This study H0P-MC-OA03 (NCT04627038) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

H0P-MC-OA03 Statistical Analysis Plan Version 2

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3556050 for the Treatment of Osteoarthritis Pain

NCT04627038

Approval Date: 11-Nov-2021

1. Statistical Analysis Plan: H0P-MC-OA03: Intervention-Specific Appendix (ISA) for LY3556050

LY3556050 Pain from Osteoarthritis of the Knee

This is a randomized, placebo-controlled, phase 2 clinical trial to evaluate LY3556050 for the treatment of pain in participants who have been diagnosed with osteoarthritis of the knee.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol H0P-MC-OA03
Phase 2

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

Approval Date: 11-Nov-2021 GMT

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3. Revision History

SAP Version 1 was approved prior to unblinding data for H0P-MC-OA03.

SAP Version 2 was approved prior to unblinding data for PoC lock. Major revisions included:

- Section 5.2, determination of sample size was adjusted along with the protocol amendment.
- Section 5.3, the method of treatment assignment description was added to align with protocol amendment.
- Section 6.1, the estimand for this ISA was described.
- Section 6.3, multiple imputation method was added as a sensitivity analyses
- Section 6.10.3, the details for the constrained model for the key secondary endpoint were added.
- Section 6.12.2, additional treatment-emergent adverse events and narratives for patients with "notable" events were updated.
- Section 6.12.4, additional orthostatic vital sign summaries added.
- Section 6.13, subgroup analyses were updated to align with H0P-MC-CPMP SAP version 5 and frequentist subgroup analyses were added.
- Section 6.14, important protocol deviations summaries and listing was updated.
- Section 6.16, planned exploratory analyses were updated, including adding frequentist MMRM as sensitivity analyses and details of propensity score analyses.

4. Study Objectives

4.1. Primary Objective

The primary objective of this ISA is stated in the H0P-MC-CPMP protocol. For H0P-MC-OA03, endpoint is defined as 8 weeks post initial treatment administration at Visit 7. The timepoint for secondary endpoint measurements is the same as the primary endpoint except for the overall measures.

4.2. Secondary Objectives

The key secondary objective is to evaluate whether LY3556050 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. Secondary objectives applicable are listed in the H0P-MC-CPMP SAP Version 5.

Additional secondary endpoints specific to H0P-MC-OA03 are listed below.

Objective	Endpoint Measure
Other Secondary	
Efficacy of LY3556050 versus placebo	• Mean change from baseline to endpoint for WOMAC® for stiffness and physical function subscale • Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% on WOMAC pain subscale across all time points • Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% on WOMAC physical function subscale across all time points • Overall mean change from baseline assessment for average pain intensity (NRS) during the treatment phase • Overall mean change from baseline assessment for WOMAC pain subscale during the treatment phase


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5. Study Design

5.1. Summary of Study Design

The H0P-MC-CPMP protocol provides a summary of the overall study design for the chronic pain master protocol. ISA-specific study design is provided in H0P-MC-OA03 protocol.

5.2. Determination of Sample Size

Up to 200 participants will be randomized in a CCI ratio to LY3556050 and placebo, respectively. Assuming an overall dropout rate of approximately 33%, CCI

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If there is no treatment difference between placebo and LY3556050, the probability of passing the efficacy criterion specified above (i.e., false positive) is less than 0.1. The simulation for the power calculation and sample size determination was carried out using the Fixed and Adaptive Clinical Trial Simulator (FACTS) Version 6.0.

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If there is no treatment difference between placebo and LY3556050, 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. Originally, all patients were randomized to 600mg LY BID or Placebo. The OA03 protocol amendment introduced a dose titration scheme, starting with 200mg BID and increasing to as much as 600mg BID, based on tolerability. More details about the dose modification can be found in the protocol amendment.

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. Unless otherwise stated, all efficacy and safety analyses will be conducted for LY vs. Placebo, where all LY doses are combined.

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.

