be enrolled. Eligible participants who successfully complete screening procedures will be randomized in a 1:1 ratio to receive either folinic acid or matching placebo during a 9-week placebo-controlled treatment phase.

Folinic acid will be administered orally as an add-on to any existing stable treatments at a target dose of 2 mg/kg/day (maximum 50 mg/day), divided into two daily doses. Study treatment will be titrated according to the schedule specified in the clinical protocol.

Following completion of the Week 9 assessment, participants will enter a second randomized active-treatment phase. During this phase, all participants will receive folinic acid and will be randomized to one of two folinic acid dose regimens for an additional 8 weeks.

The primary efficacy evaluation will be based on the placebo-controlled phase and will compare folinic acid with placebo using change from baseline to Week 9 in ABC-I score.

The second treatment phase is intended to provide additional information regarding dose-response relationships, durability of treatment effects, safety, and biomarker changes and will be analyzed separately as a secondary exploratory phase.

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## 2.2 Randomization

A randomization scheme will be generated by an independent unblinded biostatistician who is not otherwise involved in study conduct, participant assessment, or data analysis.

Randomization will be performed using stratified permuted block randomization with varying block sizes to maintain allocation concealment.

Participants will be stratified according to:

- Sex (Male/Female)
- Developmental Quotient (DQ <70 versus DQ ≥70)

Randomization will be implemented at a 1:1 allocation ratio.

The randomization schedule will contain sequential participant numbers and corresponding treatment assignments. Access to treatment assignments will be restricted to personnel directly involved in treatment allocation and investigational product preparation.

The randomization list will remain confidential and securely stored until completion of database lock unless emergency unblinding is required.

A separate randomization schedule will be generated for the second active-treatment phase.

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## 2.3 Sample Size

The planned sample size is 150 participants (75 participants per treatment group).

The sample size calculation is based on the primary endpoint, defined as change from baseline to Week 9 in the Aberrant Behavior Checklist-Irritability Subscale (ABC-I) score.

The study is powered to detect a standardized between-group effect size of 0.45 using a Mixed Model for Repeated Measures (MMRM) incorporating post-baseline assessments during the placebo-controlled phase.

Assuming a two-sided significance level of 0.05 and 80% statistical power, approximately 65 evaluable participants per treatment group are required.

To account for an anticipated dropout rate of approximately 15%, 75 participants per treatment group will be enrolled, resulting in a total planned sample size of 150 participants.

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## 2.4 Framework

This trial is designed as a superiority trial.

The primary hypothesis is that folinic acid will be superior to placebo in reducing ASD-associated behavioral problems as measured by change from baseline to Week 9 in ABC-I score.

Secondary analyses will evaluate whether folinic acid improves adaptive functioning, communication abilities, global clinical status, and other ASD-associated symptoms compared with placebo.

Exploratory analyses will evaluate whether biomarkers related to folate metabolism, FRAA status, maternal FRAA status, oxidative stress, transcriptomics, proteomics, microbiome composition, and genetic variation are associated with treatment response.

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## 2.5 Statistical Interim Analysis and Stopping Guidance

No formal efficacy interim analysis is planned.

An independent Data and Safety Monitoring Board (DSMB) may periodically review accumulating safety data, study conduct, recruitment progress, protocol adherence, and overall risk-benefit balance.

No formal statistical stopping boundaries for efficacy or futility have been defined.

The DSMB may recommend continuation, modification, temporary suspension, or termination of the study if participant safety concerns arise.

Any DSMB recommendations will be documented separately from the SAP.

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## 2.6 Timing of Analyses

The final statistical analysis will be conducted following completion of study participation by the last enrolled participant, completion of all planned data collection, resolution of data queries, completion of blinded data review, and database lock.

The primary analysis will be based on all available data collected through Week 9.

Secondary analyses will include data collected through Week 17.

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## 2.7 Timing of Outcome Assessments

Outcome assessments will be performed according to the schedule of assessments described in the clinical protocol.

The primary efficacy endpoint will be evaluated using data collected during the placebo-controlled phase through Week 9.

Secondary and exploratory analyses may utilize assessments obtained during both the placebo-controlled and active-treatment phases.

Safety assessments, adverse event monitoring, treatment compliance evaluations, and biomarker measurements will be performed throughout study participation according to protocol-defined schedules.

# 3. Statistical Principles

## 3.1 Confidence Intervals and P Values

Unless otherwise specified, all statistical tests will be two-sided and performed at a significance level of 0.05.

When confidence intervals (CIs) are presented, they will be two-sided 95% confidence intervals.

The primary efficacy endpoint will be tested confirmatorily at a two-sided alpha level of 0.05.

No formal adjustment for multiplicity will be applied for secondary, exploratory, biomarker, subgroup, or omics analyses. Nominal p-values will be presented for these analyses and interpreted as supportive and hypothesis-generating.

