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

Protocol: H0P-MC-NP03(b)

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

NCT04707157

Approval Date: 01-Oct-2021

Title Page

Master Protocol Title: A Master Protocol for Randomized, Placebo-Controlled, Phase 2 Clinical Trials of Multiple Interventions for the Treatment of Chronic Pain

Master Protocol Number: H0P-MC-CPMP

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

ISA Number: H0P-MC-NP03

Amendment Number: b

Compound: LY3556050

Study Phase: 2

Short Title: Clinical Trial to Evaluate LY3556050 for the Treatment of Diabetic Peripheral Neuropathic Pain

Acronym: NP03

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:

Master Protocol IND 144915
LY3556050 IND 129756

Approval Date: Protocol amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	12 March 2021
Original Protocol	23 September 2020

Amendment [b]

Overall Rationale for the Amendment:

This amendment allows participants to take certain doses of metformin based upon new PK modeling data and metformin prescribing information (GLUCOPHAGE package insert, 2018).

Section # and Name	Description of Change	Brief Rationale
1.2. Schema	Added a follow-up visit	Adding a telephone follow-up visit for adverse event (AE) check
1.3. Schedule of Activities (SoA)	Added a follow-up visit and a corresponding row for AEs	Adding a telephone follow-up visit for AE check AEs for the rest of the study are covered in the master CPMP SoA
4.1. Overall Design	Added follow-up visit	Adding a telephone follow-up visit for AE check
5.2. Exclusion Criteria	Updated criterion #3034 to allow particular metformin doses	The inclusion of selected doses of metformin for concomitant use is based on new PK modeling data and metformin prescribing information
5.2. Exclusion Criteria	Added criteria #3036 - #3041	For participants taking metformin
5.3. Lifestyle Considerations	Added additional alcohol restrictions for binge drinking	For participants taking metformin
6.5. Concomitant Therapy	Added a sub-section for concomitant therapy with metformin	Specific metformin doses are now allowed
7.1. Discontinuation of Study Intervention	Added sub-section Metabolic Safety	Provides additional information for participants taking metformin
7.2. Participant Discontinuation/Withdrawal from the Study	Added this section	Provides additional information for participants taking metformin
10.1. Appendix 1: Clinical Laboratory Tests	Added bicarbonate and anion gap calculation to chemistry	Participants are now allowed to take metformin
10.1. Appendix 1: Clinical Laboratory Tests	Added eGFR calculated by CKD-EPI equation based upon cystatin c	Participants are now allowed to take metformin
11. References	Added Reference section	In order to cite the metformin GLUCOPHAGE package insert
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

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1. Protocol Summary

1.1. Synopsis

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

Rationale:

The purpose of this study is to test whether LY3556050 is efficacious in relieving diabetic peripheral neuropathic pain (DPNP). Data will be collected to assess the safety and tolerability of LY3556050 in this study population. Pharmacokinetic properties and pharmacodynamic effects will also be explored. The totality of data from this proof-of-concept study will assess the benefits and risks associated with LY3556050 and inform decisions for the clinical development of LY3556050.

Objectives and Endpoints:

The primary and secondary objectives and endpoints are stated in the master protocol H0P-MC-CPMP (CPMP) and DPNP disease-state addendum (DSA; CPMP[3]).

Overall Design:

This is an 8-week, Phase 2, randomized, double-blind, placebo-controlled study that will compare LY3556050 versus placebo in participants with DPNP.

Disclosure Statement: This is a randomized, investigator- and participant-blind, placebo-controlled, Phase 2 clinical trial.

Number of Participants:

Up to 200 participants will be randomized in a CCI to LY3556050 and placebo, respectively, with the assumption that approximately 33% of the participants will drop out prior to the end of the double-blind treatment period.

Intervention Groups and Duration:

Participants will receive either LY3556050 or placebo. Based on tolerability, participants may take up to a maximum of 3 capsules orally (each capsule is CCI mg), twice daily, approximately every 12 hours, for a total dose of 600 mg.

This is an 8-week study.

Data Monitoring Committee: Yes

Safety reviews are covered by the Assessment Committee charter for the Chronic Pain Master Protocol.


