J3K-MC-KIAB Statistical Analysis Plan 1.0

An Adaptive Phase 2a/2b, Randomized, Double-Blind, Parallel-Group Study to Investigate the Safety and Efficacy of LY3541860 Compared to Placebo in Slowing the Occurrence of New T1 Gadolinium-Enhancing Lesions in Adult Participants with Relapsing Multiple Sclerosis

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Title Page

Protocol Title: An Adaptive Phase 2a/2b, Randomized, Double-Blind, Parallel-Group Study to Investigate the Safety and Efficacy of LY3541860 Compared to Placebo in Slowing the Occurrence of New T1 Gadolinium-Enhancing Lesions in Adult Participants with Relapsing Multiple Sclerosis

Protocol Number: J3K-MC-KIAB

Compound Number: CD19 Antibody, LY3541860

Short Title: An Adaptive Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of LY3541860 in Adult Participants with Relapsing Multiple Sclerosis

Acronym: KIAB

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Version history

This Statistical Analysis Plan (SAP) for study J3K-MC-KIAB is based on Protocol Amendment [b] dated 07Nov2023.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
0.0	TBD	Not Applicable	Original version
0.1	N/A		Updated for Protocol Amendment [a] dated 25Aug2023
0.2	N/A		Updated for Protocol Amendment [b] dated 07Nov2023

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelinating lesions throughout the central nervous system. Abnormalities of B cell function has been implicated in the pathophysiology of multiple sclerosis. LY3541860 is a monoclonal antibody that inhibits primary human B cell activation, proliferation, and differentiation without causing B cell depletion or inducing B cell apoptosis.

LY3541860 is a B cell nondepleting anti-CD19 IgG4-variant mAb. LY3541860 is highly selective for CD19, which is found on plasmablasts and plasma cells. LY3541860 may therefore be efficacious in patients with relapsing multiple sclerosis (RMS).

Study J3K-MC-KIAB (KIAB) will evaluate the efficacy of multiple dose levels of LY3541860 versus placebo over 36 weeks of treatment in study participants with RMS. Findings from the study will be used to assess the utility of LY3541860 for the treatment of RMS and advance understanding of the benefit/risk relationship for LY3541860 and inform the doses and design of future studies of LY3541860.

This Statistical Analysis Plan will include the details to analyze efficacy and safety data for the study. Changes to the protocol-planned analyses are described in Section 4.9. Table, figure, and listing (TFL) specifications are included in a separate document.

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1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To evaluate the efficacy of LY3541860 versus placebo on the number of new T1 GdE MRI brain lesions in participants with RMS	• The cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12[a]
Secondary	
To evaluate the efficacy of LY3541860 versus placebo on other measures of MRI activity in participants with RMS	• The cumulative number of new or enlarging T2 lesions, as measured by MRI scans, over Weeks 4, 8, and 12
To characterize the PK of LY3541860 in patients with RMS	Plasma trough concentrations of LY3541860
To describe the safety of LY3541860 in participants with RMS	Summary of safety data, including number and incidence of • TEAEs • SAEs • Discontinuations due to AEs
CCI	



Abbreviations: AE = adverse event; EDSS = Expanded Disability Status Scale; CCI [redacted]; GdE = gadolinium-enhancing; CCI [redacted] MRI = magnetic resonance imaging; CCI [redacted]; PD = pharmacodynamic; PK = pharmacokinetics; CCI [redacted] RMS = relapsing multiple sclerosis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] When counting the number of new T1 GdE lesions at each postbaseline visit, the baseline (Visit 1) scan will be used as the reference (see Protocol Section 9.3.2 for details). Lesions persisting for more than 4 weeks will be counted only once.

1.1.1. Primary Estimand

Unless otherwise specified, the information in this section applies to both phases of the study.

The primary estimand has the following attributes:

- Clinical question of interest: What is the difference in cumulative number of new T1 GdE lesions over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS if use of prohibited medication or discontinuing the study intervention had not happened?
- Treatment condition: Each dose of LY3541860 versus placebo.
- Population: Defined through appropriate inclusion and exclusion criteria (see details in Protocol Sections 5.1 and 5.2) to reflect the targeted patient population in RMS.



1.1.2. Secondary Estimand

Unless otherwise specified, the information in this section applies to both phases of the study.

The secondary estimand has the following attributes:

- Clinical question of interest: What is the difference in other MRI lesions over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS if use of prohibited medication or discontinuing study intervention had not happened?
- Treatment condition: LY3541860 versus placebo.
- Population: defined through appropriate inclusion and exclusion criteria (see details in Protocol Sections 5.1 and 5.2) to reflect the targeted patient population in RMS.





1.1.3. Supportive Estimands

The supportive estimands include three different strategies for three corresponding clinical questions of interest.

1.1.3.1. Treatment-Policy

The primary and secondary endpoints will also be evaluated using a treatment policy estimand as follows:

- Clinical question of interest: What is the difference in MRI lesions over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS regardless of the use of rescue medication or discontinuing the study intervention?
- Treatment condition: LY3541860 versus placebo.
- Population: defined through appropriate inclusion and exclusion criteria (see details in Protocol Sections 5.1 and 5.2) to reflect the targeted patient population in RMS.





1.1.3.2. Hypothetical

In addition to the primary and secondary endpoints/estimands, CCI

- Clinical question of interest: What is the difference in clinical outcomes (MS relapse and neurological symptoms), other MRI-related measures (MRI lesions and thalamic volume), patient-reported outcomes, and physical activity over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS if use of prohibited medication or discontinuing the study intervention had not happened?
- Treatment condition: Each dose of LY3541860 versus placebo.
- Population: defined through appropriate inclusion and exclusion criteria (see details in Protocol Sections 5.1 and 5.2) to reflect the targeted patient population in RMS.







1.1.3.3. Composite

Proportion of relapse-free participants over time and proportion of participants with no new T1 GdE lesions over time will be evaluated using a composite estimand as follows:

- Clinical question of interest: What is the difference in achieving clinical response over 12 weeks of treatment with LY3541860 versus placebo?
- Treatment condition: Each dose of LY3541860 versus placebo.
- Population: defined through appropriate inclusion and exclusion criteria (see details in Protocol Sections 5.1 and 5.2) to reflect the targeted patient population in RMS.



1.2. Study Design

Study KIAB is an adaptive Phase 2a/2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of multiple dose levels of LY3541860 versus placebo in patients with RMS.

As an adaptive study, Study KIAB has 2 phases that differ from one another by purpose and dose levels being tested as described in Table 1.

Table 1. Study KIAB Phases

	Phase 2a portion	Phase 2b portion
Purpose	Proof of concept	Dose ranging[a]
LY3541860 dose levels	CCI mg CCI mg	Dose Level 3 Dose Level 4

[a] Phase 2b doses will be no higher than CCI mg.

Results of interim analyses from the Phase 2a portion of this study will determine whether the Phase 2b portion will be initiated and, if so, what doses of LY3541860 will be used.

There are no differences in the study entry criteria for the Phase 2a and Phase 2b portions. In both portions, participants in the placebo group will receive treatment with LY3541860 after 12 weeks of having received placebo.

The study will consist of the following periods:

- Screening (-35 to -14 days):
  - Visit 1: Participants will be evaluated for study eligibility.
- Treatment (0 to 36 weeks):
  - Visit 2 (Baseline): Eligibility criteria will be confirmed, and all eligible participants will be randomized stratified on geographic region (North America vs Other) and presence of T1 GdE lesion (Yes vs No).
    - Phase 2a: Participants will be randomized in a 1:1 ratio to LY3541860 CCI mg for 36 weeks or placebo for 12 weeks followed by LY3541860 CCI mg.
    - Phase 2b: Participants will be randomized in a 9:9:2 ratio to LY3541860 Dose Level 3 for 36 weeks, LY3541860 Dose Level 4 for 36 weeks, or placebo for 12 weeks followed by, in a 1:1 ratio, either LY3541860 Dose Level 3 or LY3541860 Dose Level 4.
  - Visits 3 through 11: Scheduled visits approximately every 4 weeks at which safety and clinical assessments will be conducted according to the Schedule of Activities (see Protocol Section 1.3).

- Follow-up (approximately 12 and 24 weeks after Visit 11, or last dose received for participants who discontinue study intervention early):
    - Visits 801 and 802: Safety assessments and other procedures will be conducted according to the schedule of Activities (see Protocol Section 1.3).
    - The follow-up period will take longer CCI [redacted]

The study will not allow dose modifications. Discontinuation of study intervention or withdrawal from the study are described in Protocol Section 7.

2. Statistical Hypotheses

Phase 2a: The null hypothesis for the primary objective is that there is no difference in reducing the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.

Phase 2b: The null hypothesis for the primary objective is that there is no difference in reducing the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with at least 1 dose of LY3541860 versus placebo.

Then the statistical hypothesis is formulated as:

$$H_0: 1 - RR_t = 0 \; vs \; H_A: 1 - RR_t \neq 0$$

Where RR_t denotes the true rate reduction in the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.

The null hypothesis for the primary endpoint is that there is no difference between LY3541860 CCI mg and placebo in reducing the number of new T1 Gd-enhancing lesions per scan at Week 4, Week 8, and Week 12.

The hypotheses will be evaluated at a 2-sided alpha level of 0.05.

2.1. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined in Table 2.

