Statistical Analysis Plan (v1): J1A-MC-KDAD

A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants With Moderately to Severely Active Rheumatoid Arthritis

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Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis

Protocol Number: J1A-MC-KDAD

Compound Number: LY3462817

Short Title: A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis

Acronym: KDAD

Sponsor Name: Eli Lilly and Company

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Version history

This Statistical Analysis Plan (SAP) for study J1A-MC-KDAD is based on the protocol dated 05AUG2020.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	22DEC2020	Not Applicable	Original version

1. Introduction

This study aims to evaluate the efficacy of LY3462817 in adult participants with moderately to severely active RA who have had an inadequate response to csDMARDs, or to bDMARDs/tsDMARDs. This SAP will summarize the details of statistical analyses in this study.

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate the efficacy of LY3462817 in adult participants with moderately to severely active RA.	• Change from Baseline of DAS28-CRP at Week 12.
Secondary	

• To describe the safety and tolerability of LY3462817 compared to placebo
• To evaluate the effect of LY3462817 on measures of disease activity
• To describe the effect of LY3462817 on PROs
• To characterize the pharmacokinetics of LY3462817
	• Safety assessments such as AEs, SAEs
	• Proportion of participants achieving ACR20, ACR50, and ACR70
	• Change from baseline for physician-assessed individual components:
	  ○ 68 tender joint count
	  ○ 66 swollen joint count
	  ○ physician's global assessment of disease activity (VAS)
	• Change from baseline for mean SDAI
	• Change from baseline for mean CDAI
	• Change from baseline for Individual components of the ACR core set:
	  ○ patient's global assessment of disease activity (VAS),
	  ○ patient's global assessment of arthritis pain
	  ○ (VAS), and
	  ○ patient's assessment of physical function (HAQDI)
	• Change from baseline for SF-36
	• Observed drug concentration

Tertiary/Exploratory	
• To explore the effect of LY3462817 on other measures of disease activity • To explore the durability of effect of LY3462817	• Proportion of participants achieving LDA or remission using the following measures: DAS28-CRP, DAS28-ESR, SDAI, and CDAI at all time points collected • Change from baseline in the RAMRIS synovitis score by MRI imaging

	• Proportion of participants achieving LDA (with the following measures: DAS28-CRP, DAS28-ESR, SDAI, and CDAI) at Week 12 and maintaining LDA through Week 24 • Proportion of participants that achieve remission (with the following measures: DAS28-CRP, DAS28-ESR, SDAI, and CDAI) at Week 12 and maintaining remission through Week 24

Primary estimand

The primary clinical question of interest is: What is the intervention difference in change from baseline of DAS28-CRP after 12 weeks of intervention in participants with Moderately to Severely Active Rheumatoid Arthritis before intervention discontinuation for any reason and before initiation of rescue intervention or change in background intervention? The primary comparison will be assessed using a hypothetical efficacy estimand strategy to address the intercurrent event of early discontinuation where the mean change from baseline will be evaluated using only data up until discontinuation as if all subjects remained on randomized treatment.

The estimand is described by the following attributes:

Population: participants with Moderately to Severely Active Rheumatoid Arthritis. Further details can be found in Section 5.

Endpoint: change from baseline to week 12 in DAS28-CRP

Treatment condition: the randomized treatment without rescue medication or change in background medication (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention “ are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in mean changes between intervention conditions

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will not represent the true efficacy effects.

Secondary estimands

1) ACR 20/50/70

The clinical question of interest is for the secondary objective regarding Moderately to Severely Active Rheumatoid Arthritis: What is the intervention difference in the percentage of participants achieving ACR20/50/70 after 12 weeks of intervention in participants with Moderately to Severely Active Rheumatoid Arthritis before intervention discontinuation for any reason and before initiation of any interventions affecting ACR20/50/70?

The estimand is described by the following attributes:

Population: participants with Moderately to Severely Active Rheumatoid Arthritis. Further details can be found in Section 5.

Endpoint: achievement of ACR 20/50/70 at week 12

Treatment condition: the randomized intervention without any other interventions (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events intervention discontinuation for any reason and any interventions affecting ACR 20/50/70 are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in percentage of participants achieving ACR 20/50/70 at week 12 between intervention conditions

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will not represent the true efficacy effects.

2) Change from baseline in TJC, SJC, PhGADA_VAS, PaGADA_VAS, patient's global assessment of arthritis pain (VAS), HAQ-DI, SF-36, and mean scores of SDAI and CDAI

The clinical question of interest is for the secondary objective regarding Moderately to Severely Active Rheumatoid Arthritis: What is the intervention difference in change from baseline of TJC, SJC, PhGADA_VAS, PaGADA_VAS, patient's global assessment of arthritis pain (VAS), HAQ-DI, SF-36, and mean scores of SDAI and CDAI after 12 weeks of intervention in participants with Moderately to Severely Active Rheumatoid Arthritis before intervention discontinuation for any reason and before initiation of rescue intervention or change in background intervention?

The estimand is described by the following attributes:

Population: participants with Moderately to Severely Active Rheumatoid Arthritis. Further details can be found in Section 5.

Endpoint: change from baseline to week 12 in TJC, SJC, PhGADA_VAS, PaGADA_VAS, patient's global assessment of arthritis pain (VAS), HAQ-DI, SF-36, and mean scores of SDAI and CDAI

Treatment condition: the randomized treatment without rescue medication or change in background medication (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events "intervention discontinuation for any reason" and "initiation of rescue intervention or change in background intervention " are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in mean changes between intervention conditions

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will not represent the true efficacy effects.

1.2. Study Design

This is a Phase 2, proof-of-concept, placebo-controlled, double-blind, randomized study in adult participants with moderately to severely active RA who have had an inadequate response to csDMARDs, or to bDMARDs/tsDMARDs. Participants will be administered LY3462817 or placebo IV Q4W.

Screening Period (Visit 1, Days -42 to -1)

Participants will sign the informed consent document(s) at Visit 1, prior to completion of any procedures. Participants will be evaluated for study eligibility ≤42 days prior to the baseline visit (Visit 2).

Period 1: Double-blind Treatment (Visits 2 to 6; 12 weeks)

At the baseline visit (Visit 2), participants who fulfill the eligibility criteria will be randomized to receive LY3462817 700 mg, LY3462817 300 mg, or placebo in an allocation ratio of 2:1:1. The double-blind treatment period will establish the clinical efficacy and safety of LY3462817. The study will be evaluated for the primary objective at the end of the double-blind treatment period.

Period 2 (Visits 6 to 10; 12 weeks)

In Period 2, all subjects will receive LY3462817 to assess safety and tolerability data and explore clinical activity with additional dosing. At Week 14, participants will be evaluated for clinical benefit.

Posttreatment Safety Follow-up Period (Visits V801 and 802; 12 weeks)

Following Period 2, participants will be followed posttreatment for 12 weeks to assess safety, study drug exposure, and clinical disease activity measures.

