J2P-MC-LXBD Statistical Analysis Plan Version 3

A Phase 2, Randomized, Double-Blind, Placebo Controlled, Dose-Ranging Study to Evaluate LY3556050 in Adult Participants With Diabetic Peripheral Neuropathic Pain

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Statistical Analysis Plan for J2P-MC-LXBD

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo Controlled, Dose-Ranging Study to Evaluate LY3556050 in Adult Participants with Diabetic Peripheral Neuropathic Pain

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Version History

This statistical analysis plan (SAP) for Study J2P-MC-LXBD (LXBD) is based on Protocol Amendment (e) dated 14 May 2024.

Table LXBD.1.1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	Jan 5, 2024	• Not applicable	• Original version
2	Sep 27, 2024	• Removed CCI [redacted]	• Nonessential analyses
		• Section 2.1. Multiplicity Adjustment Added "…across secondary endpoints."	• Clarification that multiplicity adjustment will not be done for secondary endpoints
		• Section 4.3. Primary Endpoint Analysis Added that CCI [redacted] Added additional details on CCI [redacted] strategy	• To address EU regulatory feedback on how CCI [redacted] and how CCI [redacted] is performed.
		• Section 4.8. Interim Analyses Added further details to CCI [redacted]; Removed "At the discretion of the	• To address EU regulatory feedback on how CCI [redacted]

		sponsor, additional interim analyses may be conducted and prespecified interim analyses may not be conducted."	CCI [redacted]
		• Section 5. Sample Size Determination Added interim analyses information to ensure minimal impact to power and overall CCI [redacted]; Added 4 different plausible parametric dose-response shapes to generate the virtual participants' response	• To address EU regulatory feedback on how value of statistical power is simulated based on specific value for sample size
		• Table LXBD.4.2 and Table LXBD.4.3.	• Added dichotomized endpoint to detect clinical meaningful improvement
		• Section 4.5.3 Totality of Evidence for Efficacy	• To assess the totality of evidence (ToE) for efficacy
		• Section 4.6.8 CCI [redacted] Analysis	• To assess the responses to CCI [redacted] collected at follow up period
		• Section 6.2, Appendix 2 Treatment Compliance and eCOA Compliance	• Add eCOA compliance

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		• Section 6.4, Appendix 4 Concomitant Therapy	• Added stratification factors to the model specification
3	See approval date on Page 1	• Section 4.6.3 Narratives added hepatic event reported in eCRF	• Omitted in the previous version
		• Section 1.1 Remove "initiation of prohibited medication" from the primary estimand	• Change this estimand as a sensitivity analysis in 4.3.3
		• Section 4.3.3 Add sensitivity analysis using patients who didn't take prohibited medication	• Primary estimand in the previous versions
		• Section 4.4.1.4 Add supplementary analyses of secondary endpoints	• Analyze the impact of missing data.

1. Introduction

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate CCI dose of LY3556050 is superior to placebo in pain intensity	Mean change from baseline to Week 12 for API-NRS
Secondary	
To demonstrate CCI dose of LY3556050 is superior to placebo in • pain intensity • pain interference • physical functioning, and • sleep	Mean change from baseline to Week 12 for • WPI-NRS • PROMIS Pain Interference 8a • Pain Interference with Sleep • PROMIS Physical Functioning SF10a, and • PROMIS Sleep Disturbance SD-8b.
CCI	• Mean change from baseline to Week 12 in the Patient's Global Impression of Illness-Severity as measured by PGI-Severity • Mean change from baseline to Week 12 in the Patient's Global Impression of Illness-Status as measured by PGI-Status, and • Mean Patient's Global Impression of Change as measured by PGI-Change at Week 12.
CCI	• CCI • CCI • CCI • CCI

Objectives	Endpoints
To compare LY3556050 with placebo for the frequency and intensity of individual neuropathy sensory symptoms	• Mean change from baseline to Week 12 for NTSS-6
To describe the safety and tolerability of LY3556050 (CCI mg, CCI mg, CCI mg BID) as compared to placebo	Summary of safety data, including number and incidence of: • SAEs • TEAEs, and • AEs leading to discontinuation.
Characterize the pharmacokinetics of LY3556050 in participants with DPNP	Plasma concentrations of LY3556050
Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AE = adverse event; API = average pain intensity; BID = twice daily; DPNP = diabetic peripheral neuropathic pain; NRS = numeric rating scale; NTSS-6 = neuropathy total symptom score-6; PGI = Patient Global Impression; CCI [redacted]; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WPI = worst pain intensity.

Primary estimand for the primary objective

Hypothetical estimand

The primary clinical question of interest is:

> *What is the treatment difference in the mean change from baseline to 12 weeks for average pain intensity (API) as measured by the numeric rating scale in diabetic peripheral neuropathic pain (DPNP) participants treated with intervention LY3556050 (CCI mg, CCI mg, CCI mg twice daily [BID]) versus placebo if participants remained on their randomly assigned treatment for 12 weeks?*

The estimand is described by these attributes:

- **Population:** DPNP participants who meet the eligibility criteria.
- **Endpoint:** change from baseline to 12 weeks in API via numeric rating scale (NRS).
- **Treatment condition:** the randomized treatment along with potential use of rescue medication or other concomitant medications, regardless of adherence.
- **Remaining intercurrent events (ICEs):** the ICE is treatment discontinuation for any reason. The potential outcome of interest is the response in the efficacy measurement if participants remained on the randomly assigned treatment for 12 weeks.
- **Population-level summary:** difference in mean changes from baseline to Week 12 between treatment conditions.

Rationale for estimand*:* the hypothetical strategy, where the efficacy of LY3556050 is assessed under the assumption that the participant has continued their initially randomized treatment condition, even if they discontinued the study.

Secondary estimand for the primary objective

Treatment policy estimand

The clinical question of interest is

> *What is the treatment difference in mean change from baseline to 12 weeks for API as measured by the NRS in DPNP participants treated with intervention LY3556050 (CCI mg, CCI mg, CCI mg BID) versus placebo regardless of adherence to study intervention or initiation of prohibited medications?*

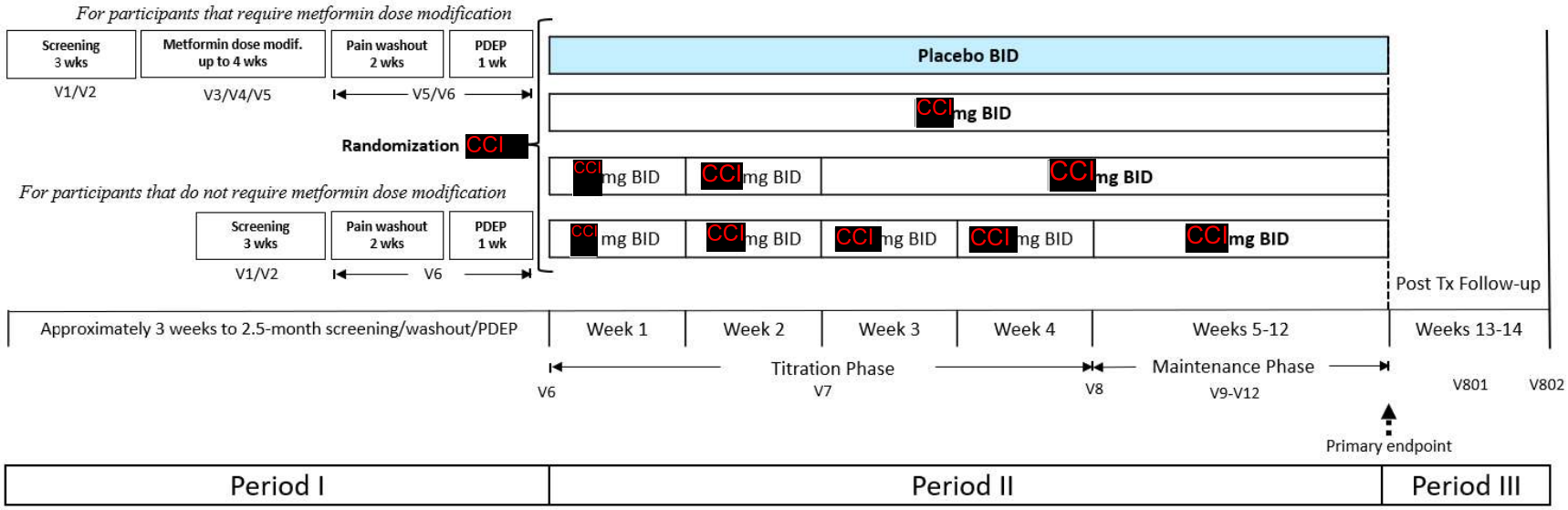
The estimand is described by these attributes

- **Population:** DPNP participants who meet the eligibility criteria.
- **Endpoint:** change from baseline to 12 weeks in API via NRS.
- **Treatment condition:** the randomly assigned treatment with allowance for potential dose interruptions and modifications regardless of adherence to study intervention or initiation of prohibited medications.
- **ICEs:** no ICEs since treatment adherence, and the initiation of rescue medications are part of the treatment condition.
- **Population-level summary:** the difference in mean changes from baseline to Week 12 between treatment conditions.