Table 2. Analysis Sets

Participant Analysis Sets	Description
mITT	All participants randomly assigned to study intervention and receive at least 1 dose of the study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Safety	All participants randomly assigned to study intervention and receive at least 1 dose of the study intervention. Participants will be analyzed according to the intervention they actually received during each study period.
PK	All participants randomly assigned to study intervention and receive at least 1 dose of the study intervention and with at least 1 postbaseline evaluable PK sample.

4. Statistical Analyses

4.1. General Considerations

4.1.1. General statistical methods

Efficacy and safety data will be analyzed and summarized by phases:

- Phase 2a: Proof-of-concept study
- Phase 2b: Dose-ranging study

For Phase 2b efficacy analysis, Phase 2a efficacy data will be combined, as appropriate, to assist with the Phase 2b analysis (see Section 4.3.2).

Descriptive summaries of continuous data will present the sample size, group mean, standard deviation (SD, median, minimum and maximum. The minimum and maximum will be formatted to the same number of decimal places as the measured value, median and mean will be formatted to one more decimal place then the measured value, and SD will be formatted to two more decimal places than the measured value.

Descriptive summaries of discrete data will present the number of participants and incidence as a frequency and as a percentage. If number of participants is zero, then the percentage display will be suppressed to draw attention to the non-zero counts. If a missing value exists, a 'Missing' row can be added for the summary where specified on the shells. No percentage will be displayed for the 'Missing' row. Percentages will be calculated based on number of participants with non-missing data unless otherwise specified and rounded to one decimal place. If the denominator and numerator are equal, then the percentage will be displayed as (100) unless specified otherwise.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CI) will be given at a 2-sided 95% level. In the case that either an estimate or CI is not estimable, it will be displayed as "NE". If neither estimate nor CI are estimable then it will be displayed as "NE" only once.

All p-values will be two-sided and rounded to three decimal places. If a p-value is less than 0.001 it will be presented as "<0.001". If a p-value is greater than 0.999 it will be presented as ">0.999".

Treatment arms will be displayed as:

- Phase 2a: LY3541860 CCI mg, LY3541860 CCI mg, and placebo.
- Phase 2b: LY3541860 Dose Level 3, LY3541860 Dose Level 4, and placebo.
  'Dose Level 3' and 'Dose Level 4' will be presented as the respective the dose level in mg.

Treatment comparison will be each LY3541860 treatment arm compared with placebo unless stated otherwise.

Because comparing between LY3541860 CCI mg vs. placebo includes participates from the same cohort, all efficacy analyses will be considered as exploratory analyses.

4.1.2. Definition of Baseline and Post-baseline Period

Baseline is defined as the last available value before the first dose of study intervention for both efficacy and safety analyses. In most cases, this value will be what is recorded at the randomization visit (Visit 2). If there are multiple available values on the same day and the recorded times cannot identify which value is the last measurement, then the value recorded during the randomization visit (Visit 2) will generally be used as the baseline value. However, if the assessment is only conducted on Visit 1 prior to the first dose of study intervention, then Visit 1 is considered as the scheduled visit; if the assessment is done in both Visit 1 and Visit 2 prior to the first dose of study intervention, then Visit 2 is considered as the scheduled visit. If no scheduled visits are available, then all measurements collected before first dose of study intervention will be used and the average value will be used as the baseline value. If multiple values are available from both scheduled and unscheduled visits, the average value of values taken from scheduled visits will be used as the baseline value.

Post-baseline is defined as any assessments performed after the first dose of study intervention.

Change from baseline will be calculated as the value at the post-baseline visit of interest minus the baseline value. For the post-treatment follow-up period, the baseline value is defined as the last non-missing assessment on or prior to entering the post-treatment follow-up period, that is, on or prior to the Week 12 visit, or the EDV (including EDV). For participants randomized to placebo, Week 12 (Visit 5), or the last available post-baseline assessment if Visit 5 is not available will be used as the scheduled baseline visit for the LY3541860 treatment period.

Protocol-defined visit windows are defined as ± 3 days for Visit 3 (Week 2) until Visit 11 (Week 36), and ± 7 days for Visits 801 and 802. If there are data within the protocol-defined window, those data will be used in by-visit analyses. If a protocol-defined visit is missing, the nearest unscheduled visit data that exists will be mapped to that visit and will be included in by-visit analyses. If two unscheduled visits are equidistant to a missing visit, the earlier unscheduled visit will be used.

4.1.3. Population for Analysis

Efficacy analyses will be conducted on the mITT analysis set, unless otherwise specified, and will combine efficacy data collected in Phase 2a and Phase 2b, as appropriate. Separate efficacy analyses by study phases may be conducted on the mITT analysis set if deemed necessary.

Safety summaries and analyses will be conducted on the safety analysis set by study phases.

Analysis set definitions are detailed in Section 3. All participants will be included in individual participant data listings.

4.1.4. Summary of Intercurrent Events

Participants with intercurrent events (i.e., subjects who use prohibited medication or discontinue study intervention) will be summarized by event type for each phase, treatment arm and overall. The number of participants without intercurrent events will also be summarized by event type, for each treatment arm and overall.

4.1.5. Statistical Modeling Considerations

4.1.5.1. Mixed Model Repeated Measures (MMRM)

The following endpoints will be analyzed using an MMRM:



Treatment group, baseline value of the endpoint, baseline stratification factors, visit (as a categorical variable), the interaction of treatment-by-visit, and the interaction of baseline value-by-visit will be included in the model as fixed effects. Type III sums of squares for the LS means will be used for all statistical comparisons.

An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If this analysis fails to converge, the following structures will be tested in this pre-specified order: CCI The first covariance structure that converges using this prespecified order will be used. The Kenward-Roger method will be used to estimate the degrees of freedom.

The following results will be presented from fitted models for each endpoint:

- Observed means and SD, by treatment arm
- LS means and 95% CI from the fitted model, by treatment arm
- Between-treatment effect:
    - LS mean difference, 95% CI and p-value for treatment comparison

CCI



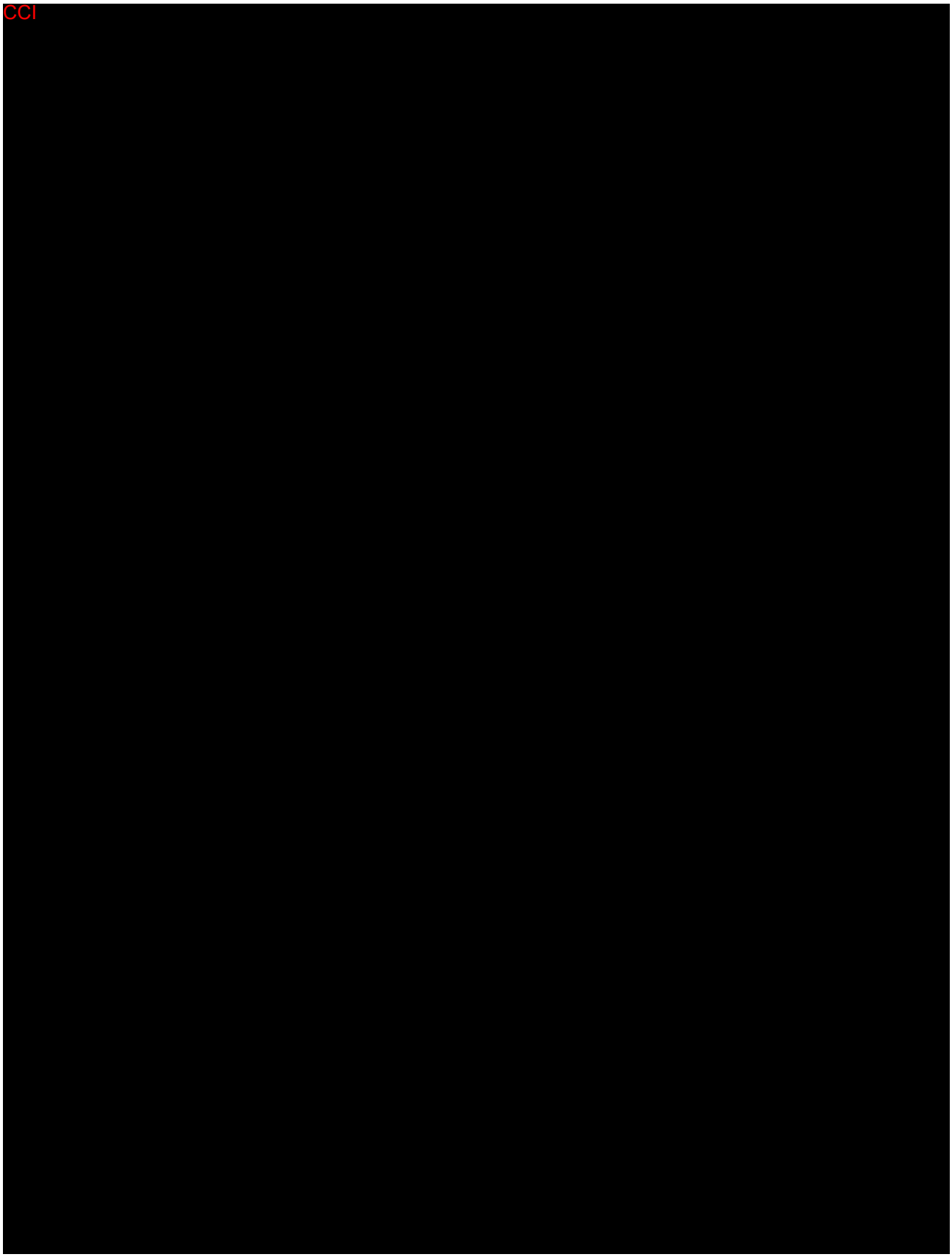
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4.1.6. Timing of Primary Analyses

Primary analysis will be performed after database lock after Last Participant Last Visit (LPLV) of each phase.

