This study H0P-MC-BP02 (NCT05086289) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

Statistical Analysis Plan Version 2 H0P-MC-BP02

Randomized Placebo-controlled Phase 2 Clinical Trial to Evaluate LY3526318 for the Treatment of Chronic Low Back Pain

NCT05086289

Approval Date: 01-Jul-2022

1. Statistical Analysis Plan: H0P-MC-BP02: Intervention-Specific Appendix (ISA) for LY3526318

Confidential Information

LY3526318 for the Treatment of Chronic Low Back Pain

This is a randomized, placebo-controlled, Phase 2 clinical trial to evaluate LY3526318 for the treatment of chronic low back pain.

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Protocol H0P-MC-BP02
Phase 2

Approved on 01 Jul 2022 GMT

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3. Revision History

Statistical analysis plan (SAP) version 1 was approved on 17 December 2021 prior to unblinding data for H0P-MC-BP02 (BP02).

SAP version 2 was approved prior to unblinding data for Proof of Concept (PoC) lock. Major revisions included:

Section 6.1, the language describing active-treatment and post–active-treatment periods was made more clear.

Section 6.2, language was added to describe the derivation of PainDETECT total score.

Section 6.8, language was added to describe handling of specific edge cases when calculating treatment compliance.

Section 6.9, language describing reporting electronic Clinical Outcomes Assessment (eCOA) compliance separately for the active-treatment period was removed, since eCOA compliance is already reported on a weekly basis.

Section 6.10.1, language describing the derivation of nominal weeks for deriving the primary outcome was updated to handle a specific edge case observed in the H0P-MC-BP03 readout.

Section 6.12.7, a section on suicidal ideation and behavior was added to include language that it would be reported separately for the active-treatment period.

Section 6.13, a new subgroup variable was added for baseline PainDETECT total score.

Section 6.17, clarified the definition of Hy's Law and added a new endpoint under the Liver Function domain called DILI (drug-induced liver injury).

Section 7, added language that a CPMP-level blinding and unblinding plan now exists.

4. Study Objectives

4.1. Primary Objective

The primary objective of this intervention-specific appendix (ISA) is stated in the H0P-MC-CPMP (CPMP) protocol. Additional blinded details regarding LY3526318 dosing that are not included in the protocol can be found in the Ethics Review Board (ERB) supplement for Study BP02. For Study BP02, endpoint is defined as 4 weeks post initial treatment administration at Visit 5. Unless otherwise specified, the time point for secondary endpoint measurements is the same as that for the primary endpoint.

Objectives	Endpoints
Primary	
Efficacy of LY3526318 versus placebo in pain intensity	Mean change from baseline assessment to 4 weeks for average pain intensity as measured by the NRS

Abbreviation: NRS = Numeric Rating Scale.

4.2. Secondary Objectives

Secondary objectives applicable to all ISAs are listed in the CPMP SAP version 5.

Additional secondary endpoints specific to Study BP02 are listed below.

Objective	Endpoint Measure
Other Secondary	
Physical Functioning Efficacy of LY3526318 versus placebo	Mean change from baseline to endpoint in RMDQ total score Proportion of participants with reduction from baseline of at least 3.5 points in RMDQ total score at each time point Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% in RMDQ total score at each time point Time to first treatment response with at least 30%, 50%, and 70% reduction from baseline in RMDQ total score

Abbreviation: RMDQ = Roland-Morris Disability Questionnaire.

4.3. Exploratory Objectives

The following exploratory objectives and endpoints are specific to Study BP02.

Objectives	Endpoints
Tertiary/Exploratory	
Measure the pharmacokinetics of LY3526318 in participants with CLBP.	Measure of plasma concentrations of LY3526318 to enable PK evaluations
(Duration of response) Efficacy of LY3526318 versus placebo	Mean change from baseline assessment up to 8 weeks for average pain intensity as measured by the NRS

Abbreviations: CLBP = chronic low back pain; NRS = numeric rating scale; PK = pharmacokinetic.

5. Study Design

5.1. Summary of Study Design

The CPMP protocol provides a summary of the overall study design for the chronic pain master protocol. ISA-specific study design is provided in the BP02 protocol.