Rationale for estimand*:* this estimand aims to evaluate the efficacy of LY3556050 such that it reflects the real-life behavior of the target population.

1.2. Study Design

Study LXBD is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to examine the safety and efficacy of 3 dose levels of BID LY3556050 compared with BID placebo in participants with DPNP. Protocol LXBD provides details of the overall study design. The study schema is shown in Figure LXBD.1.1.



Abbreviations: BID = twice daily; modif. = modification; PDEP = preliminary data entry period; Tx = treatment; V = visit.
Note: The visit window intervals from Visits 2 to 6 are targeted timeframes. These intervals may vary depending upon the time required to washout chronic pain medication.

Figure LXBD.1.1. Study LXBD schema.

2. Statistical Hypotheses

The primary objective is to demonstrate that CCI dose of LY3556050 is superior to placebo in achieving greater improvement in API as measured by the NRS from baseline at 12 weeks (about 3 months). Thus, the null hypothesis to be tested in relation to the primary objective is

- Null Hypothesis: LY3556050 (CCI mg, CCI mg, CCI mg BID) is not different from placebo with respect to the achievement of change in API-NRS from baseline at Week 12.

2.1. Multiplicity Adjustment

There is no plan to formally adjust for multiplicity across secondary endpoints.

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3. Analysis Sets

For the purposes of analysis, these analysis sets are defined:

Participant Analysis Set / Population	Description
Entered Participants	All participants who sign full informed consent.
Randomized Participants (ITT)	All participants who are randomly assigned a study intervention. Participants will be analyzed according to the treatment group to which they were randomly assigned.
Full Analysis Set (mITT)	Data obtained from all participants who are randomly assigned a study intervention, who take[redacted] dose of double-blind study intervention. Participants will be analyzed according to the treatment group to which they were randomly assigned.
Safety Analysis Set	Data obtained during the treatment period plus safety follow-up from all participants who are randomly assigned a study intervention, who take[redacted] dose of double-blind study intervention. Participants will be analyzed according to the intervention they receive.

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat.

The full analysis set is used to analyze endpoints related to the efficacy objectives. The safety analysis set is used to analyze the endpoints and assessments related to safety.

These data points sets are defined:

Data Points Set	Description
Hypothetical Estimand Data Points Set	Data points obtained during the treatment period at or after randomization up to the earliest date of discontinuation of study intervention.
Treatment Policy Estimand Data Points Set	Data points obtained during the treatment period at or after randomization regardless of discontinuation of study intervention or initiation of prohibited medications.

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4. Statistical Analyses

4.1. General Considerations

Statistical analysis of Study LXBD will be the responsibility of Lilly or its designee. Some analyses and summaries described in this analysis plan may not be conducted if not warranted by the data (for example, too few events to justify conducting an analysis). Additional analyses of the data may be conducted as deemed appropriate.

CCI analysis will consist of the posterior mean and 95% credible interval for the difference in mean response for each LY3556050 dose versus placebo for all dose levels during the 12-week treatment phase and 2-week safety follow-up phase.

CCI analyses, unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10. Unless stated otherwise, statistical summaries and analyses will be conducted based on planned randomized treatment group (placebo, LY3556050 CCI mg BID, LY3556050 CCI mg BID, or LY3556050 CCI mg BID), regardless of the actual treatment(s) received by the participant due to any dose modification.

Unless specified otherwise, safety assessments will be conducted by comparing the safety of LY3556050 doses with placebo using the safety analysis set.

Details about the analyses regarding demographic and baseline characteristics, treatment compliance and eCOA compliance, clinical trial registry, concomitant medications, and important protocol deviations can be found in Appendix 1 (Section 6.1), Appendix 2 (Section 6.2), Appendix 3 (Section 6.3), Appendix 4 (Section 6.4), and Appendix 5 (Section 6.5).

Table LXBD.4.1 describes the rules for determining the participant population and baseline and postbaseline observations for the analyses based on the observations taken in Periods II and III.

Table LXBD.4.1. Baseline and Postbaseline Definitions

Study Period/Analysis	Participant Population	Baseline Observation	Postbaseline Observation(s)
Primary/secondary/exploratory efficacy analyses (repeated measures collected from eCOA)	mITT	Up to the last seven days of the PDEP period, before the first dosing date.	Starts after the first dose and ends on the last day of the study treatment disposition visit.
Primary/secondary/exploratory efficacy analyses (repeated measures of values collected at scheduled visits)	mITT	Visit 6	Visit 7 – up to Visit 12
Primary/secondary/exploratory efficacy analyses (categorical longitudinal with weekly values based on eCOA data)	mITT	Up to the last seven days of the PDEP period, before the first dosing date.	Starts after the first dose and ends on the last day of the study treatment disposition visit.
Primary/secondary/exploratory efficacy analyses (categorical longitudinal with values based on scheduled visits)	mITT	Visit 6	Visit 7 – up to Visit 12
Primary/secondary/exploratory efficacy analyses (time-to-event based on eCOA data)	mITT	Up to the last seven days of the PDEP period, before the first dosing date.	Starts after the first dose and ends on the last day of the study treatment disposition visit.
TEAE	Safety Analysis Set	Start of screening and ends prior to the first dose at Visit 6.	Starts after the first dose and ends on the last day of the study treatment disposition visit.
Post-TEAE	Safety Analysis Set	Start of Visit 12 to Visit 802.	Starts after the first dose and ends on the last day of the study treatment disposition visit to the last day of the study disposition visit.
Serious adverse events, discontinuations due to adverse events	Safety Analysis Set	N/A	Starts after the first dose and ends on the last day of the study treatment disposition visit / the last day of the study disposition visit.
Treatment-emergent abnormal laboratory values, vital signs and ECG	Safety Analysis Set	Start of screening, ends prior to the first dose at Visit 6. All scheduled and unscheduled measurements will be included.	Starts after the first dose at Visit 6 and ends on the day of the study treatment disposition visit / the last day of the study disposition visit. All scheduled and unscheduled measurements will be included.

Study Period/Analysis	Participant Population	Baseline Observation	Postbaseline Observation(s)
Change from Last Baseline to up to Week 12 and to Last Postbaseline for Laboratory Values and Vital Signs	Safety Analysis Set	Start of screening and ends prior to the first dose at Visit 6. The last scheduled nonmissing assessment recorded prior to the date of first dose.	Starts after the first dose at Visit 6 and ends on the day of the study treatment disposition visit / the last day of the study disposition visit. Only scheduled visits will be included. The early termination visits are considered scheduled visits.
C-SSRS categorical analyses	Safety Analysis Set with a baseline and at least one post-baseline C-SSRS assessment.	Visit 1	Starts after the first dose at Visit 6 and ends on the day of the study treatment disposition visit / the last day of the study disposition visit.
Rescue medication (acetaminophen) use	Safety Analysis Set	The last seven days of the PDEP period before the first dosing date.	Starts the day of scheduled dose administration and ends on the day of the study treatment disposition visit. Starts after the first dose at Visit 6 and ends on the day of the study treatment disposition visit / the last day of the study disposition visit.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; mITT =modified intent-to-treat; N/A = not applicable; PDEP = preliminary data entry period; TEAE = treatment-emergent adverse event.

4.2. Participant Dispositions

The number and percentage of randomly assigned participants, and the safety analysis set, will be summarized by reason for study discontinuation and permanent study treatment discontinuation. These summaries will be broken down by treatment group and overall, for treatment period and safety follow-up period. Study and study treatment disposition by metformin dose modification to 500 mg BID (yes/no) may also be summarized. No inferential statistics will be reported.