For all efficacy endpoints, treatment effects will be accompanied by estimates of effect size and corresponding 95% confidence intervals whenever appropriate.

The primary interpretation of study results will be based on estimated treatment effects, confidence intervals, and clinical relevance rather than solely on statistical significance.

## 3.2 Adherence

Adherence is defined as the proportion of prescribed study medication doses actually administered during the placebo-controlled phase of the study.

Adherence will be assessed using caregiver reports, treatment accountability records, and study drug dispensing logs collected throughout study participation.

Treatment compliance (%) will be calculated as:

Compliance (%) = (Observed Doses / Expected Doses) × 100

Overall duration of exposure (days) will be calculated as:

Last Treatment Date − First Treatment Date + 1

Summary statistics for treatment compliance and treatment exposure will be presented by treatment group and study phase, including:

- Number of participants (N)
- Mean
- Standard deviation

- Median
- Minimum
- Maximum

Participants with treatment compliance below 80% may be considered major protocol deviations and may be excluded from the Per-Protocol population, as determined during blinded data review.

## 3.3 Protocol Deviations

Neither the Principal Investigator nor any sub-investigator is authorized to deviate from the protocol except when necessary to protect the safety, rights, or well-being of study participants or as otherwise permitted by applicable regulations and Good Clinical Practice (GCP) requirements.

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

Protocol deviations will be categorized as either major or minor.

Major protocol deviations are those considered capable of affecting participant safety, study integrity, treatment assignment, eligibility determination, or interpretation of efficacy outcomes.

Examples of major protocol deviations may include:

- Violation of key inclusion or exclusion criteria
- Randomization errors
- Use of prohibited medications
- Significant treatment non-compliance
- Missing primary endpoint assessment
- Unblinding events

Minor protocol deviations are deviations that are not expected to materially affect participant safety or interpretation of study outcomes.

Examples include:

- Minor visit scheduling deviations
- Administrative documentation errors

- Delayed completion of non-critical assessments

A complete review of protocol deviations will be conducted during blinded data review prior to database lock.

## 3.4 Analysis Populations

### 3.4.1 Safety Population

The Safety Population is defined as all participants who receive at least one dose of study medication.

Safety analyses will be performed using the Safety Population.

Participants will be analyzed according to the treatment actually received.

### 3.4.2 Modified Intent-to-Treat Population (mITT)

The modified Intent-to-Treat (mITT) Population is defined as all randomized participants who:

- Receive at least one dose of study medication; and
- Have at least one post-baseline efficacy assessment.

The mITT Population will serve as the primary population for efficacy analyses.

Participants will be analyzed according to their randomized treatment assignment.

### 3.4.3 Per-Protocol Population (PP)

The Per-Protocol (PP) Population will include participants from the mITT Population who complete the placebo-controlled phase without major protocol deviations.

The PP Population will be used for supportive sensitivity analyses to evaluate the robustness of efficacy findings.

Final PP eligibility will be determined during blinded data review prior to database lock.

## 3.5 Missing Data

The primary efficacy analyses will use Mixed Models for Repeated Measures (MMRM), which incorporate all available observations under the Missing At Random (MAR) assumption and do not require single-value imputation.

The primary analysis assumes that missing efficacy data are MAR, an assumption considered reasonable for this study.

The extent and timing of missing data will be summarized by treatment group and study visit.

For each efficacy endpoint, the following will be presented:

- Number of missing observations
- Percentage of missing observations
- Reasons for missingness when available

To evaluate the robustness of study conclusions, sensitivity analyses may include:

- Multiple imputation
- Per-Protocol analyses
- Alternative covariance structures
- Additional sensitivity analyses deemed appropriate by the study statistician prior to database lock

## 3.6 Harms

All participants receiving at least one dose of study medication will be included in safety analyses.

Safety will be monitored through:

- Adverse event assessments
- Physical examinations
- Vital signs
- Clinical laboratory evaluations
- Treatment compliance assessments

Adverse events will be coded and summarized according to system organ class and preferred term.

The incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), severe adverse events, treatment-related adverse events, and adverse events leading to discontinuation will be summarized by treatment group.

Laboratory safety analyses will include hematology, chemistry, folate-related biomarkers, and oxidative stress markers collected according to the protocol schedule.

## 3.7 Statistical Software

Statistical analyses will be performed using validated versions of SAS (Version 9.4 or higher), R (Version 4.0 or higher), or equivalent statistical software.

The primary efficacy analyses will generally be performed using SAS PROC MIXED, R mixed-effects modeling procedures, or equivalent validated implementations.

All statistical programs, derived datasets, tables, listings, and figures will undergo appropriate quality control procedures prior to final reporting.

# 4. Trial Population

## 4.1 Screening and Eligibility

All participants who provide informed consent and undergo screening procedures will be included in the screening population.