2. Statistical Hypotheses

For the primary estimand with primary endpoint, change from baseline to week 12 in DAS28-CRP, the following 2 (confirmatory) 1-sided hypotheses are planned to be tested for LY3462817 700 mg versus placebo. Let the mean treatment difference be defined as μ = (LY3462817 700 mg minus placebo).

H0: $\mu \geq 0.0$ against Ha: $\mu < 0.0$

Operationally the hypotheses will be evaluated by 2-sided tests.

2.1. Multiplicity Adjustment

This is a proof of concept study. No adjustments will be made to adjust the performed efficacy analysis for multiplicity.

3. Analysis Sets

The following analysis data sets are defined to estimate the estimands defined in the protocol and to address safety.

Analysis Data Sets	Description
Full Analysis Set (FAS) for the primary estimand and for the secondary estimand for the secondary objective	• All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be included in the analyses according to the planned intervention • For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.
Safety analysis set to be used for safety assessments	• All participants who are exposed to study intervention. Participants will be included in the analyses according to the intervention they actually received. • All observed data will be included in the analysis set.
Pharmacokinetic(PK) analysis set to be used for PK assessments	• All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have PK data available. • All observed data until discontinuation of intervention will be included in the analysis set.

4. Statistical Analyses

4.1. General Considerations

The independent variable, previous RA therapy population, is defined as only csDMARD experienced or bDMARD/tsDMARD experienced participants. Unless otherwise indicated in the statistical analysis plan (SAP), the analyses will be conducted as follows:

Analysis for	Description
Primary and secondary endpoint analyses comparing LY3462817 to placebo	Tested at a 2-sided level of 0.05 for frequentist analyses
Adjustments for multiplicity	None to be performed
Baseline	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).
Change from baseline	Will be calculated as the visit value of interest minus the baseline value.
Efficacy and patient-reported outcome (PRO) analysis	Analysis models may contain the independent variables such as treatment group, baseline disease activity, and previous RA therapy population. Endpoint analyses will use the FAS unless otherwise specified.
Dichotomous responder endpoints	Missing data will be imputed using the nonresponder imputation (NRI) method. Will be analyzed using a logistic regression model with treatment group, baseline disease activity, and previous RA therapy population as model covariates.
NRI analysis	Participants will be considered nonresponders if: • they do not meet all the clinical response criteria • they are noncompliant with concomitant medication rules

	• they permanently discontinue study intervention at any time before the end of the treatment period for any reason, or • they are randomized and do not have at least 1 postbaseline observation.
Continuous efficacy endpoints	Mixed-effects model for repeated measures (MMRM) will be used. The MMRM model will include treatment, strata (previous RA therapy population), baseline value, visit, treatment-by-visit interaction in the model as fixed factors, and patient as a random factor. An unstructured covariance matrix will be used to model the within-subject errors. If this analysis fails to converge, other structures will be tested (in this order: Toeplitz, Autoregressive with heterogeneity, and compound symmetry.). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least squares means and Type III tests.
Participant Disposition	A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation. A summary of important protocol deviations will be provided.
Participant Characteristics	Demographic data are collected and responded to demonstrate that the study population represents the target patient population. A summary of baseline participant characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics. Other participant characteristics will be summarized by treatment group as deemed appropriate.
Concomitant Therapy	Previous and concomitant medications will be summarized by treatment group and will be presented by Anatomical Therapeutic Chemical drug classes using the latest version of the WHO drug dictionary.

Treatment Compliance	No analyses are planned to assess treatment compliance, given that participants will receive study intervention directly from the investigator or designee at the study site, under medical supervision.

Summary statistics for continuous measures will include sample size, mean, standard deviation, median, minimum, and maximum.

For categorical data, summary statistics will include sample size, frequency, and percentages. Percentages will be rounded to one decimal place. Unless otherwise specified, Fisher's exact test will be used for making treatment comparisons.

All statistical tests of treatment effects will be performed at two-sided significance levels of 0.05 and 0.10, respectively, unless otherwise specified. All p-values will be presented to three decimal places.

The Treatment Period is defined as the combination of Period 1 with double-blind treatment and Period 2.

The baseline period is defined as Visit 1 through pre-dose Visit 2. The Double-blind Treatment Period starts after the first injection of study treatment at Visit 2 (Week 0) and ends on the date of Visit 6 (Week 12) or the early discontinuation visit. The Period 2 starts after the date of Visit 6 (Week 12) or the early discontinuation visit and lasts up to 24 weeks following the last injection of study treatment. Additional follow-up beyond 24 weeks may be deemed necessary and, if so, any data collected will be considered as part of Period 2.

Unless otherwise specified, baseline for the Treatment Period is defined as the last non-missing assessment on or prior to the date of the first injection of study treatment, scheduled to be given at the end of Visit 2. Any assessment collected after the first injection through the date of the Week 12 or early discontinuation visit is defined as post-baseline for the Treatment Period.

Data collected at early discontinuation visits will be mapped to the next planned visit number for that patient. For by-visit summaries, only visits in which a measure was scheduled to be collected will be summarized.

Summaries of safety data collected during Period 2 will be presented separately. Unless otherwise specified, follow-up baseline is defined as the last non-missing assessment on or prior to the date of Week 12 or the date of the early discontinuation visit.

Change from baseline will be calculated as the post-baseline value minus the baseline value. Percent change from baseline is defined as (100 × (post-baseline – baseline) / baseline). If all baseline values are missing for a particular variable, the change from baseline and percent change from baseline will not be calculated.

The statistical analyses of efficacy, health outcomes, and safety measures will be performed using SAS Version 9.4 or higher. Lilly will be responsible for conducting analyses.

4.2. Participant Dispositions

The number and percentage of patients randomized and treated in the study and patients included in each analysis set will be presented, together with the number and percentage of patients who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal for both double-blind treatment period and period 2. The subject completion status and discontinuation reasons in both double-blind treatment period and period 2 will be listed.

The number and percentages of screen failure and corresponding reasons will be summarized. The subjects with screen failure reasons will also be listed.

4.3. Primary Endpoint/Estimand Analysis

4.3.1. Definition of endpoint

The primary endpoint is Change from Baseline of DAS28-CRP at Week 12.

4.3.2. Main analytical approach

Observed values at baseline and changes from baseline to Week 12 endpoint in DAS28-CRP will be summarized by treatment arm and provided as listing.

A restricted maximum likelihood based, MMRM analysis will be used to analyze the primary endpoint. The MMRM model will include treatment, strata (previous RA therapy population), baseline value, visit, treatment-by-visit interaction in the model as fixed factors, and patient as a random factor. An unstructured covariance matrix will be used to model the within-subject errors. If this analysis fails to converge, other structures will be tested (in this order: Toeplitz, Autoregressive with heterogeneity, and Compound Symmetry). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least squares means and Type III tests. The data on or after the treatment discontinuation will not be included in MMRM analysis.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.3.3. Sensitivity Analysis

No sensitivity analysis will be performed.

4.3.4. Supplementary analyses

No supplementary analysis will be performed.