A listing of the participant disposition will also be produced for all enrolled participants.

Kaplan-Meier plots of time from randomization to premature study drug discontinuation, and premature study drug discontinuation due to an adverse event (AE), may be provided based on all participants who have been randomly assigned. Time-to-event analyses of premature study

treatment discontinuation, study drug discontinuation due to AE, and study discontinuation may be conducted.

4.3. Primary Endpoint Analysis

The primary analysis is aligned to the hypothetical estimand and will analyze the change in API via NRS from baseline to Week 12 using a combination of a CCI and a CCI model approach. The hypothetical estimand data points set will be used for the primary analysis. This is comprised of data collected if participants completed the treatment period or discontinued the study intervention.

The primary analysis will be performed using an CCI followed by a CCI model. CCI will be performed from Week 1 through Week 12. The adjusted dose response value from the CCI will be used for fitting a CCI . CCI

4.3.1. Definition of Endpoint

The primary analysis will evaluate the efficacy of each study intervention on the overall mean change from baseline to the endpoint for API as measured by the NRS during a 12-week, double-blind treatment period. The endpoint for the primary analysis is defined as 12 weeks post-initial treatment administration.

The API using the NRS scale will be collected daily. Average scores will be calculated over weekly time intervals up to Week 14.

To compute the weekly and biweekly mean scores from the eCOA device during Study LXBD, the following algorithm will be applied to define the time intervals.

The last seven days of the preliminary data entry period (PDEP) before the first dosing date will be grouped to one nominal week and will be used as baseline for efficacy evaluation. In the event of a participant having less than seven days of the PDEP before the first dosing, the baseline measurement will be based on the average of the available daily measurements before the first dose date. In the postbaseline period, the first visit interval will start on the first dosing date and end one day prior to the start of the next visit. The subsequent visit intervals will follow the same algorithm. The final interval will end on the treatment period disposition date.

In the postbaseline period, if the number of days in a visit interval is even, then the number of days will be evenly split and allocated to the nominal weekly intervals. In the event of an odd number of days in a visit interval, the number of days between the visits will be divided into two parts and allocated to the two nominal weekly intervals such that the second interval has one extra day as compared to the first interval.

In the postbaseline period, the biweekly mean score for a visit interval is defined as the average of the NRS scores within the interval. The weekly mean score for a nominal week is defined as the average of the NRS scores within the nominal week. If a participant has less than 50% of the daily NRS values during the prespecified time intervals in the postbaseline period, the average

score for that time interval will be set as missing. However, this rule will not be applied to the PDEP as all available data will be used to inform the baseline measurement for a participant.

4.3.2. Main Analytical Approach

The primary analysis of this study is a CCI model averaging strategy for determining the dose-response relationship in change from baseline to Week 12 in the primary outcome measure, with the goal of demonstrating CCI dose of LY3556050 is superior to placebo for the primary estimand, as described in Section 4.1. Superiority is defined as a CCI of greater improvement for CCI dose of LY3556050 compared with placebo of CCI as measured by the mean change from baseline at Week 12 of API-NRS.

The fitting of the primary analysis is a two-step process. First, a CCI analysis will be conducted first for API-NRS during a 12-week, double-blind, treatment phase. The model for this analysis will include the CCI

Next, the adjusted response value of each participant at Week 12 from the CCI model will be output and used, along with the treatment group for each participant, to fit the CCI analysis. CCI), will be used to analyze the dose response relationship in the change from baseline to Week 12. The placebo group will be included in the dose response modeling, corresponding to a dose strength of CCI The association between dose and response value will be analyzed in the CCI model, hence the treatment group will not be included as a covariate in the CCI . Superiority is defined as a CCI of greater improvement for CCI dose of LY3556050 compared with placebo of CCI , as measured by the mean change from baseline at Week 12 of API-NRS. The posterior mean change from baseline and a 95% credible interval will be reported for each group. The posterior mean and a 95% credible interval for the differences from each LY3556050 dose versus placebo will also be provided.

4.3.3. Sensitivity Analysis

Different candidate dose-response models may be explored for the CCI model as sensitivity analyses.

Sensitivity analyses of the primary analysis may be conducted for patients who did not use prohibited medication.

4.3.4. Supplementary Analyses

A supporting analysis for the primary outcome is a CCI analysis to assess whether CCI dose of LY3556050 is superior to placebo in providing greater improvement for API-NRS during a 12-week, double-blind, treatment phase. The model for this analysis will include the CCI

CCI [redacted]

Additional subgroup efficacy analyses may be explored, such as CCI [redacted]

4.4. Secondary Endpoint(s)/Estimands(s) Analysis

Table LXBD.4.2 includes the description and derivation of all primary and secondary endpoints for the efficacy measures and patient-reported outcomes.

Table LXBD.4.3 provides the detailed analyses including endpoint, estimand, data points set, method, and population for the primary and secondary endpoints.

Table LXBD.4.2. Description and Derivation of Primary and Secondary Endpoints for Efficacy Measures and Patient-Reported Outcomes

Measure	Description	Variable	Derivation/Comment
API-NRS	Per Protocol LXBD Section 8.1.3.1: This is a single-item numeric scale where participants are asked to rate their usual level of foot pain over the past 24 hours, on a scale of 0 to 10: 0 = no pain, and 10 = pain as bad as you can imagine.	API-NRS	As measured.
		Change from baseline in API-NRS.	Calculated as postbaseline API-NRS – baseline API-NRS
		CCI [redacted]	[redacted]
		[redacted]	[redacted]
WPI-NRS	Per Protocol LXBD Section 8.1.3.1: This is a single-item numeric scale where participants are asked to rate their worst level of foot pain over the past 24 hours, on a scale of 0 to 10: 0 = no pain, and 10 = pain as bad as you can imagine.	WPI-NRS	As measured.
		Change from baseline in WPI-NRS.	Calculated as postbaseline WPI-NRS – baseline WPI-NRS.

		CCI [redacted]	[redacted]
		[redacted]	[redacted]
PROMIS PI8a	Per Protocol LXBD Section 8.1.3.2.1. The PROMIS PI8a assesses the self-reported extent to which pain interferes with relevant aspects of a person's life for 8 items and each is rated on a 5-point Likert scale ranging from "not at all" to "very much."	PROMIS PI8a	Raw scores for each scale will be converted to a T-score, which is standardized with a mean of 50 and a standard deviation of 10
		Change from baseline.	Calculated as postbaseline – baseline.
PROMIS PF10a	Per Protocol LXBD Section 8.1.3.2.2. The PROMIS PF10a assesses self-reported physical function and physical activities for 10 items. The physical function is assessed at the present time through 5 items and each item is rated on a 5-point Likert scale ranging from limitations of "not at all" to "cannot do." The remaining 5 items are self-reported ability to perform specific physical activities and these items are rated using a 5-point Likert scale ranging from "without any difficulty" to "cannot do."	PROMIS PF10a	Raw scores for each scale will be converted to a T-score, which is standardized with a mean of 50 and a standard deviation of 10.
		Change from baseline.	Calculated as postbaseline – baseline.

