Statistical Analysis Plan Version 4 H0P-MC-OA01

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3016859 for the Treatment of Osteoarthritis

NCT04456686

Approval Date: 19-Oct-2021

1. Statistical Analysis Plan: H0P-MC-OA01: Intervention-Specific Appendix (ISA) for LY3016859

Epiregulin/TGFα (LY3016859) for the Treatment of Pain from Osteoarthritis of the Knee

This is a randomized, placebo-controlled, phase 2 clinical trial to evaluate LY3016859 for the treatment of pain in participants who have been diagnosed with osteoarthritis of the knee.

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Protocol H0P-MC-OA01
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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3. Revision History

H0P-MC-OA01 SAP Version 1 was approved prior to unblinding data for H0P-MC-OA01.

H0P-MC-OA01 SAP Version 2 was approved prior to unblinding H0P-MC-OA01 data for PoC lock.

H0P-MC-OA01 SAP Version 3 was approved prior to unblinding H0P-MC-OA01 data for PoC lock. The following updates were made:

- Section 6.1, the estimand for this ISA was described.
- Section 6.10.3, the details for the constrained model for the key secondary endpoint were added.
- Section 6.17, section added to describe the safety totality of evidence analysis.

H0P-MC-OA01 SAP Version 4 was approved prior to the final lock. The following updates were made:

- Section 6.11, bioanalytical and pharmacokinetic/pharmacodynamic analysis was updated.
- Section 6.12.2, definition for post-treatment-emergent adverse events was updated.
- Section 6.12.4, the analysis for renal function assessment was updated.
- Section 6.12.5, immunogenicity analysis was added.
- Section 6.13, frequentist MMRM was added as a sensitivity analysis.
- Section 6.14, ‘violations’ is replaced with ‘deviations’ for consistency across CPMP documents, and the list of IPDs is referenced in the trial issue management plan. The prohibited medications and drugs of abuse list was moved to the CPMP SAP because it applies across all ISAs, and acetylsalicylic acid was added to the list of prohibited medications.
- Section 7, text on maintaining the blind for assessment committee review was deleted from OA01 SAP V4 since it is covered in H0P-MC-CPMP SAP Version 5.
- Section 8, additional analyses for the double-blinded treatment and safety follow-up period combined was added for the final lock.

4. Study Objectives

4.1. Primary Objective

The primary objective of this ISA is stated in the H0P-MC-CPMP protocol. For H0P-MC-OA01, endpoint is defined as 8 weeks post initial treatment administration.

4.2. Secondary Objectives

Secondary objectives applicable to all ISAs are listed in the H0P-MC-CPMP SAP Version 5.

The key secondary objective for H0P-MC-OA01 is to evaluate whether LY3016859 is superior to placebo in reducing pain as measured by the mean change from baseline assessment to Week 8 for pain intensity measured by the Western Ontario and McMaster University Arthritis Index (WOMAC®) Pain Subscale.

Additional secondary endpoints specific to H0P-MC-OA01 are listed below.

Objective	**Endpoint Measure**
Other Secondary	

Physical Functioning
Efficacy of LY3016859 versus placebo
	• Change from baseline to endpoint for WOMAC® for
	  o stiffness subscale
	  o physical function subscale
	• Proportion of participants with reduction from baseline greater than 30%, 50%, and 70% on WOMAC pain subscale across all time points
	• Proportion of participants with reduction from baseline greater than 30%, 50%, and 70% on WOMAC physical function subscale across all time points
	• Proportion of participants with reduction from baseline greater than 30%, 50%, and 70% on WOMAC stiffness subscale across all time points
	• Time to first treatment response with at least 30%, 50%, and 70% reduction from baseline in WOMAC pain subscale

4.3. Exploratory Objectives

The following exploratory objectives and endpoints are specific to H0P-MC-OA01.

Objectives	**Endpoints**
Tertiary/Exploratory	
Characterize the pharmacokinetics and pharmacodynamics of LY3016859 after multiple intravenous infusions in participants with osteoarthritis	Assessment of serum concentrations of LY3016859 and epiregulin to enable pharmacokinetic and pharmacodynamic evaluations
Characterize immunogenicity of LY3016859	Appearance of anti-drug antibodies and neutralizing antibodies to LY3016859

Explore the effect of LY3016859 on the kidney	Assessment of • urine albumin/creatinine ratio • urine protein/creatinine ratio • eGFR

Abbreviations: eGFR = estimated glomerular filtration rate.