In addition to use of Bayesian MMRM model described in the H0P-MC-CPMP SAP, to examine the effect of missing data, constrained cell means MMRM with multiple imputation will be applied as a sensitivity analysis to assess change from baseline to postbaseline measure for WOMAC pain subscale, VAS, and NRS.

For these continuous efficacy endpoints, a Markov chain Monte Carlo (MCMC) method will be used to impute intermittent (non-monotone) missing visit data and a set of Bayesian regressions will be used for the imputation of monotone dropouts. Variable pooled investigative site, treatment, age, gender, baseline pain severity categories will be included for imputing non-monotone missingness, and primary AEs leading to treatment discontinuation will be included as an additional variable for imputing monotone missingness. Subject-level indicator of primary AEs leading to treatment discontinuation is set to 1 for patients experiencing AEs in PT terms,

including nausea, dizziness, fatigue, abdominal discomfort, abdominal pain lower, abdominal pain upper, constipation, lethargy, somnolence, at any time during DB treatment period; 0 otherwise. The number of imputed data sets will be 200 and the initial seed for imputing intermittent missing data is 12345 and for imputing monotone missing data is 678910. Within the program, the seed will be used to generate 200 seeds needed for imputation.

The analysis model will utilize the constrained cell means MMRM so that a common mean is estimated at the baseline for each imputed dataset. Pooled investigative site, treatment and time interaction, baseline pain severity categories will be included as fixed effects. Results across the imputed datasets will be aggregated using SAS Proc MIANALYZE in order to compute LS means and standard errors for the treatment comparisons.

6.4. Multiple Comparisons/Multiplicity

There is no plan to formally adjust for multiplicity.

6.5. Use of an "Efficacy Subset" of Patients/Subjects

There are no plans to use a modified efficacy subset.

6.6. Patient/Subject Disposition

The summary of patient disposition has been described in the H0P-MC-CPMP SAP. Kaplan Meier plot of time to last dosing by treatment group will also be provided to describe patient disposition.

6.7. Participant Characteristics

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

6.8. Treatment Compliance

Treatment percentage of compliance will be calculated as:

$$\frac{Total\ pills\ \ taken\ * 100}{Total\ pills\ expected}$$

with total pills taken calculated by total pills dispensed – total pills returned. A patient is considered to be compliant overall if the percentage is between 80% and 120% from Visit 4 to 7. The percentage of patients who are compliant with study drug will be summarized by treatment group. Comparisons between treatment group for treatment compliance will be performed using a Fisher's Exact test. In addition, a listing of dose adjustment will be provided.

6.9. Concomitant Therapy and eCOA compliance

The summary and reporting of concomitant therapy and eCOA compliance has been described in the H0P-MC-CPMP SAP Version 5. No additional covariates will be considered in the model 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, last 7 days prior to randomization at Visit 3) 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

The overall mean treatment effects in change from baseline over the double blind treatment period will be reported for evaluating treatment effect for NRS, WOMAC subscales, VAS, as well as other secondary continuous efficacy endpoints.

Borrowing placebo information by pooling from OA01 (excluding patients participating OA03) for the evaluation of treatment effect on the mean change from baseline by WOMAC pain subscale, VAS, and NRS will be performed following the description in H0P-MC-CPMP SAP Section 6.12.1. Descriptive statistics of primary outcome variables by demographics, disposition, disease characteristics, and treatment administration may be summarized by ISA, in order to examine the population homogeneity assumption between ISAs.

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-OA03 will also consider the following secondary analyses. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) (Bellamy, 2005) 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 (30%, 50%, 70%) will be calculated for each post baseline time point and will be used to compare treatment groups for WOMAC® pain and physical function subscales.

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 be conducted according to the time to event analyses specified in the CPMP SAP.

6.11. Pharmacokinetic/Pharmacodynamic Methods

The observed plasma concentrations for LY3556050 will be reported graphically and summarized descriptively. Exploratory model-based pharmacokinetic (PK) and PK-pharmacodynamic (PD) analyses may be conducted to characterize the PK of LY3556050 in participants with OA and to assess exposure-response relationships for efficacy and safety outcomes. Participant factors may be investigated to assess their effects on model parameters.

