This study H0P-MC-NP03 (NCT04707157) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

H0P-MC-NP03 Statistical Analysis Plan Version 2

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

NCT04707157

Approval Date: 06-May-2022

1. Statistical Analysis Plan: H0P-MC-NP03: Intervention-Specific Appendix (ISA) for LY3556050

LY3556050 for the Treatment of Diabetic Peripheral Neuropathic Pain

This is a randomized, placebo-controlled, phase 2 clinical trial to evaluate LY3556050 for the treatment of diabetic peripheral neuropathic pain.

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Protocol H0P-MC-NP03
Phase 2

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

Approved on 06 May 2022 GMT

2. Table of Contents

Section **Page**

1. Statistical Analysis Plan: H0P-MC-NP03: Intervention-Specific Appendix (ISA) for LY3556050 1
2. Table of Contents 2
3. Revision History 5
4. Study Objectives 6
4.1. Primary Objective 6
4.2. Secondary Objectives 6
4.3. Exploratory Objectives 6
5. Study Design 8
5.1. Summary of Study Design 8
5.2. Determination of Sample Size 8
5.3. Method of Assignment to Treatment 8
6. A Priori Statistical Methods 9
6.1. General Considerations 9
6.2. Adjustments for Covariates 9
6.3. Handling of Dropouts or Missing Data 9
6.4. Multiple Comparisons/Multiplicity 10
6.5. Use of an "Efficacy Subset" of Patients 10
6.6. Patient Disposition 10
6.7. Patient Characteristics 10
6.8. Treatment Compliance 10
6.9. Concomitant Therapy 10
6.10. Efficacy Analyses 10
6.10.1. Primary Outcome and Methodology 10
6.10.2. Additional Analyses of the Primary Outcome 11
6.10.3. Secondary Efficacy Analyses 11
6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods 13
6.12. Safety Analyses 13
6.12.1. Extent of Exposure 13
6.12.2. Deaths, Other Serious Adverse Events, and Other Adverse Events for Review 13
6.12.3. Clinical Laboratory Evaluation 15
6.12.4. Vital Signs and Other Physical Findings 17
6.12.5. Electrocardiograms 17
6.13. Subgroup Analyses 17

6.14. Protocol Deviations 17
6.15. Interim Analyses and Data Monitoring 17
6.16. Planned Exploratory Analyses 18
6.17. Totality of Evidence for Safety 19
6.18. Annual Report Analyses 20
6.19. Clinical Trial Registry Analyses 20
7. Unblinding Plan 22
8. References 23
9. Appendices 24

Table of Contents

Appendix **Page**

Appendix 1. Planned Laboratory Analytes and Direction of Interest.....25

3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to unblinding data for Study H0P-MC-NP03 (Study NP03).

Statistical analysis plan Version 2 was approved prior to the interim analysis. Major revisions include:

- Section 4.2, for physical functioning objectives, total interference score was replaced with mean interference score and mean severity score was added. Proportion of participants with reduction from baseline was updated to at least instead of greater than 30/50/70%.
- 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 6.3, additional detail was added to describe the multiple imputation method.
- 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 6.10.3, the details for the constrained model for the secondary endpoint were added. The language for categorical endpoint analysis was updated to match the H0P-MC-CPMP (Study CPMP) SAP Version 5. Proportion of participants with reduction from baseline was updated to at least instead of greater than 30/50/70%.
- 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 6.14, 'violations' is replaced with 'deviations' for consistency across CPMP documents, and the list of important protocol deviations is referenced in the trial issue management plan.
- Section 6.15, interim analyses description were added.
- 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.
- Section 7, text on maintaining the blind for assessment committee review was deleted since it is covered in Study CPMP SAP Version 5.

4. Study Objectives

4.1. Primary Objective

The primary objective of this ISA is stated in Study CPMP (a) protocol. For Study NP03, endpoint is defined at Visit 7, which is 8 weeks post initial treatment administration. The time point for secondary endpoint measurements is the same as the primary endpoint except for the overall measures.

4.2. Secondary Objectives

Secondary objectives are listed in Study CPMP SAP Version 5. Additional secondary endpoints specific to Study NP03 are listed below.