4.4. Secondary Endpoints/Estimands Analysis

4.4.1. Key Secondary Endpoints

4.4.1.1. Definition of endpoint(s)

The secondary endpoints include:

- Proportion of participants achieving ACR20, ACR50, and ACR70
- Change from baseline for physician-assessed individual components:
  - 68 tender joint count
  - 66 swollen joint count
  - physician's global assessment of disease activity (VAS)
- Change from baseline for mean SDAI
- Change from baseline for mean CDAI
- Change from baseline for Individual components of the ACR core set:
  - patient's global assessment of disease activity (VAS),
  - patient's global assessment of arthritis pain
  - (VAS), and
  - patient's assessment of physical function (HAQDI)
  - Change from baseline for SF-36

4.4.1.2. Main analytical approach

4.4.1.2.1 ACR20

The frequency and percentage of patients achieving ACR20 response will be summarized by treatment arm at each post-baseline visit. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at each post-baseline visit with treatment group, baseline disease activity, and previous RA therapy population as model covariates. Baseline DAS28-CRP score will be used as the baseline variable. NRI as described in Section 4.1 will be used to impute missing data for ACR20 in patients who were Week 12 non-responders or who discontinued prior to Week 12.

The Kaplan-Meier estimator will be used to summarize time to ACR20 response over 12 weeks and a plot by treatment arm will be presented. Week 12 non-responders will be censored on the date of the Week 12 visit. All patients ongoing at Week 12 and who have not yet responded will be censored on the date of the Week 12 visit. A Cox proportional hazards model will be used to test the treatment comparison between each LY dose and placebo in time to ACR20 response over 12 weeks.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

Subjects with ACR20 response will also be listed.

4.4.1.2.2 ACR50/70

ACR50 and ACR70 are calculated in the same manner as ACR20, but are based on 50% and 70% improvement, respectively.

Summaries and analyses similar to those described for ACR20 in Sections 16.1.3.1 will be conducted for ACR50 and ACR70.

Subjects with ACR50/70 response will also be listed.

4.4.1.2.3 Individual components of the ACR Core Set

The following individual components of the ACR Core Set will be summarized and provided as listing:

- TJC (68 joint count),
- SJC (66 joint count),
- Patient's Global Assessment of Arthritis Pain (VAS),
- Patient's Global Assessment of Disease Activity (PaGADA_VAS),
- Physician's Global Assessment of Disease Activity (PhGADA_VAS),

Summaries will be provided by treatment arm for each post-baseline visit and Week 12 endpoint. An MMRM model, as described in Section 4.3.2. will be used to test the treatment difference of each LY dose versus placebo in change from baseline to Week 12 endpoint.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.4.1.2.4 HAQ-DI

Observed values at baseline and changes from baseline to Week 12 endpoint in HAQ-DI score will be summarized by treatment arm and provided as listing. An MMRM model, as described in Section 4.3.2, will be used to test the treatment difference of each LY dose versus placebo in change from baseline to Week 12 endpoint.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.4.1.2.5 SF-36 Domain, Component and Summary Scores

Observed values at baseline and changes from baseline to Week 12 endpoint in SF-36 summary scores will be summarized by treatment arm and provided as listing. An MMRM model, as described in Section 4.3.2, will be used to test the treatment difference of each LY dose versus placebo in change from baseline to Week 12 endpoint.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.4.1.2.6 SDAI

The SDAI is calculated by adding together scores from the following assessments:

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)
- CRP in mg/dL (0.1 to 10.0)

- PaGADA_VAS (0 to 100 mm), and
- PhGADA_VAS (0 to 100 mm) (Aletaha and Smolen 2005).

Observed values at baseline and changes from baseline to Week 12 endpoint in SDAI score will be summarized by treatment arm and provided as listing. An MMRM model, as described in Section 4.3.2, will be used to test the treatment difference of each LY dose versus placebo in change from baseline to Week 12 endpoint.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.4.1.2.7 CDAI

The CDAI is calculated by adding together scores from the following assessments:

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)
- PaGADA_VAS (0 to 100 mm), and
- PhGADA_VAS (0 to 100 mm) (Aletaha and Smolen 2005).

Observed values at baseline and changes from baseline to Week 12 endpoint in CDAI score will be summarized by treatment arm and provided as listing. An MMRM model, as described in Section 4.3.2, will be used to test the treatment difference of each LY dose versus placebo in change from baseline to Week 12 endpoint.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.4.1.3. Sensitivity Analysis

No sensitivity analysis will be performed.

4.4.1.4. Supplementary Analysis

No supplementary analysis will be performed.

4.4.2. Supportive Secondary Endpoints/Estimands

There is no supportive secondary endpoints/estimands.

4.5. Tertiary/Exploratory Endpoints/Estimands Analysis

4.5.1 DAS28-CRP Remission and Low Disease Activity

Remission is defined as a DAS28-CRP score of <2.6. Low disease activity is defined as a DAS28-CRP score of ≤3.2.

The frequency and percentage of patients achieving remission and low disease activity will be summarized by treatment arm at each post-baseline visit. A logistic regression model will be used

to test the treatment difference of each LY dose versus placebo at each post-baseline visit with treatment group, baseline value, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data for DAS28-CRP remission and low disease activity in patients who were Week 12 non-responders or who discontinued prior to Week 12.

The analyses for DAS28-CRP remission and DAS28-CRP LDA will be repeated for all visits in period 2. NRI as described in Section 4.1 will be used to impute missing data for DAS28-ESR in patients who were Week 24 non-responders or who discontinued prior to Week 24.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.5.2 DAS28-ESR Remission and Low Disease Activity

Remission is defined as a DAS28-ESR score of <2.6. Low disease activity is defined as a DAS28-ESR score of ≤3.2.

The frequency and percentage of patients achieving remission and low disease activity will be summarized by treatment arm at each post-baseline visit in Double-blind Treatment Period. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at each post-baseline visit with treatment group, baseline value, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data for DAS28-ESR remission and low disease activity in patients who were Week 12 non-responders or who discontinued prior to Week 12.

The analyses for DAS28-ESR remission and DAS28-ESR LDA will be repeated for all visits in period 2. NRI as described in Section 4.1 will be used to impute missing data for DAS28-ESR in patients who were Week 24 non-responders or who discontinued prior to Week 24.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.5.3 SDAI Remission and Low Disease Activity

Remission is defined as a SDAI score of ≤3.3. Low disease activity is defined as a SDAI score of ≤11.

The frequency and percentage of patients achieving remission and low disease activity will be summarized by treatment arm at each post-baseline visit. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at each post-baseline visit with treatment group, baseline value, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data for SDAI remission and low disease activity in patients who were Week 12 non-responders or who discontinued prior to Week 12.

The analyses for SDAI remission and SDAI LDA will be repeated for all visits in period 2. NRI as described in Section 4.1 will be used to impute missing data for SDAI in patients who were Week 24 non-responders or who discontinued prior to Week 24.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.5.4 CDAI Remission and Low Disease Activity

Remission is defined as a CDAI score of ≤2.8. Low disease activity is defined as a CDAI score of ≤10.