PROMIS SD 8b	Per Protocol LXBD Section 8.1.3.2.3. The PROMIS SD8b includes 8 items that assess perceptions of sleep quality, sleep depth, and restoration associated with sleep and each item is rated on a 5-point Likert scale ranging from "not at all" to "very much" or "never" to "always," or "very poor" to "very good."	PROMIS SD 8b	Raw scores for each scale will be converted to a T-score, which is standardized with a mean of 50 and a standard deviation of 10.
		Change from baseline.	Calculated as postbaseline – baseline.
Pain Interference with Sleep	Per Protocol LXBD Section 8.1.3.3. The extent to which diabetic nerve pain interfered with the participant's sleep the previous night is measured in a single item with the answer ranging from 0 ("Not at all") to 4 ("Unable to sleep at all").	Pain Interference with Sleep	As measured.
		Change from baseline.	Calculated as postbaseline – baseline.
PGI-Severity	Per Protocol LXBD Section 8.1.3.4. The PGI-Severity scale is a patient-reported single-item instrument designed to assess the participant's severity in diabetic nerve pain over the past week. The single item is rated on a 5-point Likert scale ranging from "very severe" to "none."	PGI-Severity	As measured.
		Change from baseline.	Calculated as postbaseline – baseline

PGI-Status	Per Protocol LXBD Section 8.1.3.5. The PGI-Status scale is a patient-reported single-item instrument designed to assess the participant's status with diabetic nerve pain. This study will utilize 3 PGI-Status scales to assess physical activity, usual activity, and sleep disturbance. All 3 scales are rated on a 5-point Likert scale.	PGI-Status	As assessed.
		Change from baseline.	Calculated as postbaseline – baseline
PGI-Change	Per Protocol LXBD Section 8.1.3.6. The PGI-Change scale is a patient-reported single-item instrument designed to assess the participant's rating of change in diabetic nerve pain since they began taking the study medication. This study will utilize 4 PGI-Change scales to assess diabetic nerve pain's impact on physical activities, usual activities, sleep disturbance, and overall change. Each item is rated on a 5-point Likert scale ranging from "much worse" to "much better."	PGI-Change	As assessed.
		Percentage of participants who reported "much better."	Response = yes if participants reported "much better."
NTSS-6	Per Protocol LXBD Section 8.1.3.7. The NTSS-6 assesses the frequency and intensity of 6 diabetic peripheral neuropathic symptoms over the last 7 days. Scores on the NTSS-6 are found as weighted scores, in which intensity is given a weight of 1 and frequency has a weight of 1/3. Scores range from 0 to 21.96.	NTSS-6	As assessed.
		Change from baseline.	Calculated as postbaseline – baseline.

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		Percentage of participants who reported an NTSS-6 greater than 6	Response = yes if participants reported an NTSS-6 greater than 6

Abbreviations: API-NRS = Average Pain Intensity Numeric Rating Scale; NTSS-6 = Neuropathy Total Symptom Score; PGI-Change = Patient Global Impression of Change; PGI-Severity = Patient Global Impression of Severity; PGI-Status = Patient Global Impression of Status; PROMIS PF10a = PROMIS Short Form v2.0 Physical Function 10a; PROMIS PI8a = PROMIS Short Form v1.0 Pain Interference 8a; PROMIS SD 8b = PROMIS Short Form v1.0 Sleep Disturbance 8b; WPI-NRS = Worst Pain Intensity Numeric Rating Scale.

Table LXBD.4.3. Secondary and Exploratory Efficacy Variables and Analysis Methods

Efficacy Variable	Analyses
1. Average pain intensity as measured by the biweekly average of the NRS 2. Worst pain intensity as measured by the weekly average of the NRS 3. Worst pain intensity as measured by the biweekly average of the NRS 4. Pain Interference with Sleep 5. Rescue medication	Variable change from baseline will be analyzed using: CCI for the hypothetical estimand and treatment policy estimand, same as the supporting analyses for API via NRS described in Section 4.3.4 and 4.4.1.2.
6. PROMIS Pain Interference 8a 7. PROMIS Physical Functioning SF10a 8. PROMIS Sleep Disturbance SD8b 9. PGI-Severity 10. PGI-Status 11. NTSS-6	Variable change from baseline will be analyzed using CCI with the hypothetical estimand data points set described in Section 4.4.1.2.
12. PGI-Change	This will be analyzed by the CCI method with the hypothetical estimand data points Set without baseline as the covariate described in Section 4.4.1.2.
13. CCI 14. CCI 15. CCI 16. CCI 17. Proportion of participants with PGI-Change as “much better” 18. Proportion of participants with NTSS-6 greater than 6	The percentages of participants meeting criteria will be compared between treatments using a categorical CCI described in Section 4.4.1.2.
19. CCI	Kaplan-Meier curve and log-rank test described in Section 4.4.1.2.

20. CCI [redacted]	

Abbreviations: API = average pain intensity; CCI [redacted]; NRS = numeric rating scale; NTSS-6 = Neuropathy Total Symptom Score;. PGI-Change = Patient Global Impression of Change; PGI-Severity = Patient Global Impression of Severity; PGI-Status = Patient Global Impression of Status; PROMIS PF10a = PROMIS Short Form v2.0 Physical Function 10a; PROMIS PI8a = PROMIS Short Form v1.0 Pain Interference 8a; PROMIS SD 8b = PROMIS Short Form v1.0 Sleep Disturbance 8b.

4.4.1. Secondary Endpoint(s)/Estimand(s)

4.4.1.1. Definition of Endpoint(s)

The definitions of secondary endpoints are specified in Table LXBD.4.2. Secondary and efficacy variables and analysis methods are specified in Table LXBD.4.3.

4.4.1.2. Main Analytical Approach

Secondary estimand analysis

Secondary analysis for the primary endpoint API via NRS is aligned to the treatment policy estimand and will analyze the change in API via NRS from baseline at the 12-week visit using a combination of CCI and a CCI model approach. The full participants with treatment policy estimand data points set will be used for the primary endpoint. CCI CCI and CCI models. The main analytical approach aligns with the primary analysis.

Like the primary analysis, a supporting analysis for the secondary estimand analysis is a CCI analysis to assess whether CCI dose of LY3556050 is superior to placebo in providing greater improvement for API-NRS during a 12-week, double-blind, treatment phase. The full participants with treatment policy estimand data points set will be used for the primary analysis. CCI

Continuous secondary efficacy measures

For the continuous secondary efficacy measures, the change from baseline to each postbaseline period will be estimated for each treatment from the repeated measures analyses, as described for the analysis for the supplementary analyses of the primary outcome. These analytical approaches are listed in Table LXBD.4.3.

Worst pain intensity (WPI) via NRS and pain interference with sleep and rescue medication are collected as data regardless of early discontinuation via electronic Clinical Outcomes Assessment (eCOA), will be analyzed with the hypothetical estimand and treatment policy estimand separately, by CCI with covariates as described in Section 4.3.4.

The analysis on the Patient Global Impression of Change (PGI-Change) scale will not include baseline as a part of the response or covariates since the Patient Global Impression (PGI) is not collected at the baseline.

Binary efficacy measures

For the repeated binary efficacy measures, such as proportion of participants with greater than or equal to X% reduction from baseline in API via NRS, the binary outcomes indicating whether participants meet X% reduction criteria will be analyzed using a categorical, pseudo-likelihood-based repeated measures analysis using hypothetical estimand data points set. This analysis will be implemented using the GLIMMIX procedure in SAS to compare treatments and include the

fixed, categorical effects of CCI [redacted]

An unstructured covariance structure will be used to model the within-participant errors (denoted by TYPE=CHOL in the RANDOM statement). The Newton-Raphson method with ridging will be used for nonlinear optimization (denoted by including NLOPTIONS TECH = NRRIDG). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the model does not converge, Fisher's scoring algorithm will be utilized by the SCORING option in SAS.

If the model still fails to converge, the model will be fit using covariance matrices in the following order, specified by a decreasing number of covariance parameters until convergence is met:

1. heterogeneous Toeplitz,
2. heterogeneous autoregressive,
3. Toeplitz, and
4. autoregressive.

If necessary, both fitting algorithms will be used in the prespecified order before proceeding to the next covariance structure in the sequence.

For models where the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is utilized by the EMPIRICAL option in SAS. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM = BETWITHIN option in SAS.

Time-to-event efficacy analyses

For the time-to-event measures, a Kaplan-Meier analysis of the time to event will be performed and the Kaplan-Meier plots will be provided for each treatment arm. The treatment group comparison will be performed using log-rank test.

Participants who do not have the event of interest by the end of the treatment phase will be treated as a right censored observation. For analyses with the NRS score (see efficacy variables 18, 19, 20, 21 in Table LXBD.4.3), in cases of early discontinuation where the condition for the event is not met, participants will be censored at the nominal week associated with the discontinuation visit.

Refer to Section 4.3.2.

4.4.1.3. Sensitivity Analyses

Analysis of Covariance

The analysis of covariance (ANCOVA) model will be used to analyze the change from baseline in API via NRS at Week 12 visit, guided by treatment regimen estimand. The model will include

- treatment group as a factor variable
- strata as factor variables
- baseline value (of the dependent variable)
- interaction between strata variable and treatment group, and
- interaction between baseline value and treatment group.