5. Study Design

5.1. Summary of Study Design

The H0P-MC-CPMP SAP Version 5 provides a summary of the overall study design for the chronic pain master protocol. This section describes ISA-specific study design components.

Post-treatment Follow-up Period (Visits 801-803)

Participants must complete 3 post-treatment follow-up visits for safety, PK and immunogenicity assessment at Visits 801-803, according to the Schedule of Activities (SoA).

The site schedules Visit 801 approximately 4 weeks after Visit 7, Visit 802 approximately 8 weeks after Visit 7, and Visit 803 approximately 18 weeks after Visit 7.

If the participant receives at least one dose of intervention and discontinues during the double-blind treatment period, they should complete early discontinuation procedures per the CPMP Protocol SoA and Visit 801 should be scheduled approximately 30 days after the last dose of study intervention

5.2. Determination of Sample Size

Approximately 125 participants will be randomized in a 2:1 ratio to LY3016859 or placebo, respectively. It is expected that approximately 107 participants will complete the double-blind treatment period of the study. CCI [redacted]

[redacted] If there is no treatment difference between placebo and LY3016859, the probability of passing the efficacy criterion specified above (i.e., false positive) is approximately 0.1. The simulation for the power calculation and sample size determination was carried out in FACTS Version 6.0.

CCI [redacted] If there is no treatment difference between placebo and LY3016859, the probability of passing the efficacy criterion specified above for average pain intensity (i.e., false positive) is approximately 0.1.

5.3. Method of Assignment to Treatment

The method of treatment assignment is described in the H0P-MC-CPMP SAP Version 5.

6. A Priori Statistical Methods

6.1. General Considerations

The estimand for the primary clinical question of interest has been described in the H0P-MC-CPMP SAP Version 5.

The key secondary clinical question of interest is: What is the treatment difference between LY and placebo assessed using mean change from baseline to Week 8 for pain as measured by the WOMAC pain subscale in participants with osteoarthritis of the knee regardless of initiation of rescue medication or other allowed concomitant medication and assuming that they would have continued initially randomized treatment condition?

- **Treatment condition**: the randomized treatment along with potential use of rescue medication or other allowed concomitant medications regardless of adherence
- **Population**: participants with chronic pain conditions.
- **Endpoint**: change from baseline to Week 8 in WOMAC pain subscale
- **Intercurrent events**: The intercurrent event is treatment discontinuation for any reason.
- **Population-level summary**: difference in mean changes from baseline between treatment conditions

The estimand is following a hypothetical strategy where efficacy of LY is assessed under the assumption that the participants would have continued their initially randomized treatment condition even if they discontinued.

Other general considerations for analyses are described in the H0P-MC-CPMP SAP Version 5.

6.2. Adjustments for Covariates

The general adjustment strategy has been described in the H0P-MC-CPMP SAP Version 5.

6.3. Handling of Dropouts or Missing Data

The missing data strategy has been described in the H0P-MC-CPMP SAP Version 5.

6.4. Multiple Comparisons/Multiplicity

There is no plan to formally adjust for multiplicity.

6.5. Use of an "Efficacy Subset" of Participants

There are no plans to use a modified efficacy subset.

6.6. Participant Disposition

The summary of participant disposition has been described in the H0P-MC-CPMP SAP Version 5.

6.7. Participant Characteristics

The summary of participant characteristics has been described in the H0P-MC-CPMP SAP Version 5.

6.8. Treatment Compliance

To assess the impact of compliance to the protocol specified dosing schedule, the number of days between each infusion will be summarized and reported by treatment arm. The summaries will include descriptive statistics (sample size at visit, mean, SD, median, minimum, maximum). No inferential statistics will be reported.

6.9. Concomitant Therapy

The summary and reporting of concomitant therapy has been described in the H0P-MC-CPMP SAP Version 5. No additional covariates will be considered in the models of weekly rescue medication use.

6.10. Efficacy Analyses

6.10.1. Primary Outcome and Methodology

The analysis of the primary outcome has been described in the H0P-MC-CPMP SAP Version 5. The longitudinal model will include average NRS during the preliminary data entry period (PDEP) period and within each nominal week of the double treatment period as a longitudinal outcome. As noted in Section 4.1, endpoint for the primary analysis is defined as 8 weeks post initial treatment administration.

6.10.2. Additional Analyses of the Primary Outcome

There are no additional analyses planned for the primary outcome.