The frequency and percentage of patients achieving remission and low disease activity will be summarized by treatment arm at each post-baseline visit. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at each post-baseline visit with treatment group, baseline value, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data for CDAI remission and low disease activity in patients who were Week 12 non-responders or who discontinued prior to Week 12.

The analyses for CDAI remission and CDAI LDA will be repeated for all visits in period 2. NRI as described in Section 4.1 will be used to impute missing data for CDAI in patients who were Week 24 non-responders or who discontinued prior to Week 24.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.5.5 MRI

Observed values at baseline and changes from baseline to Week 12 in synovitis, osteitis, combined inflammation (combination of synovitis and osteitis), bone erosion, cartilage loss (scored with the validated 9-point Cartilage Loss Scale) and total joint damage which were scored using Outcome Measures in Rheumatology Clinical Trials RA MRI scoring (RAMRIS) will be summarized by treatment arm and provided as listing.

Scale-adjusted scores for combined inflammation (osteitis score + 3× synovitis score) and total joint damage (erosion score + 2.5×cartilage loss score) were calculated. Synovitis is multiplied by 3 to adjust for the about 3-fold difference between the scales for synovitis (0–24) and for osteitis (0–75). The scale difference is also adjusted when computing total damage score (bone erosion scale ranges 0–250, cartilage loss ranges 0–100).

An ANCOVA model of change from baseline with treatment and previous RA therapy population included as fixed factors, and baseline value as a continuous covariate will be used to test the treatment difference of each LY dose versus placebo. Least squares mean (LSM), standard error, within-group p-value, and two-sided 95% confidence interval for change from baseline will be reported for each treatment arm. For the treatment difference of each LY dose versus placebo, the LSM difference, standard error, p-value, and two-sided 95% confidence interval will be reported.

The frequency and percentage of patients achieving 25% improvement on total synovitis score will be summarized by treatment arm at Week 12. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at Week 12 with treatment group, baseline value, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data in patients who were Week 12 non-responders or who discontinued prior to Week 12.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.5.6 Disease Activity and PROs

Observed values at baseline and changes from baseline to Week 12 endpoint of disease activity score, PRO score, SF-36 domain score, the physical component score, the mental component

scores will be summarized by treatment arm and provided as listing. An MMRM model, as described in Section 4.3.2, will be used to test the treatment difference of each LY dose versus placebo in change from baseline to Week 12 endpoint.

The frequency and percentage of patients achieving desired response will be summarized by treatment arm at each post-baseline visit. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at each post-baseline visit with treatment group, baseline value, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data for CDAI remission and low disease activity in patients who were Week 12 non-responders or who discontinued prior to Week 12.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.5.7 Analyses in Period 2

Observed values at baseline and changes from Week 12 to Week 24 endpoint of DAS28-CRP, DAS28-ESR, HAQ-DI, SDAI, CDAI, tender joint count, swollen joint count, Patient's Global Assessment of Arthritis Pain (VAS), Patient's Global Assessment of Disease Activity (PaGADA_VAS), Physician's Global Assessment of Disease Activity (PhGADA_VAS) will be summarized by treatment arm. An MMRM model, as described in Section 4.3.2, will be used to test the treatment difference of each LY dose versus placebo in change from Week 12 to Week 24 endpoint.

The frequency and percentage of patients achieving desired responses on ACR20/50/70 at Week 14 and maintain till Week 24 will be summarized by treatment arm at each period 2 visit. A logistic regression model will be used to test the treatment difference of each LY dose versus placebo at each period 2 visit with treatment group, baseline value at double-blind treatment period, and previous RA therapy population as model covariates. NRI as described in Section 4.1 will be used to impute missing data in patients who were Week 24 non-responders or who discontinued prior to Week 23.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.6. Safety Analyses

The following safety measures will be summarized and analyzed using the Safety Analysis Set. Patients will be analyzed according to the treatment to which they were assigned. Safety summaries will be presented by treatment arm as follows: LY3462817 300 mg, LY 3462817 700 mg, All LY3462817, and Placebo. (Coming from CPT Section 9.4.5. Other Safety Analysis and 9.4.6 Other Analyses), information on this section will be copied from protocol, if needed; it can be edited and additional details may be added.

4.6.1. Extent of Exposure

Duration of Exposure to Study Treatment

Duration of exposure on treatment (defined as time since first injection in days) during the Double-blind Treatment Period will be summarized by treatment arm and provided as listing. Duration of exposure on treatment will be calculated as:

(Date of last study visit during the Double-blind Treatment Period – Date of first injection + 1).

For patients who discontinue from the treatment, the date of discontinuation prior to Period 2 will be used.

Descriptive statistics for duration of exposure and the frequency and percentage of patients falling into the following ranges will be summarized: 0, >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥84 days. The frequency and percentage of patients with duration of exposure in the following categories will also be summarized: 0 days, <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <84 days, ≥84 days.

Overall exposure for each treatment arm will also be summarized in total patient years. This will be calculated as follows:

Exposure in patient years = Sum of duration of exposure (for all patients in treatment arm) / 365.25.

The analyses in Double-blind Treatment Period will be repeated for all visits in period 2 for subjects who remain on LY3462817 300 mg or LY3462817 700 mg.

Total Dose of Study Treatment

Total dose of active study treatment per subject will be summarized by active treatment arm using descriptive statistics. The total dose (mg) will be calculated as:

Total Dose = Sum over all injections received of [dose of LY (mg) prescribed per injection]

A by-patient listing of exposure duration and total dose will be provided.

4.6.2. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all pre-existing conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, during the interval between Visits 1 and 2 and recorded with the time of onset before the first dose of study intervention). The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT before the first injection will be used as baseline. Start date of adverse events will be compared with date of first injection and the date of Visit 10 (Week 24) to determine whether an adverse event is treatment-emergent. Should there be insufficient data for adverse event start date or severity to make this comparison; the adverse event will be considered treatment-emergent.

TEAEs will be coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class (SOC) and Preferred Term.

An overview of adverse events will summarize the percentage of patients experiencing deaths, SAEs, AEs reported as reason for discontinuation, TEAEs, and AEs possibly related to study treatment.

The frequency and percentage of patients with the following will be summarized using MedDRA Preferred Term nested within SOC.

- TEAEs
- TEAEs by maximum severity
- TEAEs related to study intervention
- TEAEs leading to study discontinuation
- SAEs including death
- SAEs by maximum severity
- SAEs related to study intervention
- Deaths
- AE of Special Interests (AESIs)

Events will be sorted alphabetically by SOC and then by decreasing total frequency within SOC. For incidence counts, each patient will be counted only once within each Preferred Term and within each SOC. Percentages will be based on the number of patients in a particular treatment arm. For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

Adverse events of special interest will be identified by a standardized MedDRA query or a Lilly-defined MedDRA preferred term listing.