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1.3. Schedule of Activities (SoA)

This SoA shows visits and procedures unique to the intervention-specific appendix (ISA) H0P-MC-NP03 (NP03) for LY3556050. Please refer to master protocol and the DPNP DSA SoAs for additional information.

H0P-MC-NP03 ISA	Randomization	Double-Blind Treatment				Early Discontinuation	Follow-up	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	V801	
Study Week	0	2	4	6	8			
Visit Window (days)		±3	±3	±3	±3			
Telephone Visit	X[a,b]						X[c]	Visit window +2 days CCI [redacted] [c] Visit 801 occurs 4-10 days after last dose of study intervention.
Procedures								
Evaluate all I/E criteria	X							
Physical examination	X	X	X	X	X	X		V3-V7: Do symptom-directed physical examination
ECG	X	X	X	X	X	X		V3, V5, and V7: Single safety ECG before in-clinic dosing and at 3 hours after dosing V4, V6 and ED: Single ECG ECG includes collection of PR interval, QRS duration and interval, and heart rate.
Vital signs	X	X	X	X	X	X		**Blood Pressure and Pulse Rate** V3, V5, and V7: Collect blood pressure and pulse in supine and standing position before in-clinic dosing and at 3 hours after dosing V4, V6, and ED: Collect blood pressure once Collect orthostatic blood pressure after 5 minutes supine and then 2-3 minutes after standing and collect pulse after supine and standing blood pressure. **Temperature and Respiratory rate** Collect once at each visit

H0P-MC-NP03 ISA	Randomization	Double-Blind Treatment				Early Discontinuation	Follow-up	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	V801	
Study Week	0	2	4	6	8			
Visit Window (days)		±3	±3	±3	±3			
Telephone Visit	X[a,b]						X[c]	Visit window +2 days CCI [redacted] [c] Visit 801 occurs 4-10 days after last dose of study intervention.
Procedures								
AEs							X	
Study intervention	X	X	X	X	X			Intervention is taken orally, twice daily (BID), approximately every 12 hours. V3, V5, and V7: Participants take the morning dose in the clinic. Refer to Section 6.6 for dose titration scheme.
Intervention compliance		X	X	X	X	X		
						Laboratory Tests and Sample Collection		
Hematology	X	X	X	X	X	X		V3: Collect laboratory tests before dosing.
Chemistry	X	X	X	X	X	X		V3: Collect laboratory tests before dosing.
Urine drug screen								Performed at investigator discretion.
Serum pregnancy		X	X	X	X	X		For WOCBP only
Urine pregnancy	X							For WOCBP only Collect sample within 24 hours prior to first dose.
Lipid panel	X	X	X	X	X	X		

H0P-MC-NP03 ISA	Randomization	Double-Blind Treatment				Early Discontinuation	Follow-up	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	V801	
Study Week	0	2	4	6	8			
Visit Window (days)		±3	±3	±3	±3			
Telephone Visit	X[a,b]						X[c]	Visit window +2 days CCI [redacted] [c] Visit 801 occurs 4-10 days after last dose of study intervention.
Procedures								
Thyroid panel	X	X	X	X	X	X		
Cystatin C	X	X	X	X	X	X		
HbA1c					X	X		
PK sample	X	X	X	X	X	X		V3: Collect at 3 hours ±15 minutes after dosing. V5 and V7: Collect samples before dosing and at 3 hours ±15 minutes after dosing. V4, V6, and ED: Collect single sample at any time. Record date and time of collection.
Somatostatin-regulated hormone sample	X	X	X	X	X	X		
CCI [redacted]								

H0P-MC-NP03 ISA	Randomization	Double-Blind Treatment				Early Discontinuation	Follow-up	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	V801	
Study Week	0	2	4	6	8			
Visit Window (days)		±3	±3	±3	±3			
Telephone Visit	X[a,b]						X[c]	Visit window +2 days CCI [redacted] [c] Visit 801 occurs 4-10 days after last dose of study intervention.
Procedures								
Participant Device								
Participant returns device					X	X		CCI [redacted]

Abbreviations: AE = adverse event; ECG = electrocardiogram; ED = early discontinuation; HbA1c = glycated hemoglobin; I/E = inclusion and exclusion; ISA = intervention-specific appendix; PK = pharmacokinetic; V = visit; WOCBP = women of childbearing potential.