Screening data will be summarized descriptively, including:

- Number of participants screened
- Number of screen failures
- Number of randomized participants
- Number of participants entering each study phase
- Number of participants completing the study

Reasons for screen failure will be summarized and categorized where appropriate.

Examples of screening failure categories may include:

- Failure to meet ASD diagnostic criteria
- Failure to meet symptom severity requirements
- Age outside permitted range
- Presence of exclusionary medical conditions
- Recent changes in medications or behavioral interventions
- Laboratory abnormalities
- Withdrawal of consent prior to randomization
- Other protocol-defined exclusion criteria

Screening data will be presented using the CONSORT participant flow diagram and supporting disposition tables.

## 4.2 Participant Disposition

Participant disposition will be summarized for each treatment group and for the study overall.

The following categories will be reported:

- Screened
- Screen failures
- Randomized
- Received study treatment
- Completed Week 9
- Entered Phase 2
- Completed Week 17
- Discontinued treatment
- Withdrew consent
- Lost to follow-up
- Included in the Safety Population
- Included in the mITT Population
- Included in the PP Population

Reasons for treatment discontinuation and study withdrawal will be summarized by treatment group.

## 4.3 Withdrawal and Follow-Up

Participants may discontinue study treatment or withdraw from study participation at any time.

Whenever possible, participants who discontinue study treatment will be encouraged to continue protocol-specified assessments and safety follow-up procedures.

The reason for withdrawal will be recorded and categorized as one of the following:

- Adverse event
- Lack of efficacy
- Participant or parent decision
- Investigator decision
- Protocol deviation

- Lost to follow-up
- Withdrawal of consent
- Other

The number and percentage of participants in each category will be summarized by treatment group.

## 4.4 Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics will be summarized using the mITT Population.

Continuous variables will generally be summarized using:

- Number of observations (N)
- Mean
- Standard deviation
- Median
- Minimum
- Maximum

Categorical variables will be summarized using:

- Frequency counts
- Percentages

Baseline characteristics may include:

**Demographic Characteristics**

- Age
- Sex
- Ethnicity (if collected)
- Weight
- Height
- Body Mass Index (BMI)

**Clinical Characteristics**

- Developmental Quotient (DQ)
- CGI-S score
- ABC-I score
- ABC-C score
- SRS-2 score
- VABS-3 Communication score
- VABS-3 Socialization score
- MB-CDI score
- AIM score
- EDI score
- MAP-DB score
- CSHQ score
- QOLA score

**Medical History**

- ASD diagnostic history
- Developmental history
- Psychiatric comorbidities
- Neurological comorbidities
- Previous and concomitant treatments
- Behavioral interventions

**Biomarker Characteristics**

Where available, baseline biomarker summaries may include:

- Folate receptor alpha autoantibody (FRAA) status
- Maternal FRAA status
- Serum folate

- Vitamin B12
- Homocysteine
- Oxidative stress markers
- Genetic markers
- Other exploratory biomarkers

No formal statistical significance testing of baseline characteristics is planned.

Baseline summaries are intended to describe the study population and evaluate comparability between treatment groups.

## 4.5 Concomitant Medications and Interventions

Concomitant medications and behavioral interventions present at baseline or initiated during the study will be summarized descriptively.

Medications may be categorized according to therapeutic class.

Behavioral and educational interventions may include:

- Speech therapy
- Occupational therapy
- Behavioral therapy
- Parent-training programs
- Educational support programs

Changes in concomitant treatments during study participation will be documented and summarized.

# 5. Analyses

## 5.1 General Considerations

All efficacy analyses will be performed using the modified Intent-to-Treat (mITT) Population unless otherwise specified.

Participants will be analyzed according to randomized treatment assignment.

The primary efficacy evaluation will be based on data collected during the placebo-controlled phase through Week 9.

The primary objective of the study is to evaluate the efficacy of folinic acid compared with placebo in improving ASD-associated behavioral symptoms.

Secondary and exploratory analyses will evaluate effects on adaptive functioning, communication, global clinical status, sleep, quality of life, safety outcomes, and biological markers associated with folate metabolism and ASD pathophysiology.

All efficacy analyses will be interpreted in conjunction with estimated treatment effects, confidence intervals, and clinical relevance.

Repeatedly measured endpoints collected at Week 4 and Week 9 (ABC-I and SRS-2) will be analyzed using MMRM. Endpoints assessed only at baseline and Week 9 will be analyzed using ANCOVA models adjusting for baseline score and randomization stratification factors.

## 5.2 Outcome Definitions

### 5.2.1 Primary Endpoint

The primary endpoint is:

**Change from baseline to Week 9 in ABC-I score.**

Change from baseline will be calculated as:

Post-Baseline Score − Baseline Score

Negative values indicate improvement.