By-patient listings of all adverse events (including non-treatment-emergent events) recorded on the CRF, all TEAEs, TEAEs leading to study discontinuation, SAEs including death, and deaths during the Treatment Period will be presented by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

4.6.2.1. Hypersensitivities

Hypersensitivities will be defined using the following terms:

- Anaphylactic reaction standardized MedDRA query (SMQ) excluding the Preferred Term Anaphylactic transfusion reaction
- Angioedema SMQ excluding the Preferred Terms Oedema neonatal and Peripheral oedema neonatal
- Severe cutaneous adverse reactions SMQ Narrow Search terms and the following Broad Search terms:
    - Drug eruption
    - Drug rash with eosinophilia and systemic symptoms
    - Lip exfoliation
    - Mucosal exfoliation
    - Penile exfoliation
    - Skin exfoliation

  - Stomatitis
  - Tongue exfoliation
  - Vaginal exfoliation

- Additional Preferred Terms including:
  - Asphyxia
  - Dermatitis
  - Dermatitis allergic
  - Dermatitis atopic
  - Dermatitis contact
  - Diastolic hypotension
  - Eczema
  - Eosinophilic oesophagitis
  - Erythema nodosum
  - Hypotension
  - Immediate post-injection reaction
  - Injection related reaction
  - Orthostatic hypotension
  - Photosensitivity allergic reactions
  - Photosensitivity reaction
  - Presyncope
  - Rash vesicular
  - Reaction to drug excipients
  - Red man syndrome
  - Serum sickness
  - Serum sickness-like reaction
  - Syncope
  - Type II hypersensitivity
  - Type III immune-complex-mediated reaction
  - Type IV hypersensitivity reaction
  - Toxic skin eruption
  - Urticaria contact
  - Urticaria vesiculosa

The frequency and percentage of patients experiencing treatment-emergent hypersensitivities will be summarized by treatment arm, maximum severity, SOC, and Preferred Term during Treatment Period. The frequency and percentage of patients experiencing treatment-emergent hypersensitivities will also be summarized by treatment arm and timing category (immediate, acute reaction, delayed reaction or reaction after more than 15 days).

Exposure-adjusted incidence rates (per 100 patient years) of treatment-emergent hypersensitivities within the following time intervals will be calculated as detailed below.

- ≥ 0 to ≤ 6 weeks since the date of first injection:
  Interval start date = Date of first injection,
  Interval end date = Date of first injection + 42 days.

- > 6 to ≤ 12 weeks since the date of first injection:
  Interval start date = Date of first injection + 43 days,
  Interval end date = Date of first injection+ 84 days.
- ≥ 24 weeks since the date of first injection:
  Interval start date = Date of first injection + 85,
  No Interval end date, Treatment Period planned for 24 weeks

The time to onset of first treatment-emergent hypersensitivity during the Treatment Period and the duration of each treatment-emergent hypersensitivity during the Treatment Period will also be defined and calculated in the same way.

A by-patient listing of all treatment-emergent hypersensitivities will be provided.

4.6.2.2. Infusion Site Reactions

Infusion site reactions will be defined using terms from the infusion site reactions high level term.

The frequency and percentage of patients with a treatment-emergent infusion site reaction will be summarized by treatment arm, maximum severity, SOC, and Preferred Term during Treatment Period.

The frequency and percentage of patients with infusion site reactions will be summarized by treatment arm and redness category (normal, noticeable but very mild redness, clearly red, bright red, and dark with some scar formation) during Treatment Period and during Treatment Period. Similarly, the frequency and percentage of patients with infusion site reactions will be summarized by treatment arm and swelling category (no bump, barely noticeable, clear bump but very thin, clear bump 1mm thick, clear bump 2mm thick or more) during Treatment. Finally, the frequency and percentage of patients with infusion site reactions will be summarized by treatment arm and pain category (none, mild, moderate and severe) during Treatment Period.

The duration of each treatment-emergent infusion site reaction during the Treatment will be defined and summarized in the same way as described for infectious AEs in Section 16.4.2.1.

A by-patient listing of treatment-emergent infusion site reactions will be provided.

4.6.2.3. Infections

Infectious events include infections, serious infections, opportunistic infections, infections that require therapeutic intervention, and any events involving reactivation of TB or hepatitis. Such events will be selected using the 'Infections and Infestations' SOC.

In addition to incidence of infectious AEs by MedDRA Preferred Term as described above, the frequency and percentage of patients experiencing the following types of infectious AEs (yes or no) during the Treatment Period and during Treatment Period will be provided by treatment arm.

- Gram-positive bacterial infection
- Gram-negative bacterial infection

- Mixed aerobic-anaerobic bacterial infection
- Fungal infections
- Viral infections
- Other infections
- Opportunistic infections as assessed by the investigator

The frequency and percentage of patients experiencing infectious AEs during the Treatment Period who are treated with antibiotics will be presented by treatment arm. Note that the event ID of all infectious AEs will be cross-referenced with the Concomitant Medications eCRF page, which records whether a medication was taken as a result of a specific AE. Any antibiotics will be highlighted during a medical review of the concomitant medications prescribed.

The frequency and percentage of patients experiencing infectious AEs will be presented by treatment arm and infection diagnosis during the Treatment. The frequency and percentage of patients experiencing infectious AEs will also be presented by treatment arm and primary site of infection during the Treatment Period.

The time to onset of first treatment-emergent infectious AE during the Treatment Period will be defined as follows:

Time to onset of first treatment-emergent infectious AE (in weeks) = (Start date of first infectious AE – Date of randomization +1) / 7.

Note that if an infectious AE was pre-existing prior to the date of first injection and subsequently became treatment-emergent due to worsening post-baseline, the date of worsening will be used in place of the AE start date.

If a patient does not have a treatment-emergent infectious AE during the Treatment Period, they will be censored at the date of completion or early discontinuation from the Treatment Period. Kaplan-Meier estimates of the proportion of patients not yet experiencing their first treatment-emergent infectious AE at 1, 6, 12 and 24 weeks will be provided for each treatment arm. A Kaplan-Meier plot of the time to onset will be presented by treatment arm.

The duration of each treatment-emergent infectious AE during the Treatment Period will be defined as follows:

Duration of treatment-emergent infectious AE (in weeks) = (End date of AE – Start date of AE + 1) / 7.

If an AE has not ended by the date of completion or early discontinuation from the study, including the Post-Treatment Follow-up Period, it will be censored as of that date. Descriptive statistics for the duration of treatment-emergent infectious AEs will be summarized by treatment arm. If a patient has more than one treatment-emergent infectious AE during the Treatment Period, then each AE will contribute to the analysis. If a patient does not have a treatment-emergent infectious AE during the Treatment Period, they will not be included in the analysis.

By-patient listings of patients experiencing a treatment-emergent infectious AE, infection-related deaths, and treatment-emergent opportunistic infections will be provided. The listing will include the following: patient demographics (including geographic region), concomitant medication,

results for total leukocytes, lymphocytes and total B lymphocytes, event start and stop dates, study treatment start and end dates, and the event outcome.

4.6.2.4. Malignancies

Malignancies will be defined using terms from the Malignant or unspecified tumors SMQ.