The estimated treatment group effect and comparison between CCI mg, CCI mg, or CCI mg LY3556050 and placebo will be reported together with the variability estimated using the robust inference (Ye et al. 2023). The associated 2-sided 95% CI and corresponding p-values will also be reported. If the model fails to converge, all the interaction terms will be removed before the model fitting. The addition of interaction terms is not intended to estimate the heterogeneity effect but to provide robustness and efficiency for the estimate of treatment comparisons on the unconditional effect.

4.4.1.4. Supplementary Analyses

For continuous secondary efficacy endpoints, the Last Observation Carried Forward (LOCF) method will be applied to manage missing visit data, ensuring a robust assessment of changes from baseline to post-baseline measurements. The pre-specified binary secondary efficacy outcomes will be analyzed using the imputed dataset, adhering to the specifications detailed in Table LXBD.4.3.

4.5. Exploratory Endpoint(s) Analysis

4.5.1. Posttreatment Efficacy Analyses

To assess posttreatment efficacy of LY3556050 versus placebo, the efficacy of each study intervention on the overall mean change from baseline to the endpoint for API as measured by the numeric rating scale (NRS) at 14 weeks post initial treatment administration will be explored using CCI approach with hypothetical estimand data points set and treatment policy estimand data points set.

4.5.2. Digital Measurement Analyses

A digital wearable was used to passively collect digital measurements on physical activity, sleep, behavioral and physiological information. A variety of analyses will be performed to evaluate the efficacy of the study intervention on the digital measurements and to evaluate the association between the digital measurements and clinical scales. The digital biomarker SAP will provide the specific analyses details with the digital measurements.

4.5.3. Totality of Evidence for Efficacy

It is expected that an assessment of the totality of evidence (ToE) for efficacy will be considered in decision making. The modeling framework will allow for the synthesizing of evidence from multiple domains using a CCI [redacted] model for change from baseline to Week 12, except PGI-Change (see Table LXBD.4.4). The information from each scale within each domain will be shared through the modeling framework. Final model-based estimates will be aggregated to provide a domain-level treatment effect. The default domains and scales that will be included in each efficacy ToE model are provided below.

Table LXBD.4.4 Totality of Evidence Domains and Scales

Domain/Scale
Pain Intensity
Average Pain Intensity Over Last 24 Hours via NRS
Worst Pain Intensity Over Last 24 Hours via NRS
PGI-Severity
PGI-Change Question: How would you describe the overall change in your Diabetic Nerve Pain since you started taking the study medication?
NTSS-6
Physical Function
PROMIS Pain Interference 8a
PROMIS Physical Functioning SF10a
PGI-Status Question: How much does your Diabetic Nerve Pain limit your physical activity now?
PGI-Status Question: How much has your Diabetic Nerve Pain limited your usual activities over the past week?
PGI-Change Question: How has your ability to do physical activities due to Diabetic Nerve Pain changed since you began taking the study medicine?
PGI-Change Question: How has your ability to do usual activities due to Diabetic Nerve Pain changed since you began taking the study medicine?
Sleep Quality
PROMIS Sleep Disturbance SD8b
Pain Interference with sleep
PGI-Status Question: How much has your Diabetic Nerve Pain affected your sleep over the past week?
PGI-Change Question: How has your sleep due to Diabetic Nerve Pain changed since you began taking the study medicine?

Abbreviations: NRS = numerical rating scale; PGI-Change = Patient Global Impression of Change; PGI-Severity = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System.

4.6. Safety Analyses

Fisher's Exact test will be used to compare percentages, and odds ratios will be displayed. Odds ratios will be created with treatment as the numerator and placebo as the denominator. For document writing purposes for interpreting safety results, tests with two-sided p-values less than 0.05 will be referred to as having strong statistical evidence for a treatment difference, unless otherwise noted. However, p-values should not be over-interpreted for these safety analyses.

Except for prespecified hypotheses, p-values correspond to data-driven hypotheses and hence are only useful as a flagging mechanism.

4.6.1. Extent of Exposure

Duration of exposure (defined as the time since the first dose of study treatment to the last dose of study treatment, measured in days) to study drug will be summarized by treatment group using descriptive statistics; this summary will also include the total exposure in participant 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 participant years will be calculated as follows:

Total exposure in participant years = Sum of duration (days) of exposures for all participants in the treatment group/365.25

4.6.2. Adverse Events

Planned summaries for AEs are provided in Table LXBD.4.5.

Table LXBD.4.5. Tables and Figures Related to Adverse Events

Analysis	Details	Analysis Set
Overview of AEs	Number and percentage of participants who reported • TEAE • SAE • death, and • discontinuation from study treatment due to an AE. Statistical comparisons will be included. Causality will be included in listing.	Safety Analysis Set – TP, TP+FP
TEAEs by PT within SOC	Number and percentage of participants with TEAEs using the MedDRA PT nested within the SOC. Statistical comparisons will be applied at both the SOC and PT levels. Events will be ordered by decreasing frequency within SOC. SOCs will be listed by decreasing frequency in LY3556050 CCI mg BID group.	Safety Analysis Set – TP, TP+FP, FP
TEAEs by PT	Number and percentage of participants with TEAEs using MedDRA PT (irrespective of SOC). Events will be ordered by decreasing frequency in the LY3556050 CCI mg BID group. Statistical comparisons will be included.	Safety Analysis Set – TP, TP+FP, FP
Maximum Severity TEAEs by PT	The number and percentage of participants with TEAEs by maximum severity using the MedDRA PT. For each participant and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the nonmissing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table. Statistical comparisons will be included for the total and severe rows (that is, not for mild only and moderate only).	Safety Analysis Set – TP, TP+FP
Common TEAEs by PT	The number and percentage of participants with TEAEs using the MedDRA PT for the common TEAEs (occurred in ≥ 2% before rounding in any column in the table) Study-size-adjusted percentages are used. Statistical comparisons will be included. These are also presented as a figure.	Safety Analysis Set – TP, TP+FP

Analysis	Details	Analysis Set
SAEs by PT	The number and percentage of participants who experienced an SAE (including deaths and SAEs temporally associated with or preceding deaths). Events will be ordered by decreasing frequency in LY3556050 CCI mg BID group. Statistical comparisons will be included. Causality will be included in listing.	Safety Analysis Set – TP, TP+FP
Primary AE leading to permanent discontinuation of study treatment by PT	The number and percentage of participants who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the treatment period using the MedDRA PT. The primary AE listed on the disposition form will be used. Events will be ordered by decreasing frequency. Statistical comparisons will be included. Causality will be included in listing.	Safety Analysis Set – TP, TP+FP
Listing of SAEs	SAEs resulting in death will be identified through a flag in the listing.	Safety Analysis Set – TP, TP+FP

Abbreviations: AE = adverse event; BID = twice daily; FP = posttreatment follow-up period; LLT = Lowest Level Term; LY = Lilly Product Number; SAE = serious adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; PT = preferred term; SOC = System Organ Class; TEAE = treatment-emergent adverse event; TP = double-blind treatment period.

Treatment-emergent adverse events (TEAEs)

A TEAE is defined as an event that first occurs or worsens in severity after baseline and on or before the date of the last visit within the dosing period. The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. The double-blind treatment period will be included as postbaseline for the analysis. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, the event will be treated as mild in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as severe and treatment emergence will be determined by comparing with baseline severity. All events occurring on the day of first intervention administration will be treated as posttreatment.

System Organ Class (SOC) mapping

MedDRA preferred terms (PTs) are assigned to an SOC through primary mappings (defined by MedDRA). Thus, MedDRA PTs will appear in only 1 SOC.

Other AEs for review coded to MedDRA terms include

- Hypothyroidism (in standardised 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)
    - Blood pressure diastolic decreased
    - Blood pressure systolic decreased
    - 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 SMQ)
  - Depressed mood disorders and disturbances
- Congestive Heart Failure (in SMQ)
  - Cardiac Failure
- Substance abuse (in MedDRA HLT)
  - Substance related and addictive disorders
- Abuse liability and withdrawal potential following the Lilly Guidance for Assessment of Abuse Potential during Clinical Development
  - Drug abuse and dependence (in SMQ)
  - Drug withdrawal (in SMQ)
  - Drug abuse (in PT)
- Potential CNS Related Events of Interest (in PT)
  - Dizziness
  - Fatigue
  - Somnolence
  - Lethargy
  - Asthenia
  - Mental fatigue
- Lactic acid increase
  - Lactic Acidosis (preferred MedDRA term)
  - Metabolic Acidosis (preferred MedDRA term)
  - Ketoacidosis (preferred MedDRA term)
  - Hyperlactatemia (MedDRA LLT)
  - Hyperlactacidaemia (preferred MedDRA term)
  - Blood lactate acid increased (preferred MedDRA term)
  - Metformin associated lactic acidosis (MALA, MedDRA LLT)
- Level 2 hypoglycemia (summary of events and severe events, and listing from the electronic case report form [eCRF])

CCI , as collected via eDiary during the post treatment follow-up period, will be summarized by treatment group.