In this ISA, patients in the LY3526318 treatment arm receive LY3526318 for the first 4 weeks of the double-blind period (active-treatment period) and switch to placebo for the last 4 weeks of the double-blind period (post–active-treatment period) starting on the day of Visit 5. Placebo patients receive placebo for the entire 8-week, double-blind period. Additional details of the study design may be found in the ERB supplement for Study BP02.

For the analyses listed in this SAP, except for treatment compliance, we define the active-treatment period and post–active treatment period as follows. The first 4 weeks of the double-blind period (active-treatment period) ends at the day of Visit 5. The last 4 weeks of the double-blind period (post–active-treatment period) begins the day after Visit 5.

5.2. Determination of Sample Size

Approximately 150 participants will be randomized in a CCI ratio to LY3526318 and placebo, respectively. It is expected that approximately 85% of participants will complete the double-blind treatment period of the study CCI

CCI If there is no treatment difference between placebo and LY3526318, the probability of passing the efficacy criterion specified above (that is, false positive) is less than 0.05. The simulation for the power calculation and sample size determination was carried out in Fixed and Adaptive Clinical Trial Simulator (FACTS) version 6.0.

5.3. Method of Assignment to Treatment

The method of treatment assignment is described in the 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 CPMP SAP version 5.

Unless otherwise specified, efficacy analyses will be conducted for the first 4 weeks of the double-blind period (active-treatment phase) and separately for the entire 8-week study. A post-active-treatment population will be used for analyses of the last 4 weeks of the double-blind period (post–active-treatment phase) and will include all patients who do not discontinue at or prior to Visit 5. For treatment-emergent adverse events (TEAEs), participants in the post-active-treatment population will be analyzed according to the treatment they receive during the active-treatment phase. Adverse event (AE) analyses will be reported for the first 4 weeks of the double-blind period (active-treatment phase) and separately for the last 4 weeks of the double-blind period (post–active-treatment phase). Some AEs may be reported for the entire 8 weeks if necessary. Laboratory, electrocardiogram (ECG), and vital sign results will be reported for the active-treatment phase and separately for the entire 8-week study.

Other general considerations for analyses are described in the CPMP SAP version 5.

6.2. Adjustments for Covariates

The general adjustment strategy has been described in the CPMP SAP version 5.

Randomization into Study BP02 is stratified by the presence of neuropathic pain as defined by the painDETECT score. The following stratification factor will be included in the models for the primary, secondary, and some exploratory outcomes.

Neuropathic pain	painDETECT score
Positive presence	≥19
Unclear or negative	<19

The painDETECT total score is derived from patient responses to 9 questions on the painDETECT questionnaire. Seven questions ask about the gradation of pain, scored from 0 to 5 (never = 0, hardly noticed = 1, slightly = 2; moderately = 3, strongly = 4, very strongly = 5). One question asks about the pain course pattern, scored from −1 to 2, depending on which pain course pattern diagram is selected. Another question asks about radiating pain, answered as yes or no and scored as 2 or 0, respectively. The final score is between −1 and 38, and a score of 19 or higher suggests that pain is likely to have a neuropathic component (Freynhagen et al. 2006).

6.3. Handling of Dropouts or Missing Data

The missing data strategy has been described in the 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 CPMP SAP version 5. Disposition will additionally be reported for the first 4-week, active-treatment period.

6.7. Participant Characteristics

The summary of participant characteristics has been described in the CPMP SAP version 5.

ISA-specific considerations are described below:

painDETECT ≥19 (that is, positive for neuropathic pain)

Roland-Morris Disability Questionnaire (RMDQ) total score at baseline.

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 minus total pills returned. A patient is considered to be compliant for a given period if this percentage is between 80% and 120%. Treatment compliance will be reported for the first 4 weeks of the study period (Visit 3 to 5, not including the day of Visit 5) and separately for the last 4 weeks of the study period (Visit 5 to 7, including the day of Visit 5). Note that if a participant misses returning pills at Visit 4 or Visit 5, there will be an issue calculating compliance for the active-treatment period, and alternate methods for calculating compliance may be considered. For participants who discontinue early, time after the penultimate visit will be excluded for calculation of treatment compliance. For example, if a participant discontinued early at Visit 6, treatment compliance will be derived only from data collected through Visit 5. Comparisons between treatment group for treatment compliance will be performed using a Fisher's exact test. Listings for treatment compliance of individual patients by treatment period will also be provided.