6.10.3. Secondary Efficacy Analyses

Secondary efficacy analyses common to all ISAs within H0P-MC-CPMP have been described in the H0P-MC-CPMP SAP Version 5. H0P-MC-OA01 will also consider the following secondary analyses.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) is a validated instrument that is extensively used to evaluate the response to medications for the treatment of osteoarthritic pain. The WOMAC Version LK3.1 will be administered according to the Schedule of Activities.

This table describes the 24-question WOMAC and subscales.

Dimensions/Subscales	Number of Questions
Pain	5
stiffness	2
physical function	17

The participants will record their responses using a 0 to 4 Likert scale for each question:

0 = no pain, and

4 = extreme pain.

The scores for each subscale will be calculated by summing the scores of the questions in the respective subscale for each participant at each time point.

The range of possible scores for each subscale is pain = 0 to 20, stiffness = 0 to 8, and physical function = 0 to 68.

Key Secondary Analysis

A Bayesian longitudinal mixed-model repeated measures analysis (MMRM) will be performed to evaluate the change from baseline to each post baseline visit for the WOMAC® pain subscale, physical function subscale, and stiffness subscale. The model will utilize the constrained cell means model so that a common mean is estimated at the baseline. More details on this approach are provided in the H0P-MC-CPMP SAP Version 5.

This table describes information included in the model.

Categorical factors	• the interaction of treatment and timepoint (constrained to estimate a common mean at baseline across treatments) • average baseline pain severity category (baseline NRS < 7, baseline NRS >= 7) • pooled investigative site
Continuous covariates	• none

Other Secondary Analysis

The proportion of participants in each treatment group meeting pre-specified binary response thresholds will be calculated for each post baseline time point and will be used to compare treatment groups.

The prespecified binary response thresholds for WOMAC® pain and function subscales are 30%, 50%, and 70%.

A Bayesian pseudo-likelihood-based categorical repeated measures regression model that includes all post baseline observations will be used to estimate the probability of achieving the response level in each treatment group and will be used to compare treatment groups.

The model will include the categorical and continuous covariates described for the key secondary analysis.

In addition, time to first treatment response from baseline based on the prespecified binary thresholds above will assessed. Analyses will conducted according to the time to event analyses specified in the CPMP SAP Version 5.

6.12. Safety Analyses

The general analysis of safety has been described in the H0P-MC-CPMP SAP Version 5. However, additional ISA-specific safety considerations are described in the sections below.

6.12.1. Extent of Exposure

The cumulative dosage taken during the double-blind treatment period will be summarized. In addition, the distribution of the number of doses received during the double-blind treatment period will be summarized by reporting the number and percent of participants in the safety population who received 1, 2, 3, or 4 infusions during the double-blind treatment period.

Duration of exposure to study drug (defined as the time since first injection of the study treatment in days) will be summarized by treatment group using descriptive statistics; the summary will also include the total exposure in patient years.

Duration of exposure (days):
= Date of last study visit (scheduled or unscheduled) during the double blind treatment period – Date of first injection of the study treatment + 1

Total exposure in patient years will be calculated as follows:
Total exposure in patient years = Sum of duration (days) of exposures for all patients in the treatment group/365.25

6.12.2. Adverse Events

The general analysis of adverse events has been described in the H0P-MC-CPMP SAP Version 5.

This ISA will also consider post-treatment-emergent adverse events due to the long follow-up period.

A post-treatment-emergent adverse event (PTEAE) is defined as an event that first occurs or worsens in severity after treatment discontinuation and on or before study discontinuation. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in the post-treatment-emergent computation. The maximum severity for each LLT during the treatment period will be used as a reference.

The baseline of PTEAE is from the first dosing date to the treatment disposition in the double-blind treatment phase. The post-treatment follow-up period will be included as postbaseline for this analysis. While unusual, it is possible to have a missing severity for events. Events with a missing severity during the post-treatment period will be treated as "severe" and post-treatment emergent events will be determined by comparing with treatment period. All events occurring after the day of treatment discontinuation will be treated as post-treatment period.

PTEAEs will be summarized by preferred term and by preferred term within system organ class in participants who received LY3016859.

6.12.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

The general summary of adverse of events is described in the H0P-MC-CPMP SAP Version 5.