4.1.7. Timing of Interim Analyses

Interim analyses may be conducted for the study and the timing is detailed in Section 4.8.

4.1.8. Statistical Software

Statistical analysis will be performed using either SAS version 9.4 and higher or the R Project for Statistical Computing version 4.0.0 and higher.

4.1.9. Handling of Missing Data

For statistical analyses, the primary efficacy variable will be the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12. The average per scan is used to minimize effects of missing data. No adjustments for missing data will be performed for this analysis. Similar analyses were performed for other lesion-count endpoints as well.

4.2. Participant Dispositions

Participants that are excluded from the mITT and Safety analysis sets will be summarized by reason, treatment group and overall. A supporting listing using the Screened analysis set will be provided with unique subject ID, treatment arm, the analysis set they are excluded from, and the reason for exclusion.

The number and percentage of participants who discontinued screening, the reason for discontinuing screening, and the criterion failed for screen failures will be summarized based on the Screened analysis set.

A summary of participant disposition by treatment and overall for Phase 2a and Phase 2b will include the following counts of participants:

- Screened Analysis Set
  - Participants in mITT and Safety analysis sets
  - Participants screened but not randomized
  - Participants randomized but not treated
  - Participants randomized and treated
- mITT Analysis Set
  - Treatment disposition:
    - Participants missing treatment completion status/treatment and are ongoing
    - Participants who completed all treatment visits
    - Participants who discontinued treatment early and their reasons
  - Study disposition:
    - Participants that have study follow-up ongoing
    - Participants who completed study follow-up
    - Participants who did not complete study follow-up and their reasons for premature study withdrawal

A supporting listing for the mITT analysis set will include participants who discontinue treatment prematurely or withdraw from the study prematurely and their rationales.

4.3. Primary Analysis of Primary Estimand

4.3.1. Definition of endpoints

Phase 2a

The primary endpoint is the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.

Phase 2b

The primary endpoint is the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with each 1 dose of LY3541860 versus placebo.

For both phases, the cumulative number of new T1 GdE lesions will be obtained directly from MRI scan data at each scheduled visit (see Protocol Section 1.3). The new lesion count is defined by comparison with the baseline (Visit 1) scan; lesions that persist for more than 4 weeks will be counted only once.

4.3.2. Main analytical approach

The analysis will use the mITT analysis set.

For the primary estimand, any data collected after the first occurrence of an ICE will be excluded from the analysis (see Section 1.1.1) and will be considered as missing data. Our analytic approach assumes that any missing data are missing at random (MAR).

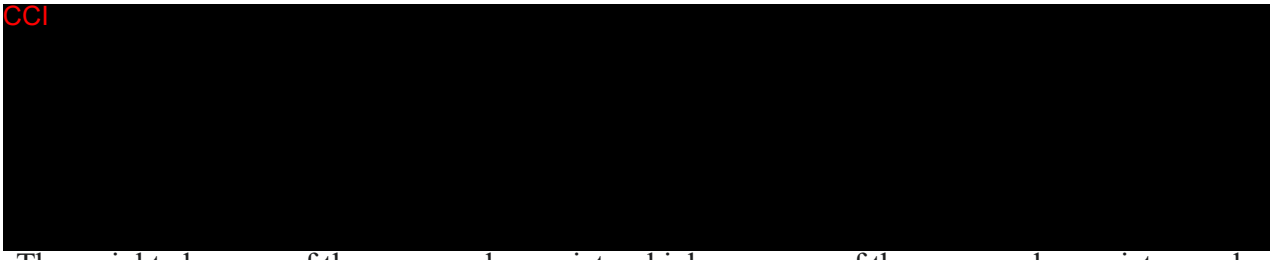
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4.3.2.2. Model Diagnostics

For both phases, model fit will be assessed graphically. Standardized Pearson residuals will be examined to detect outliers and assess the influence of single observations on the fitted model. Predicted counts will be compared with the density of a negative binomial distribution with given mean and dispersion to assess the degree to which the distributional assumptions are met.

For Phase 2b, additional descriptive modeling will be employed to compare the placebo arms between Phase 2a and 2b, to evaluate the degree to which differences between placebo arms may be impacting our estimation of the treatment effect. If the combined model does not converge, the model will be fit to the Phase 2b data alone.

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The weighted means of the measured covariates, higher powers of the measured covariates, and their interactions across treated and control groups will be compared to check for balance when using the AIPW estimator. The weights will also be examined to see if they are close to either zero or one.

4.3.3. Sensitivity Analysis

No planned sensitivity analysis will be performed.

4.3.4. Supplementary analyses

The primary endpoint analysis will be repeated using the supportive estimand (treatment policy) defined in Section 1.1.3.

4.4. Secondary Endpoints Analysis

4.4.1. Secondary Endpoints

4.4.1.1. Definition of endpoints

The following secondary endpoints are defined for each study phase:

Phase 2a

- The cumulative number of new or enlarging T2 lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.

Phase 2b

- The cumulative number of total T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with each 1 dose of LY3541860 versus placebo.
- The cumulative number of new or enlarging T2 lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with each 1 dose of LY3541860 versus placebo.

For both phases, new lesions are defined as in Section 4.3.1.

4.4.1.2. Main analytical approach

The analysis will be using the mITT analysis set.

For the secondary estimand, any data collected after the first occurrence of an ICE will be excluded from the analysis (see Section 1.1.1) and will be considered as missing data. Our analytic approach assumes that any missing data are missing at random (MAR).

All secondary endpoints will be analyzed using the same modeling approach as for the primary endpoint (see Section 4.3.2).

4.4.1.1. Model Diagnostics

See Section 4.3.2.2.

4.4.1.2. Sensitivity Analysis

No sensitivity analysis is planned.

4.4.1.3. Supplementary Analyses

The secondary endpoint analysis will be repeated using the supportive estimand (treatment policy) defined in Section 1.1.2.

4.5. Tertiary/Exploratory Endpoints Analysis

All exploratory endpoints follow the primary estimand strategy outlined in Section 1.1.1. Unless otherwise specified, exploratory endpoints are calculated separately by study phase.

4.5.1. Clinical Outcomes Endpoints

4.5.1.1. Definition of endpoints

To explore the efficacy of LY3541860 versus placebo on clinical outcomes in participants with RMS, the endpoints described below will be used. Each of these endpoints will be analyzed at each study visit, using data from baseline to that visit. For Phase 2b, data will be combined with Phase 2a as described in Section 4.3.2.

4.5.1.1.1. Annualized Relapse Rate over time

Annualized Relapse Rate (ARR) is defined as the number of confirmed relapses of multiple sclerosis / relapse exposure time in years:

- Confirmed relapses: a clinically relevant change in the EDSS performed by the Independent EDSS rater; that is, an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores (FS) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previously available rating (the last EDSS rating that did not occur during a relapse). EDSS score will be used as the sole source to confirm relapses. Only relapses that occur during the relapse exposure time period (defined below) will be counted as an event. Patients who do not have an event during the relapse exposure time period will be censored at the end of the relapse exposure time.
- Release exposure time in years: the time between the date of the first dose of study intervention to the prohibited medication start date, treatment discontinuation date, study discontinuation date, or final visit date, whichever is earliest. The final visit date is Week 36 for participants randomized to LY3541860 in Phase and Week 12 for participants randomized to placebo.

4.5.1.1.2. Proportion of relapse-free participants at over time

Defined as participants who remained relapse-free from baseline to end of study, where end of study is defined as the earliest of (ICE date, final visit date), then the responder status will be set as “Yes”. The final visit date is Week 36 for participants randomized to LY3541860 in Phase and Week 12 for participants randomized to placebo. A composite strategy will be used; if participants receive prohibited medication or discontinue study intervention, but do not have a relapse by the time of ICE event, they will be considered as having a relapse, therefore, the responder status will be set as “No”.

4.5.1.1.3. Change from baseline in EDSS over time

Defined as EDSS score at the scheduled visit minus the score at Screening.

4.5.1.2. Main analytical approach

4.5.1.2.1. ARR

The ARR will be modeled using the AIPW approach and results presented as described in Section 4.1.5.2, using number of confirmed relapses of multiple per sclerosis per year as the response and relapse exposure time in years entered into the model as an weight term.

4.5.1.2.2. Proportion of relapse-free participants at over time

The proportion will be modeled using logistic regression with the Firth penalized likelihood function (Firth 1993). The model will use relapse-free responder status (Yes/No) as the response and include treatment and stratification factors as fixed effects.

If deemed necessary, additional analyses (e.g., Fisher’s exact test) will be conducted to address sparse data or small sample sizes.

The following results will be presented:

- Observed proportions of relapse-free participants at end of study along with corresponding 95% asymptotic CI without continuity correction, by treatment arm
- Between-treatment effect:

- Difference in proportions and 95% CI derived using the Newcombe-Wilson method without continuity correction for each LY3541860 arm versus placebo
- Odds ratio, 95% CI and p-value for for each LY3541860 arm versus placebo

4.5.1.2.3. Change from baseline in EDSS over time

This endpoint will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline EDSS score, the interaction of baseline EDSS score by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow general rule specified in Section 4.1.5.2.