4.6.3. Narratives

The following are notable events, from the start of study drug administration through end of study participation:

- deaths
- SAEs
- permanent discontinuations of study treatment due to AEs

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- permanent discontinuations of study treatment due to estimated glomerular filtration rate (eGFR) falling below 45 ml/min per 1.73 m^2 based upon the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from cystatin-C
- clinically confirmed MALA
- hepatic event reported in eCRF, and
- renal treatment-emergent adverse events.

Narratives (participant-level data and summary paragraph) will be provided for participants in the safety analysis set with at least 1 notable event.

Safety topics of interest are not considered notable events, unless 1 of the above criteria is met. Displays with individual participant-level data will be created for safety topics of interest using various formats such as a customized listing and/or a customized graphical participant profile as specified in the section associated with the safety topic of interest. Medical case summaries/vignettes will be provided if deemed relevant for the discussion of the safety topic of interest.

4.6.4. Clinical Laboratory Evaluations

Planned summaries for clinical laboratory evaluations are provided in Table LXBD.4.6.

Baseline and postbaseline values are defined as follows:

- **last baseline**: the last nonmissing observation in the baseline period; unplanned measurements will be excluded.
- **last postbaseline**: the last nonmissing observation in the postbaseline period; unplanned measurements will be excluded.
- **maximum baseline**: the maximum nonmissing value during the baseline period; planned and unplanned measurements will be included.
- **maximum postbaseline**: the maximum nonmissing observation during the postbaseline period; planned and unplanned measurements will be included.
- **minimum baseline**: the minimum nonmissing value during the baseline period; planned and unplanned measurements will be included.
- **minimum postbaseline**: the minimum nonmissing observation during the postbaseline period; planned and unplanned measurements will be included.

If the last nonmissing laboratory observations are collected within 10 minutes postdosing, the measurements will be included as in the baseline or postbaseline period. Some analyses may be incorporated into interactive display tools instead of, or in addition to, a static display. The plan is to include box plots for observed values and the shifts from low to normal/high and high to normal/low summaries as static displays; the box plots for change from baseline values, scatter plots, and shift tables will be reviewed as an interactive display. Any display described below and not provided in static form will be available upon request.

Box plots are used to evaluate trends over time and to assess the potential impact of outliers on central tendency summaries. Summaries and analyses of minimum and maximum values are for

sensitivity assessment purposes and will be discussed only if deemed relevant in the overall discussion of the safety profile of the compound.

Table LXBD.4.6. Tables and Figures Produced to Support Clinical Laboratory Evaluations

Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Original-scale data will be used. • SI units will be provided in the axis within a single plot. • Descriptive summary statistics will be included in a table below the box plot in SI units. • No inferential statistics.	Safety Population
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot in SI units. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot.	Safety Analysis Set
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Includes participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** maximum baseline versus maximum postbaseline • **Min vs Min:** minimum baseline versus minimum postbaseline	Safety Analysis Set
Shift tables for baseline-by-maximum categories and baseline-by-minimum categories	• Participants in the safety analysis set will be included. • Percentages in each cell of the table are created using the safety analysis set as the denominator. • **Maximum:** the shift table will include the number and percentage of participants within each maximum baseline category (low, normal, high, or missing) vs each maximum postbaseline category (low, normal, high, or missing) by treatment. • **Minimum:** the shift table will include the number and percentage of participants within each minimum baseline category (low, normal, high, or missing) vs each minimum postbaseline category (low, normal, high, or missing) by treatment. • No inferential statistics.	Safety Analysis Set
Summary tables for shifts to high/low	• Excludes analytes collected qualitatively.	Safety Analysis Set

	• **Normal/high to low:** includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.
	  o The denominator is equal to participants whose minimum baseline result is normal or high and who have at least 1 result during the treatment period.
	• **Normal/low to high:** includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.
	  o The denominator is equal to participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.	

Listing of abnormal laboratory findings	• Includes laboratory analytes collected quantitatively (high or low during postbaseline) and qualitatively (abnormal during postbaseline) • Includes participant identification, treatment group, laboratory analyte collection day (that is, days from start of study drug), analyte name, and analyte finding.	Safety Analysis Set

Abbreviations: max = maximum; min = minimum.

In addition, the number and percentage of participants in the safety analysis set who have a least 1 high post-baseline hepatic laboratory test value will be summarized by treatment group overall. These summaries will be provided for all participants and by baseline liver function category.

High postbaseline hepatic values by baseline liver function categories are presented below:

- Postbaseline alanine transaminase (ALT) and aspartate aminotransferase (AST) ≥ 3×ULN
  - Baseline categories: ≤ 1×ULN, > 1×ULN and < 3×ULN, ≥ 3×ULN
- Postbaseline ALT and AST: ≥5×ULN
  - Baseline categories: ≤ 1×ULN, > 1×ULN and < 3×ULN, ≥ 3×ULN and < 5×ULN, ≥ 5×ULN
- Postbaseline ALT and AST: ≥10×ULN
  - Baseline categories: ≤ 1×ULN, > 1×ULN and < 3×ULN, ≥ 3×ULN and < 5×ULN, ≥ 5×ULN and < 10×ULN, ≥ 10×ULN
- Postbaseline Total bilirubin and ALP: ≥2×ULN, and
  - Baseline categories: ≤ 1×ULN, > 1×ULN and < 2×ULN, ≥ 2×ULN.

The following analyses of lab analytes are also considered to assess renal function:

- Renal data analyses
  - serum cystatin C (change from baseline in mg/L and % change)
  - eGFR calculations:
    - eGFR (CKD-EPI algorithm using serum cystatin C) (Inker et al. 2012)

Algorithm: $133 \times \min(S_{cys}/0.8, 1)^{-0.499} \times \max(S_{cys}/0.8, 1)^{-1.328} \times 0.996^{Age}$ [× 0.932 if female], where S_{cys} is serum cystatin C, α is −0.499 for cystatin C ≤0.8 and −1.328 otherwise, min indicates the minimum of S_{cys}/κ or 1, and max indicates the maximum of S_{cys}/κ or 1

- For each eGFR calculation, we will produce a shift table of eGFR changes for baseline versus postbaseline for minimum baseline result versus minimum postbaseline result, using these GFR categories:
    i. Category 1: normal or high in GFR (≥90 mL/min per 1.73m^2)
    ii. Category 2: mild in GFR (60-89 mL/min per 1.73m^2)
    iii. Category 3a: moderate in GFR (45-59 mL/min per 1.73m^2)
    iv. Category 3b: moderate in GFR (30-44 mL/min per 1.73m^2)
    v. Category 4: severe in GFR (15-29 mL/min per 1.73m^2)
    vi. Category 5: kidney failure (GFR < 15 mL/min per 1.73m^2 or dialysis)

This table will be repeated for maximum and last observed results.

- Abnormal eGFR is specified below and will be summarized in the treatment-emergent lab summary tables.
    - Abnormal Low: < 90 mL/min per 1.73m^2
    - Abnormal High: as specified by the central lab

The anion gap will be calculated based upon sodium, potassium, chloride, and bicarbonate:

- Algorithm: Anion Gap = $[Na^+] + [K^+] - ([Cl^-] + [HCO_3^-])$

4.6.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

The planned summaries and analyses are provided in Table LXBD.4.7. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, and temperature. Unless specified otherwise, the planned summaries will be provided for Period II.

Some of the analyses of vital signs may be incorporated into interactive display tools instead of, or in addition to, a static display. For example, box plots for observed values, scatter plots, and shift tables could be provided as interactive displays for medical review.

The criteria for identifying subjects with treatment-emergent abnormalities are based on Table LXBD.4.8.