Treatment emergent adverse events of special interest will be summarized separately by preferred term. These events include

- infusion site reactions (preferred MedDRA term)
- hypersensitivity and infusion-related reactions
    - Anaphylatic reaction (SMQ)
    - Anaphylatic/anaphylactoid shock conditions (SMQ)
    - Angioedema (SMQ)
    - Hypersensitivity (SMQ)
    - Infusion-related reaction (preferred MedDRA term)
- dermatological adverse events
    - Severe cutaneous adverse reactions (SMQ)
    - Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)
- abnormal renal function
    - Renal function analyses (MedDRA HLT)
    - Renal failure and impairment (MedDRA HLT)

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6.12.6. Vital Signs and Other Physical Findings

The analysis of vital sign parameters is described in the H0P-MC-CPMP SAP Version 5.

6.12.7. Electrocardiograms

The analysis of electrocardiograms parameters is described in the H0P-MC-CPMP SAP Version 5.

6.13. Subgroup Analyses

General subgroup analyses are described in the H0P-MC-CPMP SAP Version 5. H0P-MC-OA01 will also consider the following subgroup analyses for the primary efficacy outcome and key secondary outcome.

Subgroup Variable	Categories
Kellgren-Lawrence Grade	Categories: Grade 2, Grade 3, Grade 4 Note: Alternative groupings may be created based on the number of participants classified within each grade (e.g. <3, ≥3)

The subgroup analyses will be conducted using similar modeling approaches as the primary and key secondary analyses. Additional factors in the model are described in the H0P-MC-CPMP SAP Version 5. The treatment difference at the endpoint will be reported within each level of the subgroup factor along with 95% credible intervals. The results may also be presented in a forest plot. Frequentist MMRM will be performed as a sensitivity analysis using the modeling approach described in the H0P-MC-CPMP SAP Version 5.

6.14. Protocol Deviations

Participants with study important protocol deviations will be summarized by type of deviation and listed by treatment and investigative site.

Important protocol deviations for the study are described in the H0P-MC-CPMP SAP Version 5 and H0P-MC-OA01 Trial Issue Management Plans.

6.15. Interim Analyses and Data Monitoring

Interim analyses will be conducted under the auspices of an Assessment Committee according to the specifications set forth in the protocol. These analyses will be at the CPMP level and will consider data from all ongoing ISAs. Details are provided in the H0P-MC-CPMP SAP Version 5.

There are no additional interim analyses planned for H0P-MC-OA01.

6.16. Planned Exploratory Analyses

In addition, a cumulative distribution function of percent change from baseline to endpoint for the WOMAC® pain and physical function subscales will be provided for each treatment group. However, no statistical comparisons will be made between the groups.

6.17. Totality of Evidence for Safety

The totality of evidence for safety analysis has been briefly described in the H0P-MC-CPMP SAP Version 5. The key safety events to be considered for H0P-MC-OA01 are listed below by domain:

General Adverse Event Information

- Serious adverse events related to study treatment
- Study discontinuation due to adverse event
- Treatment discontinuation due to adverse event

Cardiovascular

- QTc prolongation: > 60 msec increase
- Serious cardiac disorders adverse event

Liver function

- Hy's Law case: Serum total bilirubin ≥ 2 and ALT ≥ 3 for at least one visit during the double-blind treatment period

Metabolic function

- Serious hypoglycemia adverse event
- Treatment emergent HbA1c: Shift from low/normal at baseline to high at least once during the double-blind treatment period

Renal function

- Treatment emergent abnormal eGFR: Shifts
    - Mild at baseline to moderate/severe during the double-blind treatment period
    - Moderate at baseline to severe during the double-blind treatment period

Dermatological

- Serious or severe dermal reactions

Hypersensitivity

- Moderate to severe infusion site reactions
- Serious or severe hypersensitivity reactions

6.18. Annual Report Analyses

Analyses will be produced as needed for the purposes of providing periodic safety reviews to regulatory agencies (e.g. Development Safety Update Reports.) Data from this ISA will be combined with data from other clinical studies that investigated LY3016859. In all analyses, a combined LY arm will be created which includes participants assigned to any dose of LY3016859 in the included studies, including LY-combination regimens.

The following data will be summarized by treatment group.

- Enrollment (ongoing and completed)
- Demographics (Race, ethnicity, and gender)
- Exposure
    - Cumulative number of subjects exposed to LY3016859
    - Cumulative number of subjects exposed to LY3016859 by age
    - Cumulative number of subjects exposed to LY3016859 by sex
    - Cumulative number of subjects exposed to LY3016859 by race
- Cumulative summary of serious adverse events

The following listings will be provided.