Additional analyses may be conducted, as needed. Data from this study may be pooled with data from other studies, if appropriate.

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

Duration of exposure (defined as time since first dose of study treatment in days) to study drug 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 visit (scheduled or unscheduled) during the Double Blind treatment period – Date of first dose for the treatment period + 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

See Section 6.16 for additional dosing analyses.

6.12.2. Deaths, Other Serious Adverse Events, and Other Adverse Events for Review

Treatment-emergent adverse events by preferred term will be reported.

In addition to an overall listing, additional lists by terms or organ systems of interest, including cardiovascular, thyroid, and renal functions, will be generated.

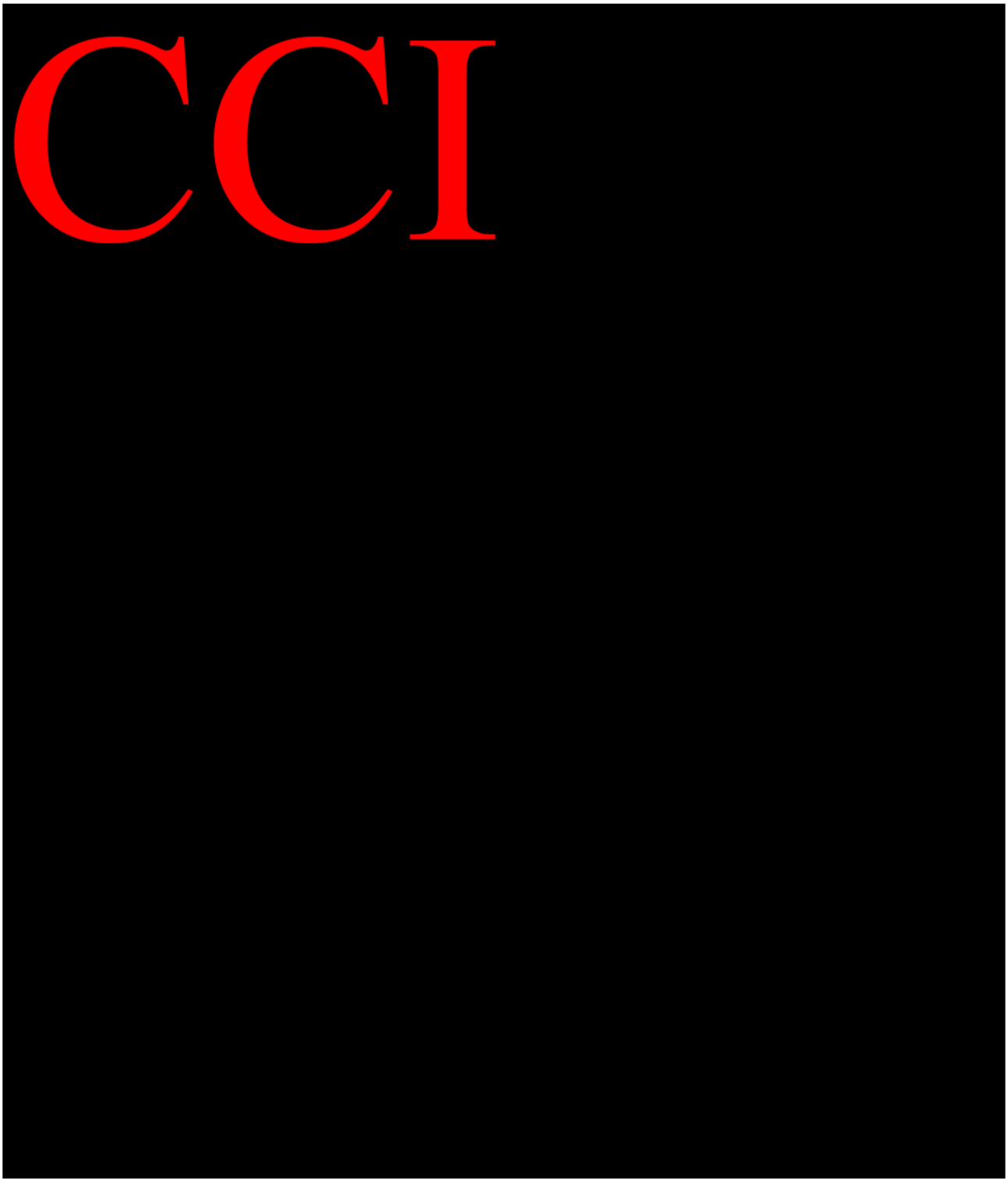
The full summary of adverse of events is described in the H0P-MC-CPMP SAP. Other adverse events for review coded to Medical Dictionary for Regulatory Activities (MedDRA) terms include