Depending on the level of observed treatment compliance, and where appropriate, sensitivity analyses of primary and key secondaries may be conducted by excluding patients with poor treatment compliance.

6.9. Concomitant Therapy

The summary and reporting of concomitant therapy has been described in the CPMP SAP version 5. As described in Section 6.2, painDETECT will additionally be included as a covariate for modelling rescue medication.

Concomitant therapy will be reported for the first 4 weeks of the double-blind period (active-treatment phase) and separately for the entire 8 weeks of the double-blind period.

6.10. Efficacy Analyses

6.10.1. Primary Outcome and Methodology

Analysis of the primary outcome has been described in CPMP SAP version 5. The longitudinal model will include average pain intensity as measured by the 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-blind treatment period as a longitudinal outcome. As noted in Section 4.1, endpoint for the primary analysis is defined as 4 weeks post initial treatment administration.

Calculation of the weekly or biweekly time intervals used for analysis of weekly or biweekly mean scores from the eCOA device will follow the algorithm described in CPMP SAP Section 6.12.1, except that the end of the final interval will be determined based on the last visual analog scale (VAS) result collection date or the last scheduled visit start date if VAS results are missing for the last scheduled visit.

6.10.2. Additional Analyses of the Primary Outcome

Borrowing placebo information by pooling from Studies H0P-MC-BP01 and H0P-MC-BP03 for the evaluation of treatment effect on the mean change from baseline in average pain intensity as measured by the NRS (and secondary outcomes of worst pain intensity as measured by the NRS and VAS) will be performed following the description in CPMP SAP version 5, Section 6.12.1. Descriptive statistics of primary outcome variables by demographics, disposition, disease characteristics, and treatment administration may be summarized by ISA to examine the population homogeneity assumption between ISAs.

6.10.3. Secondary Efficacy Analyses

Secondary efficacy analyses common to all ISAs within CPMP have been described in the CPMP SAP version 5. Unless otherwise specified, the time point for secondary endpoint measurements is the same as that for the primary endpoint. Study BP02 will also consider the following secondary analyses.

The RMDQ is a simple, sensitive, and reliable method to measure disability in patients with back pain. The RMDQ consists of 24 statements relating to the person's perceptions of back pain and associated disability based on:

physical ability/activity

sleep/rest

psychosocial

household management

eating, and

pain frequency.

Participants are asked if they feel the statement is descriptive of their own circumstance on that day. The total score is obtained by counting the number of ‘‘Yes’’ responses, ranging from 0 = no disability to 24 = maximal disability.

A Bayesian longitudinal mixed-effect model repeated measures (MMRM) analysis will be performed to evaluate the change from baseline to each postbaseline visit in the RMDQ total score. The model will utilize the constrained cell means model so that a common mean is estimated at baseline. More details on this approach are provided in the CPMP SAP version 5.

This table describes information included in the model.

Categorical effects	the interaction of treatment and time point (constrained to estimate a common mean at baseline across treatments) average baseline pain severity category (baseline NRS < 7, baseline NRS ≥ 7) presence of neuropathic pain (painDETECT ≥ 19, painDETECT < 19) pooled investigative site
Continuous covariates	none

Abbreviation: NRS = numeric rating scale.

6.10.3.1. Other Secondary Analysis

The proportion of participants in each treatment group meeting prespecified binary efficacy outcomes will be calculated for each postbaseline time point and will be used to compare treatment groups. The prespecified binary efficacy outcomes include the proportion of participants:

with a reduction greater than or equal to 30%, 50%, and 70% from baseline as measured by the RMDQ score, and

with at least a 3.5-point reduction from baseline in the RMDQ score.