Model Results Presentation:

- Observed change from baseline in EDSS will be displayed using descriptive statistics, by treatment arm and phase
- The LS mean estimate in change from baseline in EDSS, standard error,95% CI and p-value for each scheduled visit by treatment arm and phase
- The LS mean difference between each LY3541860 dose vs placebo, standard error, 95% CI and p-value will be displayed at each scheduled visit



And other quantities defined as previously.

Phase 2b

The MMRM model described above will be extended to incorporate all four treatment arms and interaction terms for the combined Phase 2a/Phase 2b data.

4.5.2. MRI-related Endpoints

4.5.2.1. Definition of endpoints

To explore the effects of LY3541860 versus placebo on other MRI-related measures, the endpoints described below will be used. For Phase 2b, data will be combined with Phase 2a as described in Section 4.3.2.

- The cumulative number of total T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.
- Proportion of participants with no new T1 GdE lesions over time: defined as the proportion of participants with no new T1 GdE lesions at each post-baseline scheduled visit, compared with results 4 weeks prior.
- Number of new T1 hypointense lesions over time: defined as the number of new T1 hypointense lesions at each post-baseline scheduled visit, compared with baseline.
- Brain volume over time: percentage change from baseline in the brain volume for each post-baseline visit
- Paramagnetic rim lesions over time: number of paramagnetic rim lesions at each post-baseline scheduled visit, compared with baseline
- Thalamic volume over time: percentage change from baseline in the thalamic volume for each post-baseline visit

4.5.2.2. Main analytical approach

All tertiary/exploratory analyses will use the mITT analysis set.

4.5.2.2.1. *Cumulative number of total T1 GdE lesions*

The cumulative number of total T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 are defined as in Section 4.3.1 .

Any data collected after the first occurrence of an ICE will be excluded from the analysis (see Section 1.1.1) and will be considered as missing data. Our analytic approach assumes that any missing data are missing at random (MAR).

All secondary endpoints will be analyzed using the same modeling approach as for the primary endpoint (see Section 4.3.2).

4.5.2.2.2. *Proportion of participants with no new T1 GdE lesions over time*

Participants with no new T1 GdE lesions at each visit compared to the previous visit will be categorized as “Yes”. A composite strategy will be used; participants who receive prohibited medication or discontinue study intervention prior to (or at the visit) will be categorized as “No”.

The proportion will be modeled using logistic regression with the Firth penalized likelihood function (Firth 1993) as described in Section 4.5.1.2.2.

4.5.2.2.3. *Number of new T1 hypointense lesions over time*

The number of new T1 hypointense lesions at each post-baseline scheduled visit, compared with baseline will be analyzed using the AIPW estimator using new T1 hypointense lesions per scan as the response and the total number of MRI scans at the corresponding visit as the weight term. Section 4.1.5.2 describes the process model results representation.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.2.2.4. *Paramagnetic rim lesions over time*

The number of new paramagnetic rim lesions at each post-baseline scheduled visit, compared with baseline will be analyzed using the AIPW estimator using new paramagnetic rim lesions per scan as the response and the total number of MRI scans at the corresponding visit as the weight term. Section 4.1.5.2 describes the process model results representation.

The hypothetical strategy, as discussed in Section 1.1.3.2 will be used for ICEs.

4.5.2.2.5. *Brain volume over time*

Percentage change of brain volume over time will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline brain volume, the interaction of baseline brain volume by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.2.2.6. *Thalamic volume*

Percentage change of thalamic volume over time will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline thalamic volume, the interaction of baseline thalamic volume by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.3. Patient Reported Outcomes

4.5.3.1. Definition of endpoints

- Change from baseline in fatigue-related symptoms as measured by the symptoms domain of the FSIQ-RMS over time

- Change from baseline in fatigue-related impacts as measured by the impact subscales of the FSIQ-RMS over time

4.5.3.2. Main analytical approach

4.5.3.2.1. *Change from baseline in fatigue-related symptoms*

Change from baseline in fatigue-related symptoms over time will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline fatigue-related symptoms, the interaction of baseline fatigue-related symptoms by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.3.2.2. *Change from baseline in fatigue-related impacts*

Change from baseline over time in the impact subscales of the FSIQ-RMS will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline subscale score, the interaction of baseline subscale score by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.4. Physical Activity

4.5.4.1. Definition of endpoints

Mean change from baseline over time in:

- Daily steps count
- Daily average movement intensity
- Average movement intensity in most active 10-hr window

For each of these endpoints:

- Baseline value is defined as the average of the non-missing assessments in the last 7 days prior to the date of first study drug administration.
- Post-baseline values collected after first study drug administration will be defined as the average of the last 7 days prior to the date of the study visit (not inclusive of the visit day).

There must be at least 4 non-missing daily measurements in the 7 days indicated. If there are less than 4 non-missing daily assessments collected prior to the date of first study drug

administration, then the value will be designated as missing. If there are multiple assessments collected on the same day, only the first collected record will be used.

4.5.4.2. Main analytical approach

4.5.4.2.1. *Mean change from Baseline Over Time in Daily Step Counts*

Mean change from baseline over time in daily step counts will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline mean step counts, the interaction of baseline mean step count by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.4.2.2. *Daily average movement intensity*

Mean change from baseline over time in daily average movement intensity will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline daily average movement intensity, the interaction of baseline daily average movement intensity by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.5.4.2.3. *Average movement intensity in most active 10-hr window*

Mean change from baseline over time in average movement intensity in most active 10-hr window will be analyzed using MMRM as discussed in Section 4.1.5.1, assuming MAR assumptions.

The model will include factors for treatment, visit (as categorical variable), randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), baseline average movement intensity in most active 10-hr window, the interaction of baseline average movement intensity in most active 10-hr window by visit, and the interaction of treatment by visit as fixed factors. The details of covariance matrix selection will follow the general rules specified in Section 4.1.5.1.

The hypothetical strategy, as discussed in Section 1.1.3.2, will be used for ICEs.

4.6. Safety Analyses

All safety data will be descriptively summarized by actual treatment groups and analyzed based on the Safety analysis set, separately for Phase 2a and Phase 2b, unless specified otherwise. Patients will be summarized according to the treatment that they actually received. The safety analyses include exposure to treatment received, AEs, safety in special groups and

circumstances, including, but not limited to, adverse events of special interest, laboratory analytes, and vital signs.

For tables that summarize events (such as AEs, categorical lab abnormalities, shift to maximum severity), post-last dose follow-up data will be included in the Safety analysis period. Follow-up data is defined as all data occurring up to and including 30 days after last dose of treatment. In general, for laboratory analytes and vital signs, planned (scheduled visits) and unplanned (unscheduled visits) measures are used for categorical analyses and planned (scheduled visits) measures are used for continuous by-visit analyses including change from last baseline to last post-baseline.

The following statistical methods will be used for Safety analyses unless otherwise noted:

- Fisher's exact test will be used for treatment comparisons of proportions, and risk difference with corresponding 95% CI and p-value.
- Treatment differences in mean change for continuous measurements will be assessed using an ANCOVA (analysis of covariance) model fitting "baseline" as a covariate. Type III sums of squares will be used.

Two-sided p-values are often reported yet should not be over-interpreted. For safety analyses, they are used primarily as a flagging mechanism. Also medical judgement may be used in drawing safety inferences/conclusions based on the totality of data.

4.6.1. Extent of Exposure

Duration of exposure is defined as the total duration a participant is exposed to the randomized treatment and is calculated as last dose date – first dose date +1, as documented in the case report form (CRF) page. If last dose date is missing, and the Drug accountability CRF pages indicate the participant has taken the treatment, then the date following the visit date of Drug accountability page will be used as the last dose date (date of drug accountability visit + 1). Missing doses are not considered in the calculation. The duration of exposure (in weeks) will be calculated as duration of exposure (in days)/7.

The duration of exposure in days and in weeks will be summarized descriptively. The duration of exposure (in weeks) will also be summarized by category (≤2 Weeks, ≤4 Weeks and >2 Weeks, ≤8 Weeks and >4 Weeks, ≤12 Weeks and > 8 Weeks, etc. through >32 Weeks and ≤36 Weeks).

For participants randomized to placebo, there will be two durations of exposure: one for exposure to placebo, the other for exposure to active treatment.

Total patient-years of exposure (PYE) to study drug will be reported for each treatment group for overall duration of exposure. Overall exposure will be summarized in total PY which is calculated according to the following formula:

Total patient-years of exposures (PYE) =
sum of duration of exposure in days for all patients in treatment group) / 365.25

4.6.2. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study

intervention. All AEs will be collected from Screening until the Safety Follow-up visit. All AE summary tables will be displayed by treatment arm.

4.6.2.1. General common rules for AEs

AE data will be summarized by actual treatment groups and analyzed based on the Safety analysis set, separately for Phase 2a and Phase 2b.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Eli Lilly at the time of database lock. Selected notable AEs of interest may be reported using high-level terms or Standardized Medical Dictionary for Regulatory Activities Queries.

A treatment-emergent adverse event (TEAE) is defined as an event that either first occurred or worsened in severity after the first dose of study treatment and on or prior to the last visit date during the analysis period. The analysis period is defined as the treatment period plus up to 30 days off-drug follow-up time.