Table LXBD.4.7. Tables and Figures Produced to Support Vital Signs and Physical Characteristics

Analysis Type	Analysis Details	Analysis Set
Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot in SI units. • No inferential statistics.	Safety Analysis Set
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot in SI units. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot.	Safety Analysis Set
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Each study individually and studies combined will be displayed. • Includes participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** maximum baseline versus maximum postbaseline. • **Min vs Min:** minimum baseline versus minimum postbaseline.	Safety Analysis Set
Shift tables for baseline-by-maximum categories and baseline-by-minimum categories	• Participants in the safety analysis set will be included. • Percentages in each cell of the table are created using the safety analysis set as the denominator. • **Maximum:** the shift table will include the number and percentage of participants within each maximum baseline category (low, normal, high, or missing) versus each maximum postbaseline category (low, normal, high, or missing) by treatment. • **Minimum:** The shift table will include the number and percentage of participants within each minimum baseline category (low, normal, high, or missing) versus each minimum postbaseline category (low, normal, high, or missing) by treatment. • No inferential statistics.	Safety Analysis Set
Summary tables for shifts to high/low	• Limits from Table LXBD.4.8 will be used to define low and high. • **Normal/high to low:** Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low. ○ The denominator is equal to participants whose minimum baseline result is normal or high and who have at least 1 result during the treatment period.	Safety Analysis Set

Analysis Type	Analysis Details	Analysis Set
	• **Normal/low to high:** Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high. ○ The denominator is equal to participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period. • Statistical comparisons will be included.	
Listing of abnormal vital signs findings	• Includes vital signs collected quantitatively (high or low during postbaseline) • Includes participant identification, treatment group, vital sign collection day (that is, days from start of study drug), vital sign name, and vital sign finding.	Safety Analysis Set

Abbreviations: max = maximum; min = minimum.

Table LXBD.4.8. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg)	Postbaseline: ≤90 and decrease from baseline ≥20	Postbaseline: ≥140 and increase from baseline ≥20
Diastolic BP (mm Hg)	Postbaseline: ≤50 and decrease from baseline ≥10	Postbaseline: ≥90 and increase from baseline ≥10
Pulse (bpm)	Postbaseline: <50 and decrease from baseline ≥15	Postbaseline: >100 and increase from baseline ≥15
Weight (kg)	(Loss) decrease from baseline ≥7%	(Gain) increase from baseline ≥7%
Temperature (°F)	Postbaseline: <96 and decrease from baseline ≥2	Postbaseline: ≥101 and increase from baseline ≥2

Abbreviations: BP = blood pressure; bpm = beats per minute.

4.6.6. Electrocardiogram Parameters

Planned summaries for electrocardiogram (ECG) parameters are provided in Table LXBD.4.9. Unless specified otherwise, the planned summaries will be provided for Period II. These analyses will include heart rate, PR interval, QRS interval, QT interval, and corrected QT using Fridericia's correction factor, [$QTcF = QT/RR^{0.333}$].

When the QRS is prolonged (for example, a complete bundle branch block), QT and QTcF should not be used to assess ventricular repolarization. Thus, for a particular ECG, QT and QTcF will be set to missing (for analysis purposes) when QRS is ≥120.

The criteria for identifying subjects with treatment-emergent ECG abnormalities are based on Table LXBD.4.10. Additionally, the percentage of participants who experienced a PR interval value greater than or equal to 240 milliseconds at any time will be summarized.

Table LXBD.4.9. Tables and Figures Produced to Support ECG and Heart Rate

Analysis Type	Analysis Details	Analysis Set
Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • No inferential statistics.	Safety Population
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline planned measurement. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot.	Safety Analysis Set

Summary tables for shift to high/low	• Limits from Table LXBD.4.10 will be used to define low and high
	• **Normal/high to low:** includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.
	  ○ The denominator is equal to participants whose minimum baseline result is normal or high and who have at least 1 result during the treatment period.
	• **Normal/low to high:** includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.
	  ○ The denominator is equal to participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.
		Safety Analysis Set

Shift tables for baseline-by-maximum categories and baseline-by-minimum categories	• Participants in the safety analysis set will be included. • Percentages in each cell of the table are created using the safety analysis set as the denominator. • **Maximum:** the shift table will include the number and percentage of participants within each maximum baseline category (low, normal, high, or missing) vs each maximum postbaseline category (low, normal, high, or missing) by treatment.	Safety Analysis Set

Analysis Type	Analysis Details	Analysis Set
	• **Minimum:** the shift table will include the number and percentage of participants within each minimum baseline category (low, normal, high, or missing) vs each minimum postbaseline category (low, normal, high, or missing) by treatment. • No inferential statistics.	
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Each study individually and studies combined will be displayed. • Includes all participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** maximum baseline vs maximum postbaseline • **Min vs Min:** minimum baseline vs minimum postbaseline	
Additional Categorical Summary tables	• The percentages of participants with QT greater than 500 msec will be summarized, and the percentages of participants with QTcF greater than 500 msec will be summarized. • The percentages of participants who experienced a treatment-emergent increase from the maximum baseline in QTcF interval of greater than 30 msec, 60 msec, or 75 msec at any time will be summarized. • Maximum baseline will be the maximum nonmissing observation in the baseline period. • The maximum value during the treatment period will be analyzed. Planned and unplanned measurements will be included. • Statistical comparisons will be included.	Safety Analysis Set
Listing of abnormal ECG findings	• Includes ECGs collected quantitatively (high or low during postbaseline) Includes participant identification, treatment group, ECG collection day (that is, days from start of study drug), ECG name, and ECG findings.	Safety Analysis Set

Abbreviations: ECG = electrocardiogram; Max = maximum; Min = minimum; QTcF = corrected QT using Fridericia's correction factor; vs = versus.

Table LXBD.4.10. Selected Categorical Limits for Electrocardiogram Data

	Low		High	
Parameter	Males Age (years): limit	Females Age (years): limit	Males Age (years): limit	Females Age (years): limit
Heart rate (bpm)	≥18: <50 and decrease from baseline ≥15	≥18: <50 and decrease from baseline ≥15	≥18: >100 and increase from baseline ≥15	≥18: >100 and increase from baseline ≥15
PR interval (msec)	All ages: <120	All ages: <120	All ages: ≥220	All ages: ≥220
QRS interval (msec)	All ages: <60	All ages: <60	All ages: ≥120	All ages: ≥120
QTcF (msec)	All ages: <330	All ages: <340	≥16: >450	≥16: >470

Abbreviations: bpm = beats per minute; QTcF = corrected QT using Fridericia's correction factor.

4.6.7. Suicidal Ideation/Behavior

Suicidal ideation/behavior will be assessed prospectively via signs and symptoms through the Columbia Suicide-Severity Rating Scale (C-SSRS). Planned summaries will include the number and percentage of subjects by treatment for each of the following suicide-related events: died by suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, non-specific active suicidal thoughts, and wish to be dead. The number and percent of subjects with self-injurious behavior with no suicidal intent occurring during treatment will also be enumerated by treatment. Summaries will be reported for the double-blind treatment period and the follow-up period.

A listing of the C-SSRS answers will be provided for participants with any yes response.

CCI [redacted].

4.7. Other Analyses

4.7.1. Pharmacokinetic/Pharmacodynamic Methods

The observed plasma concentrations for LY3556050 will be reported graphically and summarized descriptively. Exploratory model-based pharmacokinetic (PK) and 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 Study LXBD may be pooled with data from other studies, if appropriate.

4.7.2. Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy measure of API-NRS for randomized participants in Period II, unless otherwise stated. Table LXBD.4.11 provides definitions for each of the subgroup variables. The subgroup analyses will be carried out using the data from the hypothetical estimand and treatment policy estimand separately.

Table LXBD.4.11. Definition of Subgroup Variables

Subgroup Variable	Categories
Gender	Male, Female
Baseline pain severity	Baseline pain severity category (moderate or severe) defined by the baseline NRS average pain < 7 versus baseline NRS average pain ≥ 7
Pain Catastrophizing Scale	Pain Catastrophizing Scale threshold scores ≥15 versus < 15
Use of allowed concomitant medication	Concurrent prior and continued use of one allowed concomitant medication for chronic pain (Yes/No)
Country and/or region	Country (Japan, South Korea, Poland, Czech Republic, United States) and/or region (North America, EU, Asia)
Metformin dose modification	Yes, No

Abbreviation: NRS = numeric rating scale.

