This study H0P-MC-BP03 (NCT04874636) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

H0P-MC-BP03 Statistical Analysis Plan Version 2

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

NCT04874636

Approval Date: 04-Mar-2022

1. Statistical Analysis Plan: H0P-MC-BP03: Intervention-Specific Appendix (ISA) for LY3556050

LY3556050 Pain for the Treatment of Chronic Low Back Pain

This is a randomized, placebo-controlled, phase 2 clinical trial to evaluate LY3556050 for the treatment of chronic low back pain.

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Protocol H0P-MC-BP03
Phase 2

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

Approved on 04 Mar 2022 GMT

2. Table of Contents

Section **Page**

Table of Contents

Appendix **Page**

3. Revision History

SAP Version 1 was approved prior to unblinding data for H0P-MC-BP03.

SAP Version 2 was approved prior to the final lock. Major revisions include:

- Section 5.3, the method of treatment assignment description was added to align with protocol amendment. Section 6.1, the estimand for this Intervention-Specific Appendix (ISA) was described.
- Section 6.10.2, placebo borrowing analysis from previous and ongoing studies in Chronic Pain Master Protocol (CPMP) was updated and overall mean change from baseline assessment was described.
- Section 6.12.2, additional treatment-emergent adverse events, and narratives for patients with "notable" events were updated.
- Section 6.12.3, estimated glomerular filtration rate (eGFR) shift analyses was added.
- Section 6.12.4, detailed criteria of orthostatic vital sign summaries were elaborated.
- 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, 'violations' is replaced with 'deviations' for consistency across CPMP documents, and the list of important protocol deviations (IPDs) is referenced in the trial issue management plan.
- Section 6.16, planned exploratory analyses were updated, including adding frequentist mixed model for repeated measures (MMRM) as sensitivity analyses and more details of propensity score analyses; details of propensity score analyses were elaborated; exploratory placebo borrowing analyses with more types of borrowing method were added.
- Section 6.17, the totality of evidence for safety was added.

4. Study Objectives

4.1. Primary Objective

The primary objective of this Intervention-Specific Appendix (ISA) is stated in the H0P-MC-CPMP. For H0P-MC-BP03, an 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

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

Additional secondary endpoints specific to H0P-MC-BP03 are listed below.

Objective	Endpoint Measure
Other Secondary	
Physical Functioning Efficacy of LY3556050 versus placebo	• Change from baseline to endpoint for the Roland-Morris Disability Questionnaire (RMDQ) total score • Proportion of participants with a reduction from baseline of at least 3.5 points on RMDQ total score • Proportion of participants with a reduction from baseline ≥30%, 50%, and 70% on the RMDQ total score • Time to first treatment response with at least 30%, 50%, and 70% reduction from baseline in RMDQ total score • Overall mean change from baseline to endpoint for the RMDQ total score
Efficacy of LY3556050 versus placebo	• Overall mean change from baseline assessment for average pain intensity numerical rating scale (NRS) 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 CPMP. The ISA-specific study design is provided in the H0P-MC-BP03 protocol.

5.2. Determination of Sample Size

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

CCI If there is no treatment difference between placebo and LY3556050, the probability of passing the efficacy criterion specified above (ie, false positive) is <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.

5.3. Method of Assignment to Treatment

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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 estimand is following a hypothetical strategy where the efficacy of LY3556050 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.

Randomization into H0P-MC-BP03 is stratified by the presence of neuropathic pain as defined by the painDETECT score (Freynhagen et al. 2006).

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

6.3. Handling of Dropouts or Missing Data

The missing data strategy has been described in the H0P-MC-CPMP SAP Version 4.

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 imputations will be applied as a sensitivity analysis to assess change from baseline to postbaseline measure for visual analog scale (VAS) and NRS.

For these continuous efficacy endpoints, a Markov chain Monte Carlo 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. The variable pooled investigative site, treatment, age, gender, baseline pain severity categories will be included for imputing non-monotone missingness, and primary adverse events (AEs) leading to treatment discontinuation can be included as an additional variable for imputing monotone missingness. Subject-level indicator of primary AEs leading to treatment discontinuation is set 1 for patients experiencing AEs in preferred terms (PT), including nausea, dizziness, fatigue, abdominal discomfort, abdominal pain lower, abdominal pain upper, constipation, lethargy, somnolence, at any time during double-blinded (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. The 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 procedure MIANALYZE in order to compute LSmeans 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 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. 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 Version 5.

ISA-specific considerations are described below.

- painDETECT ≥19 (ie, 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 – 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 the study drug will be summarized by treatment group.