The frequency and percentage of patients with a treatment-emergent malignancy will be summarized by treatment arm, maximum severity, SOC, and Preferred Term during the Treatment Period. Exposure-adjusted incidence rates (per 100 patient years), as defined in Section 6.14.2.1, for each type of treatment-emergent malignancy will be presented by treatment arm, Preferred Term and time interval during the Treatment Period. Adverse events will be summarized under a particular time interval if they started or worsened on or after the interval start date and before the interval end date. Exposure-adjusted incidence rates will also be presented graphically by treatment arm and time interval.

A by-patient listing of treatment-emergent malignancies will be provided.

4.6.2.5. Depression

Depression will be defined using terms from the Depression and suicide/self injury SMQ.

The frequency and percentage of patients with treatment-emergent depression will be summarized by treatment arm, maximum severity, SOC, and Preferred Term during the Treatment Period. Exposure-adjusted incidence rates (per 100 patient years), as defined in Section 6.14.2.1, for each type of treatment-emergent depression will be presented by treatment arm, Preferred Term and time interval during the Treatment Period. Adverse events will be summarized under a particular time interval if they started or worsened on or after the interval start date and before the interval end date. Exposure-adjusted incidence rates will also be presented graphically by treatment arm and time interval.

A by-patient listing of treatment-emergent depression will be provided.

4.6.2.6. Suicide-related Thoughts and Behaviors

Suicide-related ideations and behaviors, based on C-SSRS, will be summarized by treatment arm separately for patients who completed the C-SSRS starting at enrollment versus patients who were already enrolled when the C-SSRS was introduced to the study during the Treatment Period.

Treatment-emergent suicide-related ideations and behaviors during the Treatment Period are defined as any ideation or behavior reported after the baseline visit (Visit 2) and on or prior to Visit 10 (Week 24) or early discontinuation. The frequency and percentage of patients with treatment-emergent suicide-related ideations and behaviors will be summarized by treatment arm for patients who completed the C-SSRS starting at enrollment by C-SSRS category (1-10), by type (ideation or behavior) and overall during the Treatment Period.

Suicide-related ideations and behaviors will be listed by patient and visit separately for patients who completed the C-SSRS starting at enrollment versus patients who were already enrolled when the C-SSRS was introduced to the study. Only patients that show suicidal ideation/behavior will be displayed, including lifetime history at screening. If a patient answers are all ‘no’ for the C-SSRS, then that patient will not be displayed. However, if a patient reported any ideation or

behavior at any time point then all their ideation and behavior will be displayed, even if not positive.

4.6.3. Clinical Laboratory Evaluation

All numerical laboratory tests for serum chemistries, fasting lipids, hematology, RF and anti-CCP antibodies, CRP, and ESR will be summarized by treatment arm for baseline, all post-baseline visits during the Treatment Period, Week 24 endpoint, and change from baseline to post-baseline visits and Week 24 endpoint.

Urinalysis, TSH, and T4 are collected at screening only, and will appear in data listings.

Summary of B-cells, immunoglobulins, immunogenicity tests, and BAFF levels are described in the subsections below.

Change from baseline to Week 24 endpoint in laboratory tests will be summarized for patients who have both a baseline and at least one post-baseline result. For all laboratory tests except CD3-CD20+B cells counts, baseline is defined as the last non-missing result on or prior to the date of the first injection of study treatment.

Change from the minimum value on or prior to the date of the first injection of study treatment to the minimum value during the Treatment Period in laboratory tests will be summarized for patients who have both a baseline and at least one post-baseline result. Similarly, change from the maximum value on or prior to the date of the first injection of study treatment to the maximum value during the Treatment Period in laboratory tests will be summarized for patients who have both a baseline and at least one post-baseline result. Scheduled visits, unscheduled visits, and repeat measurements will be included.

The frequency and percentage of patients with treatment-emergent abnormal, high, or low laboratory results at any time will be summarized. Similarly, the frequency and percentage of patients with treatment-emergent abnormal, high, or low laboratory results at Week 24 endpoint will be summarized. A treatment-emergent abnormal result is defined as a change from normal at all baseline visits to abnormal at any time during the Treatment Period. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the Treatment Period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the Treatment Period. For each laboratory test, only patients who were normal (i.e., less than or equal to the high limit for treatment-emergent high, or greater than or equal to the low limit for treatment-emergent low) at all baseline visits and who have at least one non-missing post-baseline result will be included in the denominator when computing the percentages of patients with treatment-emergent abnormal, high, or low results. Scheduled visits, unscheduled visits, and repeat measurements will be included. Covance Reference Ranges will be used to define the low and high limits.

Shifts from baseline to maximum post-baseline result during the Treatment Period for ALT, AST, and total bilirubin will be provided for the following categories:

- ALT; $\leq$ 1 x ULN, > 1 to $\leq$ 3 x ULN, > 3 to $\leq$ 5 x ULN, > 5 to $\leq$ 10 x ULN, and > 10 x ULN.

- AST; ≤ 1 x ULN, > 1 to ≤ 3 x ULN, > 3 to ≤ 5 x ULN, > 5 to ≤ 10 x ULN, and > 10 x ULN.
- Total bilirubin; ≤ 1 x ULN, > 1 to ≤ 1.5 x ULN, > 1.5 x ULN.

Shifts from baseline to minimum post-baseline result during the Treatment Period for neutrophils, lymphocytes, and leukocytes will be provided for the following categories:

- Neutrophils; < LLN to ≥ 1.5 x 10^9/L, < 1.5 x 10^9/L to ≥ 1.0 x 10^9/L, < 1.0 x 10^9/L to ≥ 0.5 x 10^9/L, and < 0.5 x 10^9/L.
- Leukocytes; < LLN to ≥ 3.0 x 10^9/L, < 3.0 x 10^9/L to ≥ 2.0 x 10^9/L, < 2.0 x 10^9/L to ≥ 1.0 x 10^9/L, and < 1.0 x 10^9/L.
- Lymphocytes; < LLN to ≥ 0.8 x 10^9/L, < 0.8 x 10^9/L to ≥ 0.5 x 10^9/L, < 0.5 x 10^9/L to ≥ 0.2 x 10^9/L, and < 0.2 x 10^9/L.

Scheduled visits, unscheduled visits, and repeat measurements will be included.

4.6.4. Pharmacodynamics

4.6.4.1. B Cells

For flow cytometry panel, the absolute count and relative count (i.e. as a percentage of the total lymphocyte population) will be summarized by treatment arm for baseline, all post-baseline visits during the Treatment Period, and Week 24 endpoint using descriptive statistics.

The change from baseline and the percent change from baseline to each post-baseline visit during the Treatment Period and Week 24 endpoint will be summarized for absolute and relative count. Note that the baseline count is defined as the average of the non-missing results on or prior to the date of the first injection of blinded study treatment, unless one is missing, in which case the non-missing result will be used. Unscheduled and repeated measurements will be included.