The MedDRA Lowest Level Term (LLT) will be used in defining which events are treatment-emergent. The maximum severity for each LLT during the baseline period up to first dose of the study medication will be used as baseline. If an event with missing severity is pre-existing during the baseline period and persists during the treatment period, then the baseline severity will be considered mild for determining treatment-emergence (that is, the event is treatment-emergent if the severity is coded moderate or severe postbaseline and not treatment-emergent if the severity is coded mild postbaseline). If an event occurring postbaseline has a missing severity rating, then the event is considered treatment-emergent unless the baseline rating is severe, in which case the event is not a treatment-emergent.

No imputation will be used if the start/end date of the AE is completely missing. Otherwise, if an AE start date is incomplete, an imputation algorithm will be used to classify the AE as below:

- UK-MMM-YYYY:
    - If the month and year are the same as the first dose of study treatment month and year, and the end date is on or after the first dose of study treatment, then impute to the date of the first dose of study treatment.
    - If the month and year are before the month and year of the first dose of study treatment, then impute to the first day of the month MMM. If after imputation the AE start date > AE end date, then impute to the AE end date.
    - If the month and year are after the month and year of the first dose of study treatment, then impute to the first day of the month MMM.
- DD-UKN-YYYY:
    - If the year is the same as the year of first dose of study treatment, and the end date is on or after the first dose of study treatment, then impute to the date of the first dose of study treatment.
    - If the year is the same as the year of first dose of study treatment, and the end date is prior to the first dose of study treatment, then impute to the AE end date.
    - If the year is different from the year of first dose of study treatment, then impute to 01-JAN-YYYY of the collected year.

- UK-UKN-YYYY:
    - If the year is the same as the first dose of study treatment, and the end date is prior to the first dose of study drug, then impute to the AE end date.
    - If the year is the different than the first dose of study treatment, then impute to 01-JAN-YYYY of the collected year.

No imputation of AE end dates will be performed.

If the start date and end date for an AE are completely missing, the AE will be considered as TEAE. If the start date of the AE is completely missing and the end date is on or after the first dose date of study treatment, the AE will also be considered as TEAE.

If the severity is missing for one of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences within the same PT. If the severity is missing for all the occurrences, the severity will be presented as severe in the summary table but as missing in the listing.

If the AE has relationship to study treatment as missing, it will be presented as related in the summary table but as missing in the listing.

4.6.2.2. Analysis of TEAEs

4.6.2.2.1. *Overview of TEAEs*

An overview summary of TEAEs will be presented by treatment. Number and percentage of participants and number of events for each category below will be provided:

- Any AEs
- AEs by maximum severity (mild, moderate, severe)
- Death
- Serious AEs (SAEs)
- Discontinuation from the study or study treatment due to adverse event (including death)

4.6.2.2.2. *Any AEs*

The number and percentage of participants with at least one TEAE will be summarized by treatment group and in the 2 formats below:

- By MedDRA PT nested within SOC with decreasing frequency in SOC, and events ordered within each SOC by decreasing frequency in the maximum LY3541860 group.
- By MedDRA PT with events ordered by decreasing frequency in the maximum LY3541860 group.

At each level of summarization, a participant is counted once if the participant reported one or more events. If the incidence for any two or more SOCs or PTs is equal, the SOCs or PTs will be presented in alphabetical order.

4.6.2.2.3. *Serious Adverse Events*

With the International Conference on Harmonisation (ICH) E2A guideline, a SAE is any AE that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threating experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

The number and percentage of participants who experience at least one SAE will be summarized by treatment group and PT nested within SOC, sorted by decreasing frequency in the maximum LY3541860 group within SOC and then by PT during the Safety analysis period.

An individual listing of all SAEs will be provided, including participant identification number, the treatment, site number, age, sex, race, SOC, PT, reported term, AE event start date, stop date, severity, action taken, outcome, relationship to study treatment, relationship to non-study treatment, if event causes study treatment discontinuation (date of treatment discontinuation), and if event causes study discontinuation (date of study discontinuation).

4.6.2.2.4. *TEAEs by maximum severity*

The severity of each AE ("Mild", "Moderate", "Severe") is determined by response of "What was the severity of the adverse event?" on the Adverse Event CRF page.

The number and percentage of patients experiencing any TEAE by maximum severity category will be summarized by treatment group. These TEAEs will be summarized by MedDRA PT nested within SOC, as well as by PT, in the same manner as the summary for any TEAEs in Section 4.6.2.2.2.

At each level of summarization, if a participant reported multiple occurrences of the same TEAE, only the most severe will be considered.

4.6.2.2.5. *Adverse Events Reported as Reasons for Temporary Study Treatment Interruption*

A TEAE leading to study treatment interruption is defined as the response of "Drug Interrupted" for the question "What action was taken with study treatment?" on the Adverse Event CRF page. The number and percentage of participants with at least one AE reported as a reason for temporary study treatment interruption will be provided. Additionally, the summary will be presented by SOC and PT, in the same manner as the summary for any TEAEs in Section 4.6.2.2.2.

A listing of all TEAEs leading to temporary study treatment discontinuation will be provided with same details as the SAE listing in Section 4.6.2.2.3.

4.6.2.2.6. *Adverse Events Reported as Reasons for Permanent Study Treatment Discontinuation*

A TEAE leading to study treatment discontinuation is defined as the response of "Drug Withdrawn" for the question "What action was taken with study treatment?" on the Adverse Event CRF Page.

The number and percentage of participants with at least one reported as a reason for permanent study treatment discontinuation will be provided. Additionally, the summary will be presented by SOC and PT, in the same manner as the summary for any TEAEs in Section 4.6.2.2.2.

A listing of all TEAEs leading to permanent study treatment discontinuation will be provided with same details as the SAE listing in Section 4.6.2.2.3.

4.6.2.2.7. *Death*

Deaths are identified by the response of "Fatal" for the question "What was the outcome of this adverse event?" on the Adverse Event CRF page.

A listing of all deaths will be provided, with the same details as the SAE listing in Section 4.6.2.2.3, with additional information including death date, time from first dose of study drug to death, and time from last dose of study drug to death (if participant had discontinued study intervention)

4.6.2.2.8. *Common TEAEs*

Common TEAEs are defined as TEAEs that occurred in ≥5% (before rounding) of patients in any treatment group including placebo. The number and percentage of patients with common TEAEs will be summarized by treatment using MedDRA PT ordered by decreasing frequency.

4.6.3. Safety Topics of Interest

Safety topics of interest include adverse events of special interest (AESI) or topics anticipated to be requested by a regulatory agency for any reason. An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the sponsor is required. Such events may require further investigation in order to characterize and understand them. The following AEs will be considered as AESIs in this trial:

- Hypersensitivity reactions, including infusion-related reactions
- Infections, including opportunistic infections
- Infusion site reactions
- Suicidal ideation and behavior

See Protocol Section 8.3.5 for details.

AESIs will be summarized overall and by AESI category and PT. At each level of summarization, a participant is counted once if the participant reported one or more events. The AESIs will be ordered by decreasing frequency within SOC. Number and percentage of participants will be provided. A listing of AESIs will also be provided.

Only treatment related AESIs will be summarized.

4.6.3.1. Hypersensitivity reactions, including infusion-related reactions

A search for relevant events related to hypersensitivity reactions will be performed using the following Standard MedDRA Queries (SMQs):

- Anaphylactic reaction SMQ (20000021)
- Hypersensitivity SMQ (20000214)
- Angioedema SMQ (20000024)

The Anaphylactic reaction SMQ consists of a narrow search containing PTs that represent core anaphylactic reaction terms, a broad search that contains additional terms (signs and

symptoms possibly indicative of anaphylactic reaction) that are added to those included in the narrow search, and an algorithm. The algorithmic approach comprises 1 or more events associated with an individual administration of study drug, where the events include:

- A narrow term from the SMQ (Category A of the SMQ)
- Multiple terms from the SMQ, comprising terms from at least 2 of the following categories from the SMQ:
  - Category B - (Upper Airway/Respiratory signs and symptoms)
  - Category C - (Angioedema/Urticaria/Pruritus/Flush signs and symptoms)
  - Category D - (Cardiovascular/Hypotension signs and symptoms).

Within the multiple terms approach using broad terms, it is important to recognize that occurrence of these events should be nearly coincident and develop rapidly after exposure to an antigen; a window wherein onset or severity change of the events occur within 2 days of one another is allowed. Events that satisfy the queries will be listed, by temporal order within patient ID, and will include SOC, PT, SMQ event categorization including detail on the scope (narrow, algorithmic, or broad), reported AE term, AE onset and end dates, severity, seriousness, outcome, etc.

The following analyses are contingent upon there being sufficient numbers of events to warrant further examination beyond the listing specified above.

The number and percentage of patients reporting a TEAE for the following will be analyzed:

- Any narrow or algorithmic term from any one of the 3 SMQs indicated above (i.e., combined search across narrow portions of all 3 SMQs, and anaphylaxis algorithm for Anaphylactic reaction SMQ)
- Any narrow scope term within each SMQ, separately (i.e., narrow SMQ search)
- Any term within each SMQ, separately (i.e., broad SMQ search)

4.6.3.2. Infections, including opportunistic infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC as described below.