- Hypothyroidism (SMQ)
- Cardiac arrhythmias
    - Arrythmia related investigations, signs and symptoms (SMQ)
    - Bradyarrhythmia terms, nonspecific (SMQ)
    - Cardiac arrhythmia terms, nonspecific (SMQ)
    - Conduction defects (SMQ)
    - Disorders of sinus node function (SMQ)
    - Supraventricular tachyarrhythmias (SMQ)
    - Tachyarrhythmia terms, nonspecific (SMQ)
    - Ventricular tachyarrhythmias (SMQ)
- Hypotension
    - Orthostatic hypotension (preferred MedDRA term)

  - Blood pressure ambulatory decreased (preferred MedDRA term)
  - Blood pressure decreased (preferred MedDRA term)
  - Blood pressure diastolic decreased (preferred MedDRA term)
  - Blood pressure systolic decreased (preferred MedDRA term)
  - Blood pressure orthostatic decreased (preferred MedDRA term)
  - Dizziness (preferred MedDRA term)
  - Dizziness exertional (preferred MedDRA term)
  - Presyncope (preferred MedDRA term)
  - Syncope (preferred MedDRA term)
- Abnormal renal function
  - Renal function analyses (MedDRA HLT)
  - Renal failure and impairment (MedDRA HLT)
- MACE (including MI and stroke)
  - Death (preferred MedDRA term)
  - Cardiac arrest (preferred MedDRA term)
  - Cardiac death (preferred MedDRA term)
  - Sudden cardiac death (preferred MedDRA term)
  - Sudden death (preferred MedDRA term)
  - Ischemic heart disease (SMQ)
  - Ischemic central nervous system vascular conditions (SMQ)
- Depression
  - Depressed mood disorders and disturbances (MedDRA HGLT)
- Congestive Heart Failure
  - Cardiac Failure (SMQ)
- Substance abuse
  - Substance related and addictive disorders (MedDRA HLT)

Narratives will be provided for patients with the following "notable" events, in addition to the "notable" events listed in the H0P-MC-CPMP SAP.

- Elevated amylase or lipase >3x ULN
- Renal Treatment Emergent Adverse Events



6.12.4. Vital Signs and Other Physical Findings

The analysis of vital sign parameters are described in the H0P-MC-CPMP SAP Version 5. Supine, standing, and orthostatic vital signs data will be summarized by treatment, together with changes from baseline, where baseline is defined as Visit 3 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment. Additional

categorical criteria for abnormal treatment-emergent blood pressure and pulse measurement for adults in OA03 are:

Parameter	Criteria
Orthostatic hypotension (Orthostatic Systolic BP, in mmHg)	Decrease in SBP when going from 5 minutes supine to 2-3 minutes standing of ≥ 20mm Hg
Orthostatic hypotension (Orthostatic Diastolic BP, in mmHg)	Decrease in DBP when going from 5 minutes supine to 2-3 minutes standing of ≥ 10mm Hg
Orthostatic Pulse Rate (Postural Orthostatic Tachycardia, in bpm)	Increase in pulse when going from 5 minutes supine to 2-3 minutes standing of ≥ 30

6.12.5. Electrocardiograms

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

The percentages of participants who experienced treatment-emergent increase from PR interval, QRS interval, and heart rate will be summarized according to CPMP SAP Version 5 Table 6.10. Additionally, the percentages of participants who experienced a PR interval value greater or equal to 240 msec at any time will be summarized.