In addition, the mean absolute and relative counts during the Treatment Period will be presented graphically over time (in weeks) by treatment arm. Similarly, the mean percentage change from baseline in absolute and relative counts will be presented graphically over time (in weeks) by treatment arm.

The change from baseline to Weeks 12 and 24 endpoints in absolute count will also be plotted against the change from baseline to Weeks 12 and 24 endpoints in the following variables:

- ACR20, 50, DAS28-CRP, HAQ-DI.

Similar plots will be generated for T, NK cells and peripheral helper T cells.

The change from baseline to Weeks 12 and 24 endpoints in absolute count will also be plotted against the total number of treatment-emergent infectious adverse events during the Treatment Period. Treatment arms will be identified using different symbols in the scatter plots.

A by-patient listing of cytometry cell counts during the Treatment Period will be provided.

4.6.4.2. Serum Immunoglobulin (Ig) Levels and Cytokines

Serum Ig levels, including IgA, IgG and IgM, and cytokines will be summarized by treatment arm for baseline, all post-baseline visits, Week 24 endpoint, and both change from baseline and percent change from baseline to each post-baseline visit and Week 24 endpoint. Baseline is defined as the last non-missing result on or prior to the date of the first injection of study treatment.

The change from baseline in Ig levels and cytokines to each post-baseline visit will also be summarized by treatment arm and whether the patient has positive anti-drug antibodies (ADAs) (yes or no) at that visit.

For each parameter, the mean percentage change from baseline over time (in weeks) will be summarized graphically by treatment arm.

Shift tables will be produced showing the frequency and percentage of patients with a minimum post-baseline result during the Treatment Period in each relevant category, by treatment arm and baseline result. Such shift tables will be produced for the following parameters and categories:

- IgA; < LLN to ≥ 0.35g/L, and <0.35g/L.
- IgG: < LLN to ≥2.82g/L, and <2.82g/L.
- IgM: < LLN to ≥0.20g/L, and <0.20g/L.

The change from baseline to Weeks 12 and 24 endpoints in Ig levels and cytokines will also be plotted against the change from baseline to Weeks 12 and 24 endpoints in the following variables:

- ACR20, ACR50, DAS28-CRP, HAQ-DI,

The change from baseline to Week 24 endpoint in Ig levels and cytokines will also be plotted against the total number of treatment-emergent infectious adverse events during the Treatment Period. Treatment arms will be identified using different symbols in the scatter plots.

A by-patient listing of serum Ig levels and cytokines during the Treatment Period will be provided.

4.6.4.3. RO, sPD-1 and Biomarkers

RO, sPD-1 and biomarkers will be summarized by treatment arm for baseline, all post-baseline visits, Week 24 endpoint, and both change from baseline and percent change from baseline to each post-baseline visit and Week 24 endpoint. Baseline is defined as the last non-missing result on or prior to the date of the first injection of study treatment.

4.6.4.4. Immunogenicity

The frequency and percentage of patients with positive anti-drug antibodies (ADAs) by visit will be summarized by treatment arm. The frequency and percentage of patients with positive ADAs

at any time point during the Treatment Period (including pre-treatment visits) up to and including Visit 9 (Week 24) will also be summarized by treatment arm.

The frequency and percentage of patients with a treatment-emergent positive ADA incidence will be summarized by treatment arm. A treatment-emergent incidence is defined as a four-fold increase [2 dilution increase] in immunogenicity titer over the baseline titer during the Treatment Period. Scheduled visits, unscheduled visits, and repeat measurements will be included.

The time to the development of treatment-emergent ADAs will be calculated as:

Time to development of treatment-emergent ADAs (in weeks) = (Date of development of treatment-emergent ADAs – Date of randomization + 1) / 7.

If a patient has not developed treatment-emergent ADAs, they will be censored at the date of the last immunogenicity assessment during the Treatment Period. If they did not have an immunogenicity assessment, they will be censored at the date of first injection.

The time to development of treatment-emergent ADAs will be analyzed using a Cox proportional hazards model, with treatment arm and strata (previous RA therapy population) fitted as explanatory variables. The estimated hazard ratio, 95% confidence interval and p-value for treatment comparisons between each LY dose and placebo will be presented. A Kaplan-Meier plot of the time to development of treatment-emergent ADAs will be presented by treatment arm.

The frequency and percentage of patients with both a treatment-emergent positive ADA incidence (yes, no) and at least one treatment-emergent Hypersensitivity adverse event (yes, no) will be summarized by treatment arm. Similarly, the frequency and percentage of patients with both a treatment-emergent positive ADA incidence (yes, no) and at least one treatment-emergent injection site reaction (yes, no) adverse event will be summarized by treatment arm.

4.6.5. Vital Signs and Other Physical Findings

Vital signs and physical characteristics to be summarized include temperature, sitting heart rate, sitting blood pressure (systolic and diastolic), weight, and BMI. Vital signs and physical characteristics will be summarized by treatment arm for baseline, all post-baseline visits, Week 24 endpoint, and change from baseline to post-baseline visits and Week 24 endpoint.

Change from baseline to Week 24 endpoint in vital signs and physical characteristics will be summarized for patients who have both a baseline and at least one post-baseline result. Baseline is defined as the last non-missing result on or prior to the date of the first injection of study treatment.

Change from the minimum value on or prior to the date of the first injection of study treatment to the minimum value during the Treatment Period in vital signs and physical characteristics will be summarized for patients who have both a baseline and at least one post-baseline result. Similarly, change from the maximum value on or prior to the date of the first injection of study treatment to the maximum value during the Treatment Period in vital signs and physical characteristics will be summarized for patients who have both a baseline and at least one post-baseline result. Scheduled visits, unscheduled visits, and repeat measurements will be included.

The percentages of patients with treatment-emergent high or low vital signs and physical characteristics at any time during the Treatment Period will be summarized. Similarly, the percentages of patients with treatment-emergent high or low vital signs and physical

characteristics at Week 24 endpoint will be summarized. A treatment-emergent high result is defined as a change from a value less than the high limit at all baseline visits to a value greater than or equal to the high limit at any time during the Treatment Period. A treatment-emergent low result is defined as a change from a value greater than the low limit at all baseline visits to a value less than or equal to the low limit at any time during the Treatment Period. For each vital sign and physical characteristic, only patients who were normal (i.e., less than the high limit for treatment-emergent high, or greater than the low limit for treatment-emergent low) at all baseline visits and who have at least one non-missing post-baseline result will be included in the denominator when computing the percentages of patients with treatment-emergent high or low results. Scheduled visits, unscheduled visits, and repeat measurements will be included. Table 2 will be used to define the low and high limits.

A by-patient listing of all vital signs and physical characteristics during the Treatment Period will be provided. Additionally, a by-patient listing of treatment-emergent high or low vital signs and physical characteristics during the Treatment Period will be provided.