Treatment-emergent infections will be analyzed according to various groups of infectious events including:

- All infections:
  All PTs in the Infections and Infestations SOC
- Serious infections:
  All PTs in the Infections and Infestations SOC that meet SAE criteria
- Infections that result in permanent study drug discontinuation:
  All PTs in the Infections and Infestations SOC resulting in permanent study drug discontinuation

For each infection event, the number and percentage of participants with at least one infection event will be summarized by treatment group, and additionally, the frequency for each PT will be provided, ordered by decreasing frequency in the LY3541860 CCI mg treatment group. The

summary will be repeated for serious infections and infections that result permanent in study drug discontinuation. A listing of infections by MedDRA PTs will also be produced.

Medical will identify and review opportunistic infections. A summary of opportunistic infections based on MedDRA PTs will be produced in the same manner as described above. A listing of opportunistic infections based on MedDRA PTs during the study will also be provided.

4.6.3.3. Infusion site reactions

Infusion site reactions (ISRs) are AEs localized to the immediate site of the administration of a drug. The evaluation of study drug related ISRs will be through the unsolicited reporting of ISR TEAEs and through the use of an Infusion Site Reaction Follow-up Form completed by the investigator for each ISR reported.

Infusion site reactions will be defined using the following MedDRA High Level Term (HLT): Infusion site reaction, excluding certain Preferred Terms (PTs) (e.g., those PIs related to joint).

Analyses will include:

TE ISR, HLT and PT

The additional data collected on the ISR follow-up form will be summarized in two distinct ways: at the patient level and at the event level. A by-patient listing of these data will be provided.

4.6.3.4. Suicidal ideation and behavior , as identified in the Columbia–Suicide Severity Rating Scale (C-SSRS)

C-SSRS is a questionnaire that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period. It includes the following outcome categories with binary responses (yes/no):

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Suicidal Ideation Score is a numerical score derived from the C-SSRS categories, defined as the maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. If no ideation is present, a score of 0 is assigned.

The following endpoints are of interest:

- Suicidal ideation: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.
- Treatment-emergent suicidal ideation compared to all prior history: An increase in the maximum suicidal ideation score during treatment compared to baseline.
- Emergence of serious suicidal ideation compared to all prior history: An increase in the maximum suicidal ideation score to 4 or 5 during treatment from no suicidal ideation (scores of 0) at baseline.
- Treatment-emergent serious suicidal ideation compared to all prior history: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from not having serious suicidal ideation (scores of 0-3) at baseline.
- Improvement in suicidal ideation at Week 12 compared to baseline: a decrease in suicidal ideation score at Week 12 from the baseline measurement.
- Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (Categories 6-10) during treatment from not having suicidal behavior (Categories 6-10) at baseline.

The number and percentage of participants with suicidal ideation, suicidal ideation by categories, suicidal behavior, suicidal behavior by categories, suicidal ideation or behavior, and self-injurious behavior without suicidal intent will be summarized by treatment arm.

The number and percentage of participants with treatment-emergent suicidal ideation compared to all prior history, emergence of serious suicidal ideation compared to all prior history, treatment-emergent serious suicidal ideation compared to all prior history, improvement in suicidal ideation at Week 12 compared to baseline, and emergence of suicidal behavior compared to all prior history will also be summarized by treatment arm.

A listing of participants with suicidal ideation, suicidal behavior or self-injurious behavior without suicidal intent will also be provided.

4.6.4. Device Product Complaints

A product complaint (PC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention.

An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

A listing of all device product complaints, inclusive of device product complaints that lead to an AE or that could have led to an SAE had intervention not been taken will be provided. Additional summaries will be provided as deemed appropriate.

4.6.5. Additional Safety Assessments

Additional safety data will be summarized by actual treatment groups and analyzed based on the Safety analysis set, separately for Phase 2a and Phase 2b.

4.6.5.1. Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained for Baseline, Weeks 4, 12, 24, 36, and follow-up scheduled visits using a local ECG machine. ECG data will not be analyzed.

4.6.5.2. Clinical Safety Laboratory Tests

The following laboratory tests and vital signs will be analyzed using standard international units:

- **Hematology**
  - Hemoglobin
  - Hematocrit
  - Erythrocyte count (RBCs – red blood cells)
  - Mean cell volume
  - Mean cell hemoglobin
  - Mean cell hemoglobin concentration
  - Absolute neutrophil count (segmented and bands) (calculation)
  - Leukocytes (WBCs –- white blood cells)
  - Differential
  - Percent and absolute count of
    - Neutrophils, segmented
    - Lymphocytes
    - Monocytes
    - Eosinophils
    - Basophils
  - Platelets
  - Cell morphology (RBCs and WBCs)

- **Clinical Chemistry**
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total bilirubin
  - Direct bilirubin
  - Alkaline phosphatase
  - Alanine aminotransferase
  - Aspartate aminotransferase
  - Gamma-glutamyl transferase
  - Blood urea nitrogen
  - Creatinine
  - Creatine kinase
  - Uric acid

  - Total protein
  - Albumin
  - Calcium
  - Phosphorus
  - Glucose
  - Amylase

- **Lipid Panel**
  - High-density lipoprotein
  - Low-density lipoprotein
  - Very low-density lipoprotein
  - Cholesterol
  - Triglycerides

- **Coagulation**
  - Prothombrin time, INR
  - Partial thromboplastin time

- **Urinalysis**
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Bilirubin
  - Urobilinogen
  - Blood
  - Nitrite
  - Urine leukocyte esterase
  - Microscopic examination of sediment

- **Hormones (female)**
  - Serum pregnancy
  - Urine pregnancy
  - Follicle-stimulating hormone

All laboratory tests will be presented using the International System and United States conventional units.

Only results from central laboratory will be used for analysis. When a participant has more than one result from the central laboratory for the same laboratory parameter on the same date, the average of the results will be used. For the same laboratory parameter, if a participant has more than one result on different dates for the same scheduled visit, the result closest to the scheduled visit will be used for the scheduled visit. When the results for the same scheduled visit are equidistant, the last value will be used.

Numeric clinical laboratory tests results will be summarized by observed value (for each scheduled visit) and change from baseline (for each post-baseline scheduled visit), by treatment arm.

Additionally, a box plot will summarize the numeric clinical laboratory test results by observed value and change from baseline for each scheduled visit, by treatment arm.

For the categorical laboratory analyses (shift and treatment-emergent) described below, the analysis period is defined as the treatment period plus 30 days off-drug follow-up time. The analysis period for the continuous by-visit laboratory analyses including change from baseline by visit and to last observation is defined as the treatment period excluding off-drug follow-up time.

Categorical laboratory analyses not described elsewhere will include the number and percentage of patients who shift from normal/high to low (i.e., treatment-emergent low) and the number and percentage of patients who shift from normal/low to high (i.e., treatment-emergent high).

4.6.5.3. Vital Signs and Physical Characteristics

For the treatment-emergent categorical analyses of vital signs, the analysis period is defined as the treatment period plus 30 days off-drug follow-up time. The analysis period for the continuous by-visit laboratory analyses including change from baseline by visit and to last observation is defined as the treatment period excluding off-drug follow-up time.

The planned summaries for vital signs (systolic blood pressure [BP], diastolic BP, pulse, weight, BMI, temperature) are listed in **Table 3** and are described more fully in compound-level safety standards and in the vitals-related PhUSE (Pharmaceutical Users Software Exchange) white papers (PhUSE, Analyses and Displays Associated with Measures of Central Tendency - Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte MEasurements in Phase 2-4 Clinical Trials and Integrated Submission Documents, 2013); (PhUSE, Analyses and Displays Asssociated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte MEasurements in Phase 2-4 Clinical Trials and Integrated Summary Documents, 2015).

Box plots will provide the summary for observed values by visit and change from baseline values by visit and at last observation, excluding records collected during the follow-up period.

Additionally, a summary table with the number and percentage of patients who shift from normal/high to low (i.e., treatment-emergent low) and the number and percentage of patients who shift from normal/low to high (i.e., treatment-emergent high) will also be provided. For weight, the number and percentage of patients are based on a percentage gain/loss that exceeds defined limits. The limits are based on literature defined in Table 3.

Table 3. Parameter Definitions Related to Vital Signs

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15

Weight (kg)	(Loss) decrease ≥ 7%	(Gain) increase ≥ 7%
Temperature	< 96 degrees F and decrease ≥ 2 degrees F	≥ 101 degrees F and increase ≥ 2 degrees F

4.7. Other Analyses

4.7.1. Receptor Occupancy monitoring

Receptor occupancy (RO) will be used to measure how well LY drug binds with receptor on the samples. All participants across all time points will be split into two samples (one original free form, one saturated with high LY) to serve as internal controls.

Occupancy will be calculated for each participant at each timepoint follows:

- $RO = \frac{(Max\ Readout - Sample\ Readout)}{(Max\ Readout - Min\ Readout)}$
- Max Readout is defined as the pre-dose original free form sample readout for a given participant. If a participant is missing this sample readout, then it will be imputed as the average pre-dose sample readout from the placebo arm.
- Sample Readout is defined as the original free form sample readout for a given participant at a given timepoint.
- Min Readout is defined as the saturated with high LY sample readout for a given participant at a given timepoint.
- If a Sample Readout or Min Readout is missing for a given participant at a given timepoint, then RO will be set to missing.

The unblinded PPD team will calculate occupancy and identify participants who fall below 50% at any post-baseline visit.