- List of serious adverse events during the reporting period
- List of subjects who died
- Cumulative list of subjects who discontinued due to an adverse event (discontinued from treatment or study)
- List of subjects who discontinued due to an adverse event during the reporting period

Additional analyses may be added or omitted at the time of report submission as needed.

6.19. 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.

- A serious adverse event is an adverse event that is considered 'Serious' whether 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 participants 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.

A summary of a baseline characteristics XML file will be provided.

7. Unblinding Plan

The general unblinding plan is described in the H0P-MC-CPMP SAP Version 5. Unblinding considerations specific to H0P-MC-OA01 are provided below.

Immunogenicity Analysis Planning

To support the assessment committee's evaluation of immunogenicity, a limited number of preidentified individuals may also gain access to the unblinded data. The project statistician will work with the clinical immunogenicity scientist and clinical lab data scientist to determine an appropriate amount of ISA-level data to support this objective. The timing of the transfer of treatment assignment and immunogenicity data will be based on this collaboration. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

8. Reports to be Generated at Final Database Lock

The following analysis will be performed for final database lock.

- Patient disposition - the analysis of patient disposition conducted in POC lock will be conducted for double-blind treatment and safety follow-up period combined.
- eCOA compliance - the overall eCOA compliance analysis conducted in POC lock will be summarized for the PDEP period plus at each nominal week up to Visit 801.
- Concomitant therapy – the analysis conducted in POC lock will be repeated including safety follow up period combined (may also include PDEP) except the listing of rescue medication use above protocol specified limits.
- Efficacy endpoint – The weekly average pain intensity via NRS will be calculated with extension to week 12 (Visit 801). The following analysis will be conducted across all time points in the double-blinded treatment and safety follow-up period combined (DB plus FU) based on the same model conducted in DB treatment period only.
    - Change from baseline in average pain intensity measured by weekly average of NRS
    - Change from baseline in worst pain intensity measured by weekly average of NRS
    - Change from baseline in DSA-specific physical functioning measures
    - Proportion of participants with a pain reduction from baseline greater than or equal to 30%, 50%, and 70% as measured by the average pain responses on the NRS
    - Proportion of participants with reduction from baseline greater than 30%, 50%, and 70% on DSA-specific physical function subscale
    - Overall improvement as Measured by Patients' Global Impression of Change (PGI)

      A frequentist MMRM analysis will be conducted as a sensitivity analysis for the primary and some secondary endpoints.

      A Bayesian MMRM subgroup analysis of baseline pain severity (<7, >=7) will be also evaluated for the primary and key secondary endpoint. A frequentist MMRM analysis will be performed as a sensitivity analysis for subgroup analysis.
- Safety analyses for TEAEs – the following analysis will be repeated including double-blind and safety follow-up period unless otherwise specified.
    - Overview of adverse event
    - SAE and a listing of SAE

  - TEAE and Post-treatment emergent adverse event (PTEAE) by PT, by PT within SOC. A listing of TEAE and PTEAE will be provided.
  - Post-treatment emergent AE by PT, by PT within SOC for safety follow-up period only
  - Adverse event of special interest (ISA specific)
- Laboratory measures – the analysis conducted in POC lock will be repeated in DB plus FU period. The additional analysis will be included
  - The shift table of eGFR at baseline vs. postbaseline by minimum, maximum and last observed eGFR result will be summarized.
  - Summary of treatment-emergent ADA positive anytime in DB treatment period by ADA positive titer status at the last non-missing assessment in safety follow-up period will be presented by treatment.
  - A shift table of ADA from maximum baseline ADA titer to maximum postbaseline ADA titer in LY3016859 arm will be reported.
  - A listing of participants with ADA Detected at any time for safety population will be provided.
  - Summary of hepatic function laboratory maximum observed result will be presented.
- Vital signs – the analysis conducted in POC lock will be repeated for combined DB plus FU period.
- ECG - the analysis conducted in POC lock will be repeated for combined DB plus FU period. Additionally, a summary of ECG measures and boxplot will be provided as well as a listing of out of range of ECGs.
- Protocol deviations - the analysis conducted in POC lock will be repeated for combined DB plus FU period.

9. References

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10. Appendices

Appendix 1. Planned Laboratory Analytes and Direction of Interest

The H0P-MC-CPMP SAP Version 5 describes tests that may be performed broadly for the Chronic Pain Master Protocol. This table describes additional tests in H0P-MC-OA01.

Chemistry		Other Tests
Cystatin-C	CCI	Immunogenicity
		Serum Epiregulin
		LY3016859 concentration
.		Urine pregnancy

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