Table 2 Selected Categorical Limits for Blood Pressure, Heart Rate and Weight

Parameter	Low	High
Systolic BP (mm Hg) [1] (supine or sitting – forearm at heart level)	≤ 90 and decrease from baseline ≥ 20	≥ 160 and increase from baseline ≥ 20
Diastolic BP (mm Hg) [1] (supine or sitting – forearm at heart level)	≤ 50 and decrease from baseline ≥ 10	≥ 100 and increase from baseline ≥ 10
Heart Rate (bpm) [1] (supine or sitting)	< 50 and decrease from baseline ≥ 15	> 120 and increase from baseline ≥ 15
Weight (kg) (consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease from baseline ≥ 7%	(Gain) increase from baseline ≥ 7%

1. Chobanian, AV, et al., The JNC 7 Report, The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, *JAMA*, 289:2560(2003).

4.6.6. Electrocardiograms

For each patient, a single 12-lead digital ECG was collected according to the Schedule of Activities. ECGs had to be recorded before collecting any blood for safety or PK tests. Unscheduled ECGs could be obtained at additional times, when deemed clinically necessary.

Digital ECGs were electronically transmitted from the investigator sites to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory conducted a full overread on ECGs (including all intervals). All data from the overreads were placed in the Lilly database for analytical and study report purposes.

Results for each ECG parameter will be summarized by treatment group at each visit for the observed data and for changes from baseline.

The overall ECG assessment as determined by the investigator will be reported as "Normal" or "Abnormal – not clinically significant", or "Abnormal – clinically significant" and summarized by visit and across visits. A shift table of overall ECG assessment from baseline to the most extreme post-baseline value will be presented.

Additionally, the highest post-baseline value for QTc interval (using Fridericia's correction) will be summarized descriptively as a categorical variable. Each QTcF value for a given subject will be grouped into 3 categories:

- QTcF interval ≥ 450 - <480 msec
- QTcF interval ≥ 480 - <500 msec
- QTcF interval ≥ 500 msec

The largest post-baseline change in QTcF measures will also be analyzed as categorical variables. The change in QTcF in a given subject will be grouped into 2 categories:

- QTcF interval increases from baseline ≥ 30 msec
- QTcF interval increases from baseline ≥ 60 msec

Relevant ECG data will also be displayed in separate listings for:

- Subjects who shifted from normal or abnormal not clinically significant at baseline to abnormal clinically significant during the treatment period
- Subjects who had an abnormal clinically significant assessment at any time during the study
- Subjects who ever had a QTcF interval increase from baseline ≥ 30 msec during the treatment period
- Subjects who ever had any value of QTcF interval ≥ 450 msec at any visit

4.6.7. Pregnancy

Any reported positive pregnancy results or reported pregnancies will be listed.

4.7. Other Analyses

4.7.1. Other variables and/or parameters

LY3462817 concentrations will be illustrated graphically and summarized descriptively. To facilitate the planning of future clinical studies, a model-based approach implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software may be conducted. Receptor occupancy and soluble PD-1 data over time will be summarized by dose level. Exploratory PK/PD analyses may be conducted to evaluate the relationship between LY3462817 exposure and selected measures of response (for example, RO, sPD-1, clinical endpoints, and/or biomarkers). As appropriate, data from the present study may be combined with data from other

studies in model-based analyses. Additional analyses may be conducted if deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

4.7.2. Subgroup analyses

Subgroup analyses of the primary endpoint will be made to assess consistency of the intervention effect across the following subgroups:

- previous RA therapy population (prior use of csDMARD only or prior tsDMARD/bDMARD use)
- gender
- race
- geographic region
- previous therapies,
- disease duration.

If the number of participants is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study.

A MMRM analysis will be used to analyze the subgroup analyses. The MMRM model will include treatment, strata (previous RA therapy population), subgroup, baseline value, visit, treatment-by-visit interaction, and treatment-by-subgroup in the model as fixed factors, and patient as a random factor. An unstructured covariance matrix will be used to model the within-subject errors. If this analysis fails to converge, other structures will be tested (in this order: Toeplitz, Autoregressive with heterogeneity, and Compound Symmetry). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

4.8. Interim Analyses

The analysis method for the primary efficacy endpoint described in Section **Error! Reference source not found.** Primary Endpoints/Estimands Analysis will be used for the interim analysis.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Some team members, who are responsible for providing the interim analysis results, will be unblinded to the individual treatment group assignments. Interim analysis results will not be shared with investigators, participants, or the study team who are involved in the conduct of the study before the final database lock.

Analyses for the primary database lock will be conducted when all participants have completed the Double-blind Treatment Period or discontinued treatment.

An interim analysis of the safety and efficacy data may be conducted prior to database lock, to support planning activities. This will be done when approximately 40% to 60% of participants have completed Period 1 (double-blind treatment) or have discontinued treatment.

A Bayesian posterior probability rule will be used to assess the efficacy of 700 mg vs placebo for DAS28-CRP for period 1. Two pairwise comparisons will be made and the corresponding posterior probability will be provided. Specifically, the pairwise comparisons will be 700mg vs placebo and 300mg vs placebo. The prior distribution for each arm will be assumed to a normal distribution with mean of 0 and standard deviation of 10. The error parameter will use an Inverse-Gamma distribution assuming central value of 10 and weight of 1. The posterior probabilities will be provided for each of the CSF's for both pairwise comparisons at the interim and also at the final analysis.

All interim analyses will be used to support planning activities associated with the clinical development program and to aid in the development of PK/PD modeling. Since the study may terminate early only for safety and/or futility, no adjustment of type I error will be performed.

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

There will be no DMC in this study. An Internal Assessment Committee (IAC) will be used to conduct the interim analysis. The IAC will consist of a limited number of prespecified members not part of the blinded study team who do not have direct site contact or data entry or validation responsibilities. Further details will be provided in the IAC charter.

4.9. Changes to Protocol-Planned Analyses

There is no change to protocol-planned analyses.

5. Sample Size Determination

Approximately 80 participants will be randomly assigned to study intervention. At the completion of the study, approximately 40 participants will have been randomized to LY3462817 700 mg and 20 participants will have been randomized to LY3462817 300 mg and placebo during the double-blind treatment. All randomized participants in FAS will be considered evaluable.

Assuming -1.80 and -0.75 as the DAS28-CRP change from baseline for LY3462817 700 mg and placebo, respectively, with standard deviation equal to 1.25, a 2-sided t-test with alpha = 0.05 has greater than 80% power to detect a statistically-significant difference in DAS28-CRP change from baseline at Week 12.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients in the FAS by treatment arm (LY3462817 300 mg, LY3462817 700 mg, and placebo) and overall and provided as listing:

Demographics:

- Sex (Female, Male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and their subcategories)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and their subcategories)
- Age (years)
- Baseline Weight (kg) and Height (cm)
- Baseline BMI (kg/m2)

Baseline characteristics:

- DAS28-CRP
- TJC
- SJC
- PhGADA_VAS (VAS)
- PaGADA_VAS (VAS)
- Patient's global assessment of arthritis pain (VAS)
- Patient's assessment of physical function (HAQ-DI)
- SDAI
- CDAI

6.2. Appendix 2: Treatment Compliance

Treatment compliance will not be calculated in this study.

6.3. Appendix 3: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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