6.13. Subgroup Analyses

General subgroup analyses are described in the H0P-MC-CPMP SAP Version 5.

H0P-MC-OA03 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.

A sensitivity analysis with frequentist MMRM may be performed as deemed appropriate in H0P-MC-OA03 using the modeling approach described in the H0P-MC-CPMP SAP Version 5.

6.14. Protocol Deviations

Patients 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 and H0P-MC-OA03 Trial Issue Management Plans.

6.15. Interim Analyses and Data Monitoring

Safety review 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.

No interim analyses are planned for H0P-MC-OA03. If an unplanned interim analysis is deemed necessary, the interim analysis will be conducted under the auspices of the Assessment Committee (AC), and the AC will disseminate interim results, if it is necessary, in a manner that will not affect the conduct of the ongoing study.

6.16. Planned Exploratory Analyses

The following analyses may be conducted for exploratory purposes:

- Sensitivity analyses by including only post protocol amendment patients to conduct efficacy analyses on NRS, WOMAC pain subscale, and VAS, with Bayesian MMRM model described in the H0P-MC-CPMP SAP will be conducted to compare with statistical inferences based on analyzing overall patient population.
- A frequentist MMRM analysis will be conducted as a sensitivity analysis for the primary and some secondary endpoints.
- 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.
- The following analysis is to explore different doses of LY3556050:

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6.17. 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 LY3556050. In all analyses, a combined LY arm will be created which includes participants assigned to any dose of LY3556050 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 LY3556050
  - Cumulative number of subjects exposed to LY3556050 by age
  - Cumulative number of subjects exposed to LY3556050 by sex
  - Cumulative number of subjects exposed to LY3556050 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.

6.18. 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 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.

7. Unblinding Plan

The general unblinding plan is described in the H0P-MC-CPMP SAP. Unblinding considerations specific to H0P-MC-OA03 are provided below.

PKPD Analysis Planning

A limited number of prespecified individuals who are not part of the blinded study team and do not have direct site contact, data entry, or data validation responsibilities, may receive access to unblinded data, prior to the interim or final database lock, in order to initiate the final population PKPD model development processes. This will be described in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

8. References

Bellamy N. The WOMAC Knee and Hip Osteoarthritis Indices: Development, validation, globalization and influence on the development of the AUSCAN Hand Osteoarthritis Indices. *Clin Exp Rheumatol*. 2005;23(Suppl.39):148-153.

Oliver Kuss, Maria Blettner, etc. Propensity score: an alternative method of analyzing treatment effects. *Dtsch Arztebl Int*. 2016 Sep; 113(35-36): 597–603.

9. Appendices

Appendix 1. Planned Laboratory Analytes and Direction of Interest

The H0P-MC-CPMP SAP describes tests that may be performed broadly for the Chronic Pain Master Protocol. This table describes tests unique to H0P-MC-OA03.

Chemistry	Additional Thyroid Tests	Other SST-Regulated Hormones	Other Tests
Cystatin-C	Free Triiodothyronine (FreeT3)	Growth hormone	Amylase
TSH	Total Triiodothyronine (T3)	Insulin-like Growth Factor-1 (IGF-1)	Lipase
	Free Thyroxine (FreeT4)	Prolactin	LY3556050 concentration
	Total Thyroxine (T4)	Gastrin	Serum pregnancy test
		Glucagon	HbA1c
		Insulin	

Abbreviations: HbA1c = glycated hemoglobin; SST = somatostatin; TSH = thyroid-stimulating hormone.

Thyroid Safety Follow-Up

TSH
Free Triiodothyronine (FreeT3)
Total Triiodothyronine (T3)
Free Thyroxine (FreeT4)
Total Thyroxine (T4)
Thyroglobulin
Anti-Thyroglobulin
Anti-Thyroperoxidase Antibodies
Iodine

Abbreviation: TSH = thyroid-stimulating hormone.

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Approver: PPD

Approval Date & Time: 11-Nov-2021 14:49:25 GMT

Signature meaning: Approved