Objective	Endpoint Measure
Other Secondary	
Physical Functioning Efficacy of LY3016859 versus placebo	• Mean change from baseline to endpoint for the Brief Pain Inventory-Short Form (BPI-SF) for the o mean interference score o mean severity score o individual severity score, and o individual interference score. • Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% on BPI-SF for the o mean interference score o mean severity score o individual severity scores, and o individual interference scores.
Efficacy of LY3556050 versus Placebo	• Overall mean change from baseline assessment for average pain intensity numerical rating scale during the treatment phase

Note: Other key secondary objectives are listed in the H0P-MC-CPMP Statistical Analysis Plan Version 5.


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5. Study Design

5.1. Summary of Study Design

Study CPMP protocol provides a summary of the overall study design for the CPMP. Intervention-Specific Appendix-specific study design is provided in Study NP03 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 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 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 Study 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 LY3556050 versus placebo, where all LY3556050 doses are combined.

Other general considerations for analyses are described in Study CPMP SAP Version 5.

6.2. Adjustments for Covariates

The general adjustment strategy has been described in Study CPMP SAP Version 5.

6.3. Handling of Dropouts or Missing Data

The missing data strategy has been described in Study CPMP SAP Version 5.

In addition to the Bayesian MMRM model described in Study CPMP SAP Version 5, 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 (nonmonotone) 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 nonmonotone 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 (PTs), including Nausea, Dizziness, Fatigue, Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Constipation, Lethargy, and Somnolence at any time during double-blinded 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, and 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 least squares 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

There are no plans to use a modified efficacy subset.

6.6. Patient Disposition

The summary of patient disposition has been described in Study 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. Patient Characteristics

The summary of participant characteristics has been described in Study CPMP SAP Version 5. Intervention-Specific Appendix-specific considerations are described below.

- Michigan Neuropathy Screening Instrument
    - Part A - history subscale (less than 7 versus 7 or higher)
    - Part B - physical assessment subscale (less than 3 versus 3 or higher).

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 Visit 7. The percentage of patients who are compliant with study drug will be summarized by treatment group. For patients who discontinue early, time after the penultimate visit will be excluded for calculation of treatment compliance. For example, if patient discontinued early at Visit 6, treatment compliance will be derived only from data collected through Visit 5.

6.9. Concomitant Therapy

The summary and reporting of concomitant therapy and electronic clinical outcome assessment compliance has been described in Study 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 Study CPMP SAP Version 5. The longitudinal model will include average NRS during the preliminary data entry period (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 8 weeks post initial treatment administration.

Calculation of the weekly/bi-weekly time intervals used for analysis of weekly/bi-weekly mean scores from the electronic clinical outcome assessment device will follow the algorithm described in the CPMP SAP Version 5, Section 6.12.1, except that the end of the final interval will be determined based on the last VAS collection date, or the last scheduled visit start date if VAS is missing for the last scheduled visit.

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, as well as other secondary continuous efficacy endpoints.

6.10.3. Secondary Efficacy Analyses

Secondary efficacy analyses common to all ISAs within Study CPMP have been described in Study CPMP SAP Version 5. Study NP03 will also consider the following secondary analyses.

The Brief Pain Inventory-Short Form (is a numeric rating scale that assesses the severity of pain (severity scale), its impact on daily functioning (interference scale), and other aspects of pain (eg, location of pain, relief from medications) in various disease states (Cleeland and Ryan 1994).

The table below describes the pain scales and corresponding NRS used in a modified version of the Brief Pain Inventory, validated for pain in diabetic polyneuropathy. Participants will rate their pain severity and how, during the past 24 hours, the pain has interfered with the activities described in this table.

Assessment	Topic	Numeric Rating Scale 0-10
4-item pain severity	• Worst pain in last 24 hours • Least pain in the last 24 hours • Average pain • Pain right now	0 = no pain 10 = pain as bad as you can imagine
7-item pain interference	• General Activity • Mood • Walking ability • Normal work • Relations with others • Sleep • Enjoyment of life	0 = does not interfere 10 = completely interferes

A Bayesian longitudinal mixed-effect MMRM analysis will be performed to evaluate the change from baseline to each postbaseline visit for the mean pain interference scale and the mean pain severity scale. 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 Study CPMP SAP Version 5.