A Bayesian pseudo-likelihood–based categorical repeated measures model will be used to estimate the proportion of participants in each treatment group meeting the prespecified threshold for each postbaseline time interval up to Week 4 (or visit up to Visit 5) and separately up to Week 8 (or visit up to Visit 7). These estimates will be used to compare treatment groups. More details on this approach are provided in the CPMP SAP version 5.

The model will include the categorical and continuous covariates described for the secondary analysis of RMDQ total score.

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

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

The observed plasma concentrations for LY3526318 over time will be reported in tabular format using descriptive statistics and graphically using individual and mean concentration time plots. Nominal protocol time will be used for the descriptive summary and mean plot and actual time for the plots of individual data.

Additional analyses may be conducted as deemed necessary on review of the data. For example, graphical and/or model-based pharmacokinetic (PK) and PK-pharmacodynamic (PD) analyses to explore exposure-response relationships for safety and/or efficacy may be conducted. 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 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 to last 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. Extent of exposure will be reported separately for the first 4 weeks (active treatment) and the last 4 weeks (post-active treatment) of the double-blind period. All patients will receive placebo starting the day of Visit 5.

Duration of exposure (days):

> For the first 4-week, active-treatment period:
> = Date of last dose during the active-treatment period − Date of first dose for the active-treatment period + 1.
>
> For the last 4-week, post–active-treatment period:
> = Date of last dose during the post–active-treatment period − Date of first dose for the post–active-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

6.12.2. Adverse Events

The general analysis of AEs has been described in the CPMP SAP version 5.

This ISA will report TEAEs for the first 4 weeks as well as post–treatment-emergent adverse events (PTEAEs) for the last 4 weeks of the double-blind period. For TEAEs in the first 4 weeks of the double-blind period (active-treatment phase), the baseline will be prior to first dose date.

A PTEAE is defined as an event that first occurs or worsens in severity after the active-treatment phase (after Visit 5) 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 active-treatment period (Visits 3 to 5) will be used as a reference.

The baseline of PTEAE is from the first dosing date to Visit 5. The post–active-treatment phase (after Visit 5) will be included as postbaseline for this analysis. While unusual, it is possible to have a missing severity for events. For an event with a missing severity during the baseline period, it will be treated as "mild" in severity for determining post–active-treatment emergence. Events with a missing severity during the post–active-treatment period will be treated as "severe" and PTEAEs will be determined by comparing with the active-treatment period.

PTEAEs will be summarized by Preferred Term and by Preferred Term within System Organ Class in participants who received LY3526318.

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

TEAEs by Preferred Term will be reported.

The full summary of AEs is described in the CPMP SAP version 5.

6.12.4. Clinical Laboratory Evaluation

The general analysis of laboratory parameters is described in the CPMP SAP version 5.

In this ISA, laboratory results will be reported for the first 4-week, active-treatment period and separately for the entire 8-week study period.

Study BP02 will also consider the following analyses of laboratory analytes used to assess renal function. The planned summaries for these analytes are the same as those that have been described in the CPMP SAP. However, the reporting of these analytes will be separate from the general analysis of laboratory parameters.

Renal data analyses:

- Serum creatinine (change from baseline in mg/dL)
- Estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] algorithm using serum creatinine). Algorithm provided by the central laboratory.
- For eGFR calculation, we will summarize shift tables of eGFR changes for baseline versus postbaseline by minimum, maximum, and last observed eGFR result.
  - Category 1: Normal or increase in GFR (≥90 mL/min/1.73 m^2)
  - Category 2: Mild reduction in GFR (60 to 89 mL/min/1.73 m^2)
  - Category 3a: Moderate (a) reduction in GFR (45 to 59 mL/min/1.73 m^2)
  - Category 3b: Moderate (b) reduction in GFR (30 to 44 mL/min/1.73 m^2)

- Category 4: Severe reduction in GFR (15 to 29 mL/min/1.73 m^2)
- Category 5: Kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis)

Abnormal eGFR is specified below and will be summarized in the laboratory summary tables.

Abnormal low: <90 mL/min/1.73 m^2

Abnormal high: as specified by the central laboratory.