For the subgroup analyses, the CCI method will be utilized, with the addition of a subgroup factor and interactions of treatment-by-subgroup, visit-by subgroup, and treatment-visit-subgroup will be used. The treatment-by-subgroup interaction will be tested at each visit at a significance level of 0.10. Within each category of subgroup, the CCI model specified in Section 4.3.4 will be used. The least squares (LS) mean, LS mean difference, standard error, and 95% CI will be presented.

If the subgroup factor is part of the strata variable, a new strata variable that excludes the subgroup categories will be used as covariates in CCI model.

If any category within the subgroup (for example, status of yes/no) is < 5% of the total population, only descriptive statistics will be provided for that category (that is, no inferential testing will be performed within the subgroup category).

4.8. Interim Analyses

4.8.1. Assessment Committee

An interim analysis will be conducted under the auspices of an assessment committee according to the specifications set forth in Protocol LXBD and the assessment committee charter.

There will be up to [redacted] interim analyses that occur when approximately [redacted] of participants complete 12 weeks of Study LXBD or discontinue treatment. The exact timing of the interim analysis will be based on the enrollment speed or other factors at the sponsor's discretion. Such factors will be detailed in the SAP or separate unblinding plan document. The purpose of any interim analyses is primarily for internal decision-making. [redacted] The purpose of these analyses may include futility and/or early efficacy analyses, safety analyses, or other reasons. Details regarding decision criteria will be included in the SAP and will be finalized prior to the first unblinding analysis.

An internal assessment committee is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if needed for the safety of their participants.

The analyses conducted by the assessment committee will follow the analyses outlined in Protocol LXBD. The assessment committee will provide oversight for safety. The structure and the responsibilities of the assessment committee will be detailed in the assessment committee charter.

Database lock will occur after all randomized participants complete the 12-week treatment period and the posttreatment safety follow-up period of Study LXBD, or discontinue the study early. The primary objective of the Study LXBD will be assessed following database lock.

Details of the assessment committee are described in the assessment committee charter. Details regarding maintaining the blind during the conduct of Study LXBD will be specified in the blinding and unblinding plan document.

4.9. Changes to Protocol-Planned Analyses

There are no changes to the protocol-planned analyses.

5. Sample Size Determination

To achieve the primary objective of Study LXBD, a total of 410 participants will be randomly assigned to 1 of 4 treatment groups in a CCI ratio (participants are blinded to the randomization ratio) to receive placebo or LY3556050 (CCI mg, CCI mg, and CCI mg, respectively). This sample size will provide approximately CCI power to show that CCI CCI has a CCI of greater improvement in change from baseline at Week 12 of API-NRS over placebo.

CCI

The sample size calculation is based on a CCI). For the sample size simulations, a mean treatment difference of CCI based on prior data. To ensure robustness of the operating characteristics across different true dose-response profiles, the virtual response is generated from 4 different plausible parametric dose-response shapes (CCI) for 410 participants. The trial operating characteristics, including the power, are maintained under each of the assumed dose-response profiles. CCI .

CCI

CCI . Sample size calculations were conducted using CCI .

The simulation for the power calculation and sample size determination was carried out using CCI

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Baseline characteristics will be summarized for all enrolled participants by treatment group and overall. These characteristics are

- demographic
  - age
  - age groups (<65, ≥65 and <75, ≥75 and <85, ≥85 years)
  - sex
  - race (Caucasian, Black or African American, Asian, Other, American Indian or Alaska Native, Multiple, and Native Hawaiian or Other Pacific Islander)
  - ethnicity (Hispanic or Latino, Not Hispanic or Latino, Missing)
  - height
  - weight, and
  - body mass index.
- baseline pain and rescue medication data collected daily at home during the last 7 days prior to randomization
  - average pain severity as measured by numeric rating scale
  - worst pain severity as measured by numeric rating scale, and
  - rescue medication use during baseline period (defined as at least use of rescue medication during the baseline period).
- visual analog scale at screening
- Pain Catastrophizing Scale total score at screening (to calculate total score, each of the 13 items is scored 0 to 4 by the participant and the total score is the sum of the individual 13 items and ranges from 0 to 52)
- medical history and preexisiting condition at visit 1
- family history
- prespecified medical history: diabetic peripheral neuropathic pain (DPNP) (Type 1 and Type 2, mean years of DPNP condition, % participants with DPNP in their lower arms and hands)
- metformin dose modification (yes/no)
- Michigan Neuropathy Screening Instrument
  - Part A - history subscale (less than 7 versus at least 7)
  - Part B - physical assessment subscale (less than 3 versus at least 3).

For all participant characteristics, the summaries will include descriptive statistics for continuous measures (number of observations, mean, standard deviation, median, minimum, maximum) and categorical measures (number of observations, frequency counts, percentages, and missing). No inferential statistics will be reported.

A listing of the participant demographics will also be produced for all enrolled participants.

6.2. Appendix 2: Treatment Compliance and electronic Clinical Outcomes Assessment 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 participant is considered to be compliant overall if the percentage of compliance is between 80% and 120% from Visit 6 to Visit 12. The percentage of participants who are compliant with study drug will be summarized by treatment group. For participants who discontinue early, the expected number of capsules on the day of the last dose is only for the morning administration and time after the penultimate visit will be excluded for calculation of treatment compliance. For example, if a participant discontinued early at Visit 10, treatment compliance will be derived only from data collected through Visit 9. Treatment compliance will be calculated by clinical visit and overall treatment duration.

Overall electronic Clinical Outcomes Assessment (eCOA) (eDiary) compliance will be summarized for the PDEP period, at each nominal week throughout the double-blind period, and across the double-blind period. eCOA compliance at a prespecified time interval is calculated as

$$\frac{\text{Actual number of days with eCOA entries in the time interval}}{\text{Total no. of days in the time interval}}$$

A participant is eCOA compliant in the time interval if the above ratio is greater than or equal to 50%; eCOA compliance during the double blind treatment period up to 12 weeks will be summarized by treatment group.

6.3. Appendix 3: Clinical Trial Registry Analyses

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

Analyses provided for CTR requirements include:

- A 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 adverse event and 'Other' adverse event, 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' adverse events that occur in fewer than 5% of participants or 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.

6.4. Appendix 4: Concomitant Therapy

Prior therapy is defined as started and ended prior to the first dose administration. Concomitant therapy is defined as started prior to and ongoing at first dose or started after first dose but prior to treatment disposition.

A listing of prior and concomitant therapies will be provided.

The number and percentage of enrolled participants using Preferred Names of concomitant medication or select classes of medications will be summarized. The Preferred Names or select classes of medications will be ordered by decreasing frequency. No inferential statistics will be reported.

Rescue medication use will be collected daily using the electronic Clinical Outcomes Assessment device. Within each nominal week described in Section 4.3.1, a participant will be considered a user of rescue medication if at least one use of rescue medication is reported during the nominal week. The number and percentage of participants who use rescue medication will be summarized by nominal study week.

The analysis of rescue medication will be performed using a categorical longitudinal model with nominal Week 1 to Week 12 values. The analysis model will include the fixed categorical effects of CCI [redacted]. The estimated probability of rescue medication use along with a confidence interval will be reported by treatment group.

In addition, the weekly average dosage of rescue medication based on the nominal weeks will be analyzed using an CCI [redacted] method and summarized. The analysis model will include the fixed

covariates of treatment, visit, and treatment-by-visit interaction, region, average baseline pain severity category (mild or moderate versus severe), as well as concurrent use of allowed concomitant medications (yes /no).

Acetaminophen is the only allowed rescue medication during the treatment period. A listing of rescue medication above the following protocol-specified limits will be provided:

- During the PDEP of up to 7 days, rescue medication use should be limited to 4 days or less.
- This table describes acetaminophen use guidance during the double-blind treatment period.

Acetaminophen Use Guidance during Visit 3 through Visit 7	
Maximum dose per day	3000 mg
Maximum consecutive days	3 days
Maximum total days	21 days

6.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan. A listing and summary of important protocol deviations by treatment group will be provided for all randomly participants. No inferential analysis will be performed.

7. References

Diggle PJ, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data*. Oxford: Clarendon Press; 1994.

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