Additional Bayesian MMRM analyses will be used to analyze the change from baseline to each postbaseline visit for

- individual pain interference and
- individual pain severity scales.

The table below describes information included in the model.

Categorical factors	• the interaction of treatment and visit
	  ○ (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

Abbreviation: NRS = numeric rating scale.

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 of at least 30%, 50%, and 70% from baseline as measured by the

- mean pain interference score
- mean pain severity score

- individual interference scores, and
- individual severity scores.

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 8 (or visit up to visit 7). These estimates will be used to compare treatment groups. More details on this approach are provided in Study CPMP SAP Version 5.

In addition, 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 diabetic peripheral neuropathic 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 Study 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 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 last dose 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 PT will be reported.

In addition to an overall listing, additional lists by PTs or System Organ Classes of interest, including Cardiovascular, Thyroid, and Renal functions, will be generated.

The full summary of AEs is described in Study CPMP SAP Version 5. Other AEs for review coded to Medical Dictionary for Regulatory Activities (MedDRA) terms include

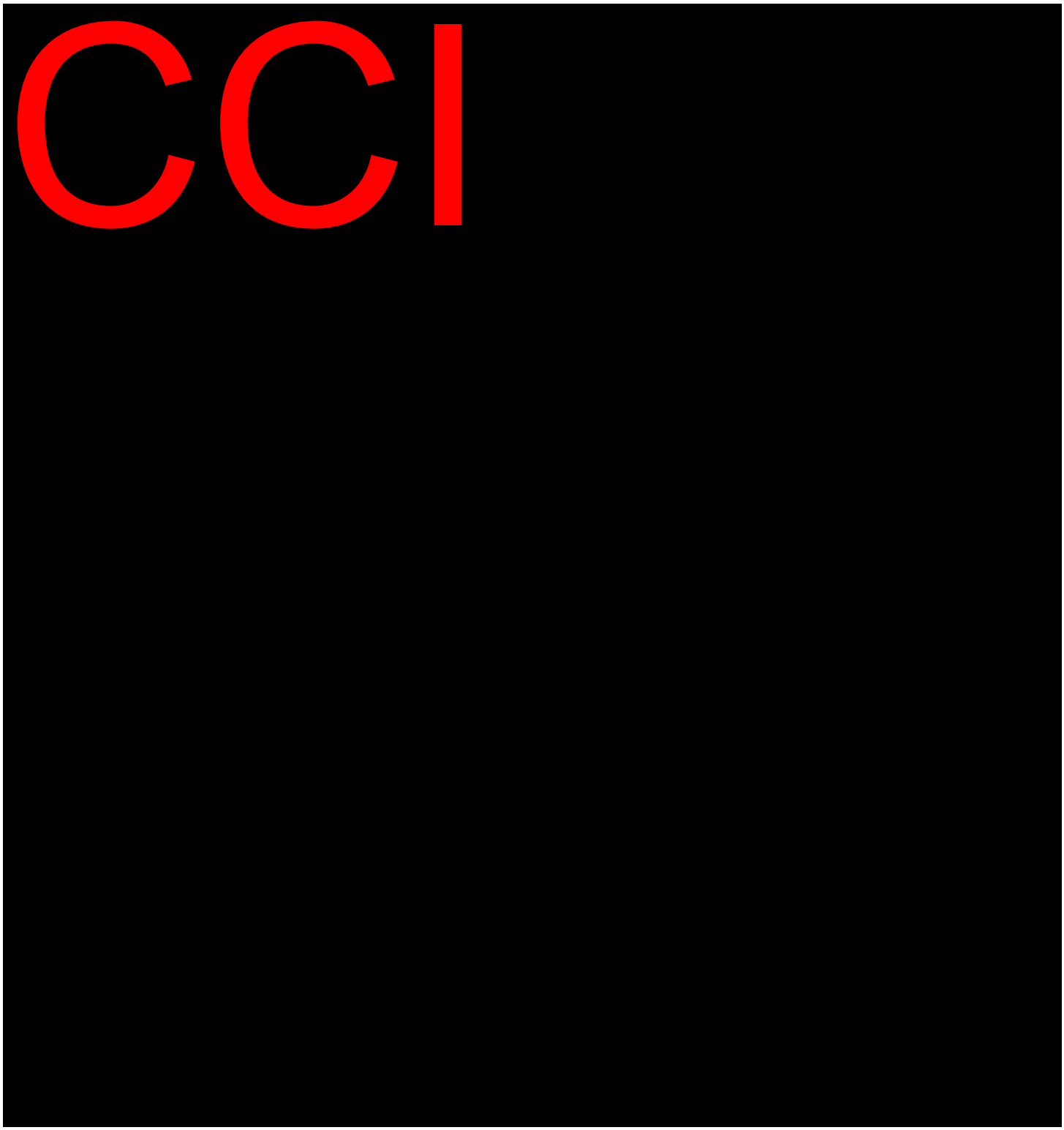
- Hypothyroidism (in Standardized MedDRA Query [SMQ])
- Cardiac arrhythmias (in SMQ)
    - Arrhythmia related investigations, signs, and symptoms
    - Bradyarrhythmia terms, nonspecific
    - Cardiac arrhythmia terms, nonspecific
    - Conduction defects
    - Disorders of sinus node function
    - 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 High Level Term)
    - Renal function analyses
    - Renal failure and impairment
- Major adverse cardiovascular event (including myocardial infarction and stroke)
    - Death (MedDRA PT)
    - Cardiac arrest ((MedDRA PT)