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4.7.3. Subgroup analyses

Subgroup analyses will be performed separately for Phase 2a and Phase 2b on the primary endpoint with hypothetical estimand on mITT set, with below subgroups:

- Geographic region (North America, Other)
- Presence of T1 Gd-enhanced weighted lesions (0, ≥1)
- Baseline EDSS (≤3.5, >3.5)

Additional subgroups might be added in the future if necessary.

The AIPW estimator analysis used for the primary endpoint (Section 4.3.2.1) will be repeated for the subgroup analysis by repeating the analysis performed for the primary endpoint on each subgroup level, removing the subgroup variable in the model if it is also in the stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)). Model representation and results will be the same as the primary endpoint, by subgroup levels.

Separately, a negative binomial regression (with a log-link) will be used for an additional subgroup analysis. The model will use new T1 Gd-enhancing lesions per scan as the response, and the weight term will be defined by the total number of MRI scans of Week 4, Week 8 and Week 12. The model will include treatment, randomization stratification factors (i.e., Geographic region (North America vs Other) and Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)), subgroup and subgroup-by-treatment interaction. The subgroup variable will be removed from the model if it is also a stratification factor.

The model presentation for the negative binomial regression subgroup analysis will present the p-value of the subgroup by treatment interaction only.

4.8. Interim Analyses

4.8.1. Phase 2a

Up to three interim analyses may be conducted during the Phase 2a period prior to the primary lock for benefit/risk evaluation and internal business decision making. At the discretion of the sponsor, the prespecified interim analyses may not be conducted. An assessment of unblinded interim data will be conducted by an internal assessment committee (IAC) with a limited number of prespecified members who do not have direct site contact or data entry or validation responsibilities.

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Results of interim analyses from the Phase 2a portion of this study will determine whether the Phase 2b portion will be initiated and, if so, what doses of LY3541860 will be used.

4.8.2. Phase 2b

Up to 3 interim analyses may be conducted during Phase 2b period prior to the primary database lock for benefit/risk evaluation and internal business decision making. At the discretion of the sponsor, the prespecified interim analyses below may not be conducted. An assessment of unblinded interim data will be conducted by an IAC with a limited number of prespecified members who do not have direct site contact or data entry or validation responsibilities.

The first interim may be conducted when approximately 50 patients have reached or had the opportunity to reach Visit 5 (Week 12). The second interim may be conducted when approximately 50 patients have reached or had the opportunity to reach Visit 8 (Week 24). The third interim may be conducted when all patients have reached or had the opportunity to reach Visit 8 (Week 24). The interims may be used to discontinue the trial due to futility, to evaluate benefit/risk, or for research and development business decisions. No adjustment of Type I error will be performed.

Relevant Phase 2a data may be considered for inclusion in the interim analyses in Phase 2b.

4.8.3. Data Monitoring Committee (DMC) or Other Review Board

Review board details will be added as appropriate.

4.9. Changes to Protocol-Planned Analyses

There are no changes to protocol-planned analyses.

5. Sample Size Determination

Phase 2a

Approximately 100 participants will be equally randomly assigned to LY3541860 CCI mg or placebo (approximately 50 participants per arm). All randomized participants in the mITT analysis set will be considered evaluable. At the time of primary outcome, the LY3541860 CCI mg and placebo groups will each have a sample size of approximately 45 participants, assuming 10% drop-out rate from the study intervention.

The sample size calculation is based on the primary efficacy estimand and its endpoint, the cumulative number of new T1 GdE lesions over Weeks 4, 8 and 12. Assuming CCI [redacted]

Phase 2b

Approximately 100 participants will be randomly assigned to either LY3541860 Dose Level 3, or LY3541860 Dose Level 4, or placebo in a ratio of 9:9:2. All randomized participants in the mITT analysis set will be considered evaluable.

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6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

AE: adverse event
AESI: adverse event of special interest
AIPW: Augmented Inverse Propensity Weight
ARR: annualized relapse rate , annualized relapse rate
BEAVER: BMA of Covariate Adjusted Negative-Binomial Dose-Response
BMA: Bayesian Model Averaging
BMI: body mass index
BP: blood pressure
CI: confidence interval
CRAN: Comprehensive R Archive Network
CRF: case report form
C-SSRS: Columbia–Suicide Severity Rating Scale
DMC: data monitoring committee
DREAMER: **D**ose **RE**sponse b**A**yesian **M**odel averaging
ECG: electrocardiogram
EDSS: Expanded Disability Status Score
EDV: early discontinuation visit
FDA: Food and Drug Administration
FS: functional scores
FSIQ-RMS: Fatigue Symptoms and Impact Questionnaire - Relapsing Multiple Sclerosis
GdE: gadolinium-enhancing
HLT: High Level Term
IAC: internal assessment committee
ICE: intercurrent event
IgG: immunoglobulin G
ISR: infusion site reaction
IV: intravenous
LLT: Lowest Level Term
LS: least squares
MAR: missing at random
MCP-Mod: Multiple Comparison Procedure - Modeling
MedDRA: Medical Dictionary for Regulatory Activity
mITT: modified intent-to-treat
MMRM: mixed model repeated measures
MRI: magnetic resonance imaging
MS: multiple sclerosis
NE: not estimable
NfL: neurofilament light
NONMEM: Non-linear Mixed Effects Modelling
PC: product complaint
PD: pharmacodynamic
PhUSE: Pharmaceutical Users Software Exchange

PK: .....pharmacokinetic
PT:.....Preferred Term
PYE:.....patient-years of exposure
RMS:.....relapsing multiple sclerosis
RO:..... receptor occupancy
SAE:..... serious adverse event
SAP:..... statistical analysis plan
SD: .....standard deviation
SE:..... standard error
SMQ:..... Standard MedDRA Query
SMQ:..... Standard MedDRA Query
SOC:..... system organ class
TEAE: ..... treatment-emergent adverse event

6.2. Appendix 2: Demographic and Baseline Characteristics

A summary will present demographic and baseline characteristics by treatment arm using mITT set, the following information will be included:

- Demographics
  - Sex (Female, Male)
  - Age (years)
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Baseline characteristics
  - Height (cm)
  - Weight (kg)
  - Body mass index (BMI) (kg/m^2)
  - Geographic region (North America, Rest of World)
  - Presence of T1 Gd-enhanced weighted lesions (0 or ≥1)
  - Baseline EDSS score
  - Baseline EDSS score category (<=3.5, >3.5)
  - Number of T1 Gd-enhancing lesions
  - Number of T2 lesions
  - Volume of T2 lesions
  - Normalized Brain volume
  - Number of T1 hypointense lesions

Age (years) is calculated using year of informed consent date – year of birth.

BMI is calculated as weight (kg) / [height (m)]^2.

6.3. Appendix 3: Prior and Concomitant Medication/Therapy

All medications will be coded according to the World Health Organization drug dictionary.

A prior medication/therapy is defined as those for which the end date is prior to the date of first study treatment.

A concomitant medication/therapy is defined as any medication that has a stop date that is on or after the date of first dose of study treatment.

Partial start/end dates for medication will be imputed using the following rule:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Impute to 01-MMM-YYYY. If the month and year are the same as the month and year of first dose of study treatment, then impute to the first dose date of study treatment.
- UK-UKN-YYYY: If the year is prior to the year of first dose of study treatment, impute to 01-JAN-YYYY of the collected year. If the year is the same as the year of first dose of study treatment, then impute to the date of first dose of study treatment.
- UK-UKN- UNKN: impute to date of first dose of study treatment.

Missing stop dates (where UK, UKN and UNKN indicate unknown or missing day, month, and year respectively):

- UK-MMM-YYYY: Impute to the last day of the month.
- UK-UKN-YYYY: Impute to 31-DEC-YYYY.
- UK-UKN- UNKN: Consider as ongoing and leave it missing.

The total number of concomitant medications and the number and percentages of participants with at least one concomitant medication will be summarized by treatment arm. The number and percentages of all concomitant medications will be summarized and listed by Anatomical Therapeutic Chemical (ATC) level 4 and preferred term. The summary will be repeated for Prespecified concomitant medications Acetaminophen / Paracetamol.

The summary described above will be repeated for the prior medications/therapies.

All summaries will be performed using the mITT set.

6.4. Appendix 4: Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. Study participant identification will be confirmed prior to the time of dosing. The dose, date, and time of each dose administered on site will be recorded in the source documents and will be provided to the sponsor as requested.

Overall treatment compliance will be summarized descriptively by treatment arm for mITT set, separately for Phase 2a and Phase 2b.

6.4.1. Rescue Medicine

The investigator should attempt to consistently maintain therapies or treatments for symptoms related to MS throughout the study.

Participants who experience an MS relapse during the study treatment period may, if judged clinically appropriate by the investigator, receive treatment with intravenous (IV) or oral corticosteroids. If a participant meets this criterion during the study treatment period, the decision to implement rescue medication is per the investigator's judgment and is not a protocol requirement. The standardized treatment regimen of 1 g IV methylprednisolone per day for a

maximum of 5 consecutive days should be used as warranted. Corticosteroids may be stopped or tapered over a maximum of 10 days, at the investigator's discretion. Participants experiencing relapse should not discontinue the treatment period due to the occurrence of a relapse alone, unless the investigator determines the participant has met any discontinuation criteria or the participant requests to discontinue.

6.4.2. Prohibited Therapy

Therapies listed in Protocol Section 5.2 (Exclusion Criteria #12, #13, #14, and #22) are not permitted during the study treatment period, except for systemic corticosteroids for the treatment of a relapse as described above.