### 5.2.2 Main Secondary Endpoints

The main secondary endpoints are:

- Change from baseline to Week 9 in VABS-3 Communication GSV.
- Change from baseline to Week 9 in VABS-3 Socialization GSV.

Positive values indicate improvement.

VABS standard scores will be analyzed supportively.

#### 5.2.3 Additional Secondary Endpoints

Additional endpoints include:

- SRS-2
- MB-CDI
- ABC-C subscales other than ABC-I
- AIM
- EDI
- MAP-DB
- CGI-I
- CGIC
- CSHQ
- QOLA
- Modified GISSI

## 5.3 Primary Efficacy Analysis

#### 5.3.1 Primary Estimand

Population:
mITT Population.

Treatment:
Folinic acid versus placebo.

Variable:
Change from baseline to Week 9 in ABC-I score.

Intercurrent Events:
Treatment-policy strategy.

Summary Measure:
Difference in LS mean change between treatment groups at Week 9.

### 5.3.2 Statistical Model

The primary endpoint will be analyzed using a Mixed Model for Repeated Measures (MMRM).

Fixed effects:

- Treatment
- Visit
- Treatment-by-Visit interaction
- Sex stratum
- DQ stratum

Covariate:

- Baseline ABC-I score

Repeated factor:

- Participant

Primary covariance structure:

- Unstructured covariance matrix

The primary comparison will evaluate folinic acid versus placebo at Week 9.

### 5.3.3 Missing Data

The primary analysis assumes data are Missing At Random (MAR).

No single-value imputation will be performed.

All available observations will contribute to model estimation.

### 5.3.4 Sensitivity Analyses

Sensitivity analyses will include:

- Per-Protocol analysis
- Multiple imputation
- Alternative covariance structures
- Additional covariate-adjusted models

## 5.4 Main Secondary Efficacy Analyses

VABS-3 Communication and Socialization GSV endpoints will be analyzed using ANCOVA. The Week 9 score will be analyzed using an ANCOVA model with treatment as a fixed effect and baseline score, sex stratum, and DQ stratum as covariates. Adjusted least-squares means, treatment differences, 95% confidence intervals, and nominal p-values will be reported.

## 5.5 Additional Secondary Efficacy Analyses

Continuous endpoints will generally be analyzed using MMRM (SRS-2) or ANCOVA models. Endpoints assessed only at baseline and Week 9 will be analyzed using ANCOVA.

The following endpoints will be analyzed:

- SRS-2
- MB-CDI
- ABC-C subscales other than ABC-I
- AIM
- EDI
- MAP-DB
- CSHQ
- QOLA
- Modified GISSI

For each endpoint, treatment differences, 95% confidence intervals, and nominal p-values will be presented.

## 5.6 Global Clinical Improvement Analyses

**CGI-I**

CGI-I scores will be analyzed using ordinal logistic regression models.

A responder analysis will additionally define responders as:

CGI-I ≤ 2 (Much Improved or Very Much Improved).

**CGIC**

CGIC analyses will be performed using methods analogous to CGI-I analyses.

Odds ratios, 95% confidence intervals, and nominal p-values will be reported.

## 5.7 Responder Analyses

The following responder definitions will be evaluated:

**ABC-I Responders**

≥25% improvement

**CGI-I Responders**

CGI-I ≤2

**Combined Responders**

ABC-I improvement ≥25%

AND

CGI-I ≤2

Responder rates will be compared using logistic regression models and Chi-square tests.

Odds ratios, risk differences, and confidence intervals will be reported.

## 5.8 Safety Analyses

Safety analyses will use the Safety Population.

The following outcomes will be summarized:

- TEAEs
- SAEs
- Treatment-related adverse events
- Severe adverse events
- Adverse events leading to discontinuation

Safety analyses will be descriptive.

No formal hypothesis testing is planned.

## 5.9 Biomarker Analyses

Exploratory biomarker analyses will evaluate associations between clinical outcomes and:

- FRAA status
- Maternal FRAA status
- Serum folate
- Vitamin B12
- Homocysteine
- Oxidative stress markers

Treatment-by-biomarker interaction models may be explored.

## 5.10 Omics Analyses

Exploratory analyses may evaluate:

- Transcriptomics
- Proteomics
- Microbiome composition

Associations with treatment response and baseline clinical characteristics will be investigated.

False discovery rate correction may be applied where appropriate.

## 5.11 Subgroup Analyses

Predefined subgroups may include:

- Sex
- DQ category
- FRAA status
- Maternal FRAA status
- Baseline severity

Subgroup analyses will be considered exploratory.

## 5.12 Exploratory Analyses

Additional exploratory analyses may be performed to investigate:

- Predictors of treatment response
- Biological mechanisms associated with treatment response
- Relationships between biomarker changes and clinical outcomes
- Precision-medicine approaches for future studies

# References


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