6.12.5. Vital Signs and Other Physical Findings

The analysis of vital sign parameters is described in the CPMP SAP version 5.

Vital signs will be reported for the first 4-week, active-treatment period and separately for the entire 8-week study period.

6.12.6. Electrocardiograms

The analysis of ECG parameters is described in the CPMP SAP version 5. ECG results will be reported for the first 4-week, active-treatment period and separately for the entire 8-week study period.

6.12.7. Suicidal Ideation or Behavior

Reporting of suicidal ideation or behavior through the Columbia Suicide-Severity Rating Scale (C-SSRS) has been described in the CPMP SAP version 5. C-SSRS will additionally be reported separately for the first 4-week, active-treatment period.

6.13. Subgroup Analyses

General subgroup analyses are described in the CPMP SAP version 5.

Study BP02 will also consider the following subgroup analyses for the primary outcome.

Subgroup Variable	Categories
Neuropathic pain	Categories: Positive presence (painDETECT total score ≥19), Unclear or negative (painDETECT total score <19)

The subgroup analyses will be conducted using similar modeling approaches as the primary analysis. Additional factors in the model are described in the 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. Frequentist MMRM may be performed as a sensitivity analysis using the modeling approach described in the 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 CPMP and BP02 Trial Issue Management Plans.

6.15. Interim Analyses and Data Monitoring

Safety review will be conducted under the auspices of an Assessment Committee (AC) 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 CPMP SAP version 5.

Interim analyses are planned for Study BP02 to be conducted when 60% of participants have completed the 4-week, active-treatment period. Details of the interim analysis can be found in the TRPA1 Statistical Analysis Center (SAC) SAP. The interim analysis will be conducted by an independent AC, and the AC will disseminate interim results, if 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:

- CCI [redacted]

6.17. Totality of Evidence for Safety

The totality of evidence for safety analysis has been briefly described in the CPMP SAP version 5. This may be reported for any of the active-treatment period, post–active-treatment period, and entire 8-week study period. The key safety events to be considered for Study BP02 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 (TBL) ≥2 Upper limit normal (ULN) and at least one of the following 2 conditions:
  - Alanine aminotransferase (ALT) ≥3 ULN for at least one visit
  - Aspartate aminotransferase (AST) ≥3 ULN for at least one visit.
- DILI (drug-induced liver injury): At least one of the following 2 conditions:

- Hy's Law
- ALT ≥5 ULN for at least one visit.

Metabolic Function

Serious hypoglycemia adverse event

Treatment-emergent HbA1c: Shift from low/normal at baseline to high at least once.

Renal Function

Treatment-emergent abnormal eGFR: Shifts

- Mild at baseline to moderate/severe
- Moderate at baseline to severe.

6.18. Annual Report Analyses

Analyses will be produced as needed for the purposes of providing periodic safety reviews to regulatory agencies (for example, Development Safety Update Reports). Data from this ISA will be combined with data from other clinical studies that investigated LY3526318. In all analyses, a combined LY arm will be created, which will include participants assigned to any dose of LY3526318 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 LY3526318
- Cumulative number of subjects exposed to LY3526318 by age
- Cumulative number of subjects exposed to LY3526318 by sex
- Cumulative number of subjects exposed to LY3526318 by race

Cumulative summary of serious AEs.

The following listings will be provided.

List of serious AEs during the reporting period

List of subjects who died

Cumulative list of subjects who discontinued due to an AE (discontinued from treatment or study)

List of subjects who discontinued due to an AE 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 AEs provided as a dataset that will be converted to an XML file. Both "Serious" AEs and "Other" AEs are summarized: by treatment group and by MedDRA Preferred Term.

A serious AE is an AE that is considered "Serious" whether or not it is treatment emergent.

An AE 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 Clinical Study Report (CSR) and manuscripts.

7. Unblinding Plan

The general unblinding plan is described in the CPMP SAP version 5 and in the Study CPMP Blinding and Unblinding Plan version 1. Unblinding considerations specific to BP02 are provided below.

7.1. 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 the blinded study team until the study has been unblinded.

8. References

Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22(10):1911-1920.

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