6.9. Concomitant Therapy

The summary and reporting of concomitant therapy have been described in the H0P-MC-CPMP SAP Version 5. As described in Section 6.2, PainDETECT will additionally be included as a covariate for modelling rescue medication.

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, the 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 effect in change from baseline over the double blind treatment period will be reported for evaluating treatment effect for NRS, VAS, Roland Morris Disability Questionnaire (RMDQ), as well as other secondary continuous efficacy endpoints.

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6.10.3. Secondary Efficacy 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 circumstances 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 for the RMDQ total score. The model will utilize the constrained cell means model so that a common means is estimated at the baseline. More details on this approach are provided in the H0P-MC-CPMP SAP Version 5.

This table describes the information included in the model.

Categorical effects	• 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) • Presence of neuropathic pain (painDETECT ≥19, painDETECT <19) • Pooled investigative site
Continuous covariates	• None

Other Secondary Analysis

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

- with a reduction ≥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 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, the time to first treatment response from baseline based on the prespecified binary thresholds above will be assessed. Analyses will be 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 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 chronic low back pain 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 the time since the first dose of study treatment to the 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.

Duration of exposure (days):

= Date of the last dose during the double blind treatment period – Date of the 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.

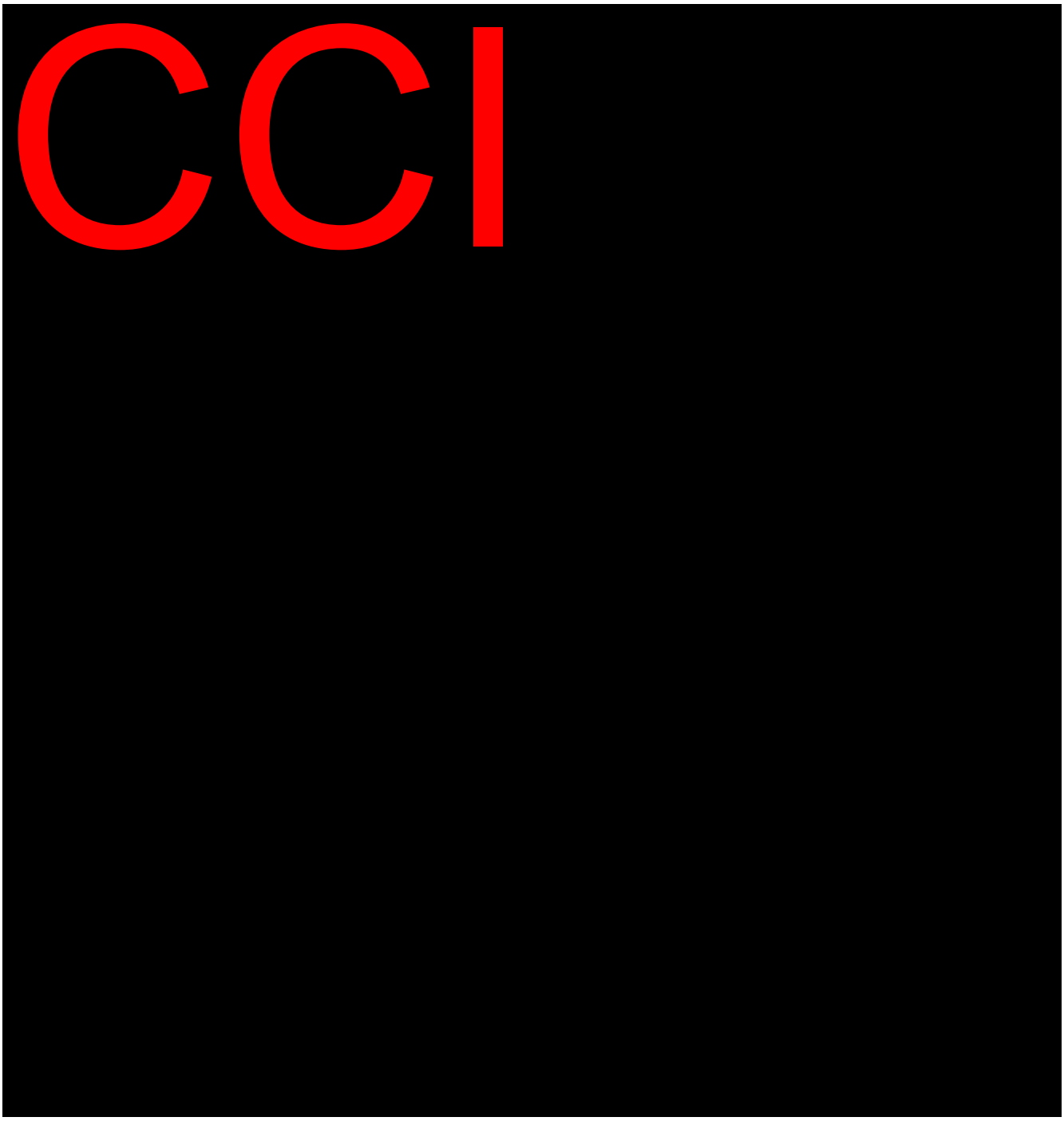
The full summary of adverse events is described in the H0P-MC-CPMP SAP. Other adverse events for review coded to Medical Dictionary for Regulatory Activities (MedDRA) terms include