6.5. Appendix 5: Protocol Deviations

Protocol deviations will be provided from clinical trial management system (CTMS) and categorized according to the rules document approved by Lilly. A table will summarize important protocol deviations in the mITT set and the number of participants with at least one important protocol deviation. A summary of deviations by deviation category, subcategory and deviation term will also be provided.

A listing will present all important protocol deviations, with subject identifier, site number, age, sex, geographic region, deviation category, subcategory and deviation term.

6.6. Appendix 6: Table for Efficacy Analysis

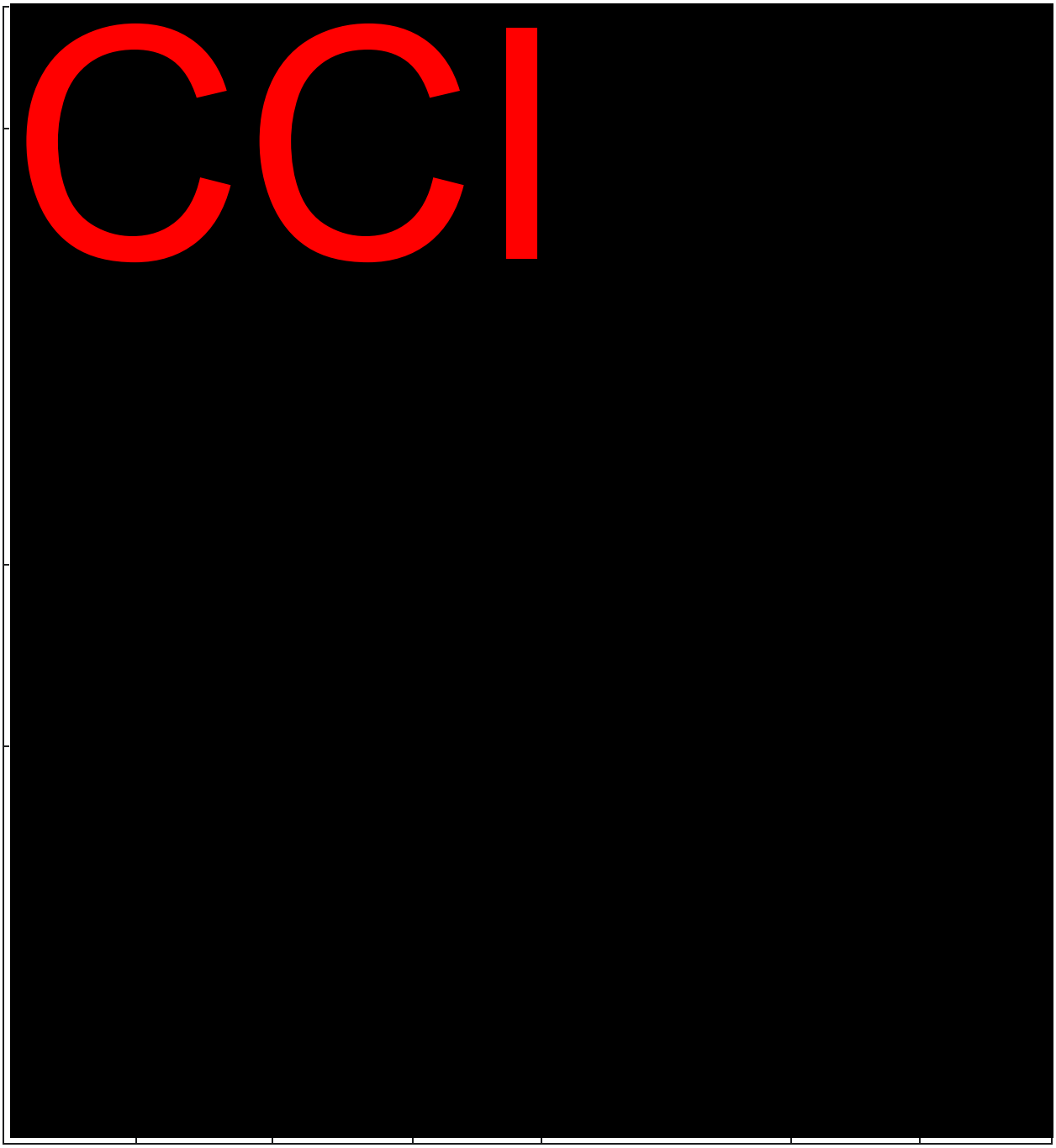
Table 4. Table for Efficacy Analysis

Measure	Endpoint	Estimand Strategy	Analysis Population	Comparison/Timepoint	Analysis Method	Analysis Type
MRI: New T1 GdE lesions	Cumulative number of new T1 GdE lesions over Weeks 4, 8, and 12	Hypothetical	mITT	Phase 2a: LY3541860 CCI mg vs. placebo	AIPW Estimation	Primary
		Treatment Policy	mITT	Phase 2a: LY3541860 CCI mg vs. placebo	AIPW Estimation; Negative binomial regression	Primary
		Hypothetical	mITT	Phase 2b: Each dose of LY3541860 vs. placebo	AIPW Estimation; Negative binomial regression	Primary
		Treatment Policy	mITT	Phase 2b: Each dose of LY3541860 vs. placebo	AIPW Estimation; Negative	Primary

					binomial regression	
MRI: Total T1 GdE lesions	Cumulative number of total T1 GdE lesions over Weeks 4, 8, and 12	Hypothetical	mITT	Phase 2a: LY3541860 CCI mg vs. placebo	Negative binomial regression	Secondary
		Treatment Policy	mITT	Phase 2a: LY3541860 CCI mg vs. placebo	Negative binomial regression	Secondary
		Hypothetical	mITT	Phase 2b: Each dose of LY3541860 vs. placebo	Negative binomial regression	Secondary
		Treatment Policy	mITT	Phase 2b: Each dose of LY3541860 vs. placebo	Negative binomial regression	Secondary
MRI: New and/or enlarging T2 lesions	Cumulative number of new and/or enlarging N2 lesions over Weeks 4, 8, and 12	Hypothetical	mITT	Phase 2a: LY3541860 CCI mg vs. placebo	Negative binomial regression	Secondary
		Treatment Policy	mITT	Phase 2a: LY3541860 CCI mg vs. placebo	Negative binomial regression	Secondary
		Hypothetical	mITT	Phase 2b: Each dose of LY3541860 vs. placebo	Negative binomial regression	Secondary
		Treatment Policy	mITT	Phase 2b: Each dose of LY3541860 vs. placebo	Negative binomial regression	Secondary




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7. References

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-748. https://doi.org/ 10.1111/j.1541-0420.2005.00344.x

[FDA] Food and Drug Administration. Office of Clinical Pharmacology Division of Pharmacometrics. Request for Qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. 22 April 2015. Accessed December 09, 2022. https://www.fda.gov/media/99313/download

Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993; 80(1):27-38.

Gould AL. BMA-Mod: A Bayesian model averaging strategy for determining dose-response relationships in the presence of model uncertainty. Biom J. 2019;61(5):1141-1159. https://doi.org/ 10.1002/bimj.201700211

Montalban X, A. D. (2019). Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. *N Engl J Med*, 380:2406-2417.

Reich DS, A. D. (2021). Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*, 20(9):729-738.

Statistical Analysis Plan v1.0 Approvals:

Eli Lilly and Company:

Statistics Supervisor Signature: DocuSigned by: PPD

Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 01-Feb-2024 | 4:18:49 PM GMT

Date (dd-mmm-yyyy): PPD

PK\PD\Pharmacometrics Supervisor Signature: DocuSigned by: PPD

Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 01-Feb-2024 | 4:28:36 PM GMT

Date (dd-mmm-yyyy): PPD

PPD, part of Thermo Fisher Scientific:

Statistics Supervisor Signature: DocuSigned by: PPD

Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 01-Feb-2024 | 4:40:06 PM GMT

Date (dd-mmm-yyyy): PPD

DocuSign

Certificate Of Completion

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Status: Completed
Subject: Complete with DocuSign: LILJ3KMCKIAB_Statistical Analysis Plan.docx
Source Envelope:
Document Pages: 55
Signatures: 3
Envelope Originator:
Certificate Pages: 3
Initials: 0
PPD
AutoNav: Enabled
EnvelopeId Stamping: Disabled
IP Address: PPD
Time Zone: (UTC) Monrovia, Reykjavik

Record Tracking

Status: Original
01 February 2024 | 16:02
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 01 February 2024 | 16:06 Viewed: 01 February 2024 | 16:18 Signed: 01 February 2024 | 16:19
Electronic Record and Signature Disclosure: Accepted: 16 May 2023 | 14:35 PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 01 February 2024 | 16:06 Viewed: 01 February 2024 | 16:08 Signed: 01 February 2024 | 16:28
Electronic Record and Signature Disclosure: Accepted: 23 May 2023 | 14:54 ID: PPD		

Signer Events	Signature	Timestamp
PPD CCI 21 CFR Part 11 Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 01 February 2024 | 16:06 Viewed: 01 February 2024 | 16:39 Signed: 01 February 2024 | 16:40
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 01 February 2024 | 16:06
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	01 February 2024 | 16:06
Certified Delivered	Security Checked	01 February 2024 | 16:39
Signing Complete	Security Checked	01 February 2024 | 16:40
Completed	Security Checked	01 February 2024 | 16:40
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

CCI has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, CCI [redacted], Appropriate Use of Electronic Records and Electronic Signatures