  - Cardiac death ((MedDRA PT)
  - Sudden cardiac death ((MedDRA PT)
  - Sudden death ((MedDRA PT)
  - Ischemic heart disease (SMQ)
  - Ischemic central nervous system vascular conditions (SMQ)
- Depression (in MedDRA High Group Level Term)
  - Depressed mood disorders and disturbances
- Congestive Heart Failure (in SMQ)
  - Cardiac Failure
- Substance abuse (in MedDRA High Level Term)
  - Substance related and addictive disorders

Post treatment emergent adverse event (TEAE) collected at Visit 801 may be summarized separately.

Narratives will be provided for patients with the following "notable" events, in addition to the "notable" events listed in Study CPMP SAP Version 5:

- treatment-emergent elevated amylase or lipase greater than 3× upper limit of normal and
- renal treatment-emergent AEs.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6.12.4. Vital Signs and Other Physical Findings

The analysis of vital sign parameters is described in Study 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 NP03 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

Abbreviations: BP = blood pressure.

6.12.5. Electrocardiograms

The analysis of electrocardiograms parameters is described in Study 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 Study 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 Study CPMP and Study NP03 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 Study CPMP SAP Version 5.

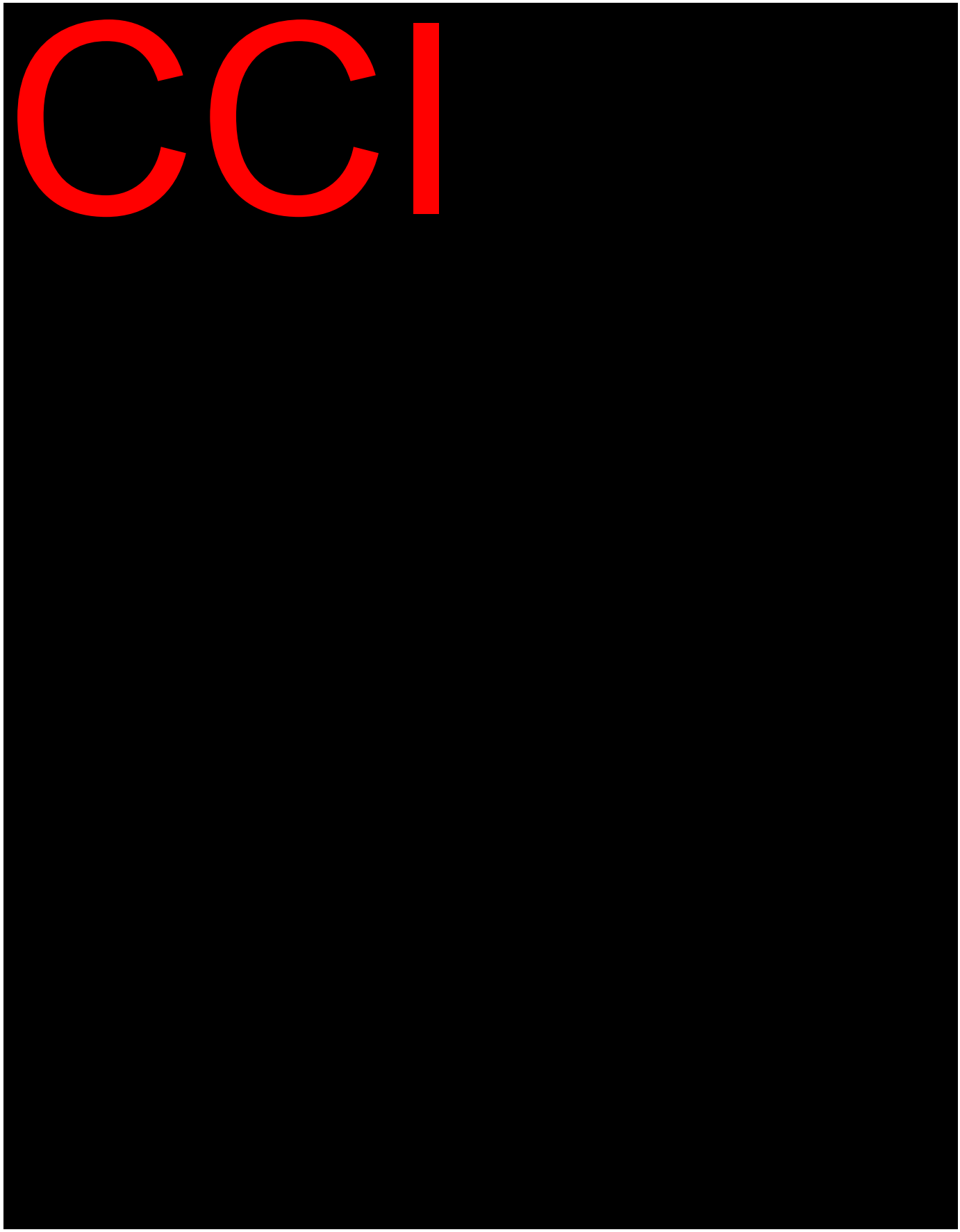
Interim analyses are planned for Study NP03. The potential reasons for interim analyses could include futility analyses, early efficacy analyses, safety analyses, or other analyses needed for key business decisions and planning.

6.16. Planned Exploratory Analyses

The following analyses may be conducted for exploratory purposes:

- Other placebo borrowing strategies may be explored as described in Study CPMP SAP Version 5, Section 6.12.1.
- A frequentist MMRM analysis will be conducted as a sensitivity analysis for the primary and some secondary endpoints.
- In addition, a cumulative distribution function of percent change from baseline to endpoint for the following Brief Pain Inventory-Short Form score will be provided for each treatment group:
    - mean interference score
    - mean severity score
    - individual severity scores, and
    - individual interference scores

  However, no statistical comparisons will be made between the groups.
- The follow analysis is to explore different doses of LY3556050: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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 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 requirements.

Analyses provided for the Clinical Trial Registry requirements include the following:

Summary of AEs, 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 PT.

- A serious adverse event is an AE that is considered 'Serious' whether or not it is a TEAE.
- 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, and
    - 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).
- Adverse event reporting is consistent with other document disclosures for example, the clinical study report, 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 Study CPMP SAP Version 5 and Study CPMP blinding and unblinding plan Version 1. Unblinding considerations specific to Study NP03 are provided below.

PK/PD 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 PK/PD 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

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129-138.

Inker LA, Schmid CH, Tighiouart H, et al.; CDK-EPI Investigators. 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.; Chronic Kidney Disease Epidemiology Collaboration. 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 Statistical Analysis Plan Version 5 describes tests that may be performed broadly for the Chronic Pain Master Protocol. This table describes tests unique to H0P-MC-NP03.

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 = hemoglobin A1c; 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-039488 v1.0

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