- Hypothyroidism (in SMQ)
- Cardiac arrhythmias (in SMQ)
    - Arrhythmia related investigations, signs, and symptoms
    - Bradyarrhythmia terms, nonspecific
    - Cardiac arrhythmia terms, nonspecific
    - Conduction defects
    - Disorders of sinus node function
    - Supraventricular tachyarrhythmias
    - Tachyarrhythmia terms, nonspecific
    - Ventricular tachyarrhythmias
- Hypotension (in preferred MedDRA term)
    - Orthostatic hypotension
    - Blood pressure ambulatory decreased
    - Blood pressure decreased
    - Blood pressure diastolic decreased
    - Blood pressure systolic decreased
    - Blood pressure orthostatic decreased
    - Dizziness

  - Dizziness exertional
  - Presyncope
  - Syncope
- Abnormal renal function (in MedDRA HLT)
  - Renal function analyses
  - Renal failure and impairment
- 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)
  - Ischaemic heart disease (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ)
- Depression (in MedDRA HGLT)
  - Depressed mood disorders and disturbances
- Congestive Heart Failure (in SMQ)
  - Cardiac Failure
- Substance abuse (in MedDRA HLT)
  - Substance related and addictive disorders

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

- Treatment-emergent elevated amylase or lipase >3x ULN
- Renal treatment-emergent adverse events.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6.12.4. Vital Signs and Other Physical Findings

The analysis of vital sign parameters is 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 the 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 BP03 are:

Parameter	Criteria
Orthostatic hypotension (Orthostatic Systolic BP, in mmHg)	Decrease in systolic BP when going from 5 minutes supine to 2-3 minutes standing of ≥20mm Hg
Orthostatic hypotension (Orthostatic Diastolic BP, in mmHg)	Decrease in diastolic BP 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 a 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.

There are no additional subgroup analyses planned.

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-BP03 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-BP03. 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:

- 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 RMDQ total score 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:

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-BP03 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
- Treatment discontinuation due to gastrointestinal disorders
- Treatment discontinuation due to potential nervous system disorder.

Cardiovascular

- QTc prolongation: >60 msec increase
- Serious cardiac disorders adverse event
- Cardiac Failure
- Arrhythmia Event
- MACE
- Hypotension 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 based on Cystatin C: Shifts
    - Mild at baseline to moderate/severe during the double-blind treatment period
    - Moderate at baseline to severe during the double-blind treatment period
- Serious renal event.

Thyroid

- Hypothyroidism.

6.18. Annual Report Analyses

Analyses will be produced as needed for the purposes of providing periodic safety reviews to regulatory agencies (eg 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.

6.19. Clinical Trial Registry Analyses

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

Analyses provided for the Clinical Trial Registry 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.
- An adverse event is considered in the 'Other' category if it is both a treatment emergent adverse event 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), 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-BP03 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 pharmacokinetic/pharmacodynamic (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.

Blinding/Unblinding plan for placebo borrowing analyses

For placebo borrowing analyses that borrow data from other CPMP ISAs that are ongoing at the time of BP03 final database lock, only the CPMP unblinded statistical support team will have access to the unblinded Study Data Tabulation Model (SDTM) or Analysis Date Model (ADaM) datasets from ongoing studies, including patient-level treatment allocation information. The BP03 study team will remain blinded to individual patient-level data from ongoing studies, but will have access to demographics and disease characteristics summaries for the placebo arm of each ISA (to assess the population homogeneity assumption for pooling) as well as aggregated efficacy results based on the pooled placebo data.

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. https://doi.org/10.1185/030079906x132488

Inker, LA., Schmid CH., Tighiouart H., et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20-29. https://doi.org/10.1056/nejmoa1114248

Levey, AS., Coresh J., Greene T., et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Int Med.* 2006;145(4):247-254. https://doi.org/10.7326/0003-4819-145-4-200608150-00004

9. 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 tests unique to H0P-MC-BP03.

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.

Signature Page for VV-CLIN-020674 v1.0

Approval	PPD

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