2. Introduction

This intervention-specific appendix (ISA), H0P-MC-NP03 (NP03) is an appendix to the master protocol H0P-MC-CPMP (CPMP) and contains unique study elements specific for LY3556050. The master protocol contains the overarching study elements that govern the diabetic peripheral neuropathic pain (DPNP) disease-state addendum (DSA) and this ISA.

2.1. Study Rationale

The purpose of this study is to test whether LY3556050 is efficacious in relieving DPNP. Data will be collected to assess the safety, and tolerability of LY3556050 in this study population. Pharmacokinetic (PK) properties, and pharmacodynamic (PD) effects will also be explored. The totality of data from this proof-of concept study will assess the benefits and risks associated with LY3556050 and inform decisions for the clinical development of LY3556050.

2.2. Background

Somatostatin (SST) is an inhibitory neuropeptide exerting its activity via 5 different somatostatin receptor (SSTR) subtypes named SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5. Most are involved in homeostatic regulation of polypeptide hormones. Given its neuronal distribution, SSTR4 has been of interest for its ability to modulate sensory nerve transmission and pain response.

LY3556050 is a selective, potent, and full agonist of the human somatostatin receptor subtype 4 (SSTR4) and is under development as an oral analgesic for chronic pain. A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3556050 is provided in the w)o)Aw B

Two Phase 1 clinical studies in healthy participants are completed, CNTX-0290-101 (CNTX) and J2P-MC-LXBA (LXBA). CNTX and LXBA study results are available in the IB.

Pharmacokinetics

The PK data from Study LXBA Part A were consistent with those observed in Study CNTX and support twice-daily dosing.

Safety

The highest dose of 600 mg every 12 hours is considered safe and well tolerated in healthy participants.

2.3. Benefit/Risk Assessment

The IB provides detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3556050.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention LY3556050		
Cardiovascular	HR: Variable data across clinical studies and across doses PR interval: Concentration-related increase in duration with large variability QRS interval: Concentration-related increase in duration	Vital signs and ECGs evaluated at each visit. Cardiovascular safety parameters to be evaluated include: HR, PR and QRS intervals, and orthostatic vital signs. Additional participant exclusion criteria to protect those with a potential risk. Discontinuation criteria for clinically significant changes.
Thyroid	TSH increases observed in Study LXBA	Labs evaluated at each visit to monitor thyroid function. Additional participant exclusion criteria to protect those with a potential risk. Discontinuation criteria for clinically significant changes.

Abbreviations: ECG = electrocardiogram; HR = heart rate; TSH = thyroid-stimulating hormone.

2.3.2. Benefit Assessment

This is the first study evaluating efficacy of LY3556050 in participants with DPNP.

Potential benefits for the study participants include

study-related medical procedures
- physical examinations
- laboratory tests
- electrocardiograms (ECGs)

detailed evaluations of diabetic nerve pain, and
questionnaires that may improve participants understanding of their own condition.

As part of the master protocol, participants to this ISA will report their experiences using standard tools that will contribute to the assessment of novel treatments for DPNP. In addition, data collected from this study may also improve our understanding of chronic pain. Together, these may lead to the development of a new treatment with an improved safety and efficacy profile compared to standard of care.

2.3.3. Overall Benefit: Risk Conclusion

The measures taken to minimize risk to participants in this study and the potential risks identified in association with this ISA are justified by the anticipated benefits to participants with DPNP.

3. Objectives and Endpoints

The master protocol and DPNP DSA include objectives and endpoints applicable for this study. This table describes objectives and endpoints specific for LY3556050.

4. Study Design

4.1. Overall Design

The master protocol describes the overall study design and study design rationale. This section describes visits and overall procedures unique to this ISA for LY3556050 in addition to the procedures outlined in the master protocol and DPNP DSA.

Double-Blind Treatment Period (Visits 3 through 7)

If the participant receives at least 1 dose of intervention and discontinues during the double-blind treatment period, they should complete early discontinuation procedures per the master protocol, DPNP DSA, and this ISA Schedule of Activities (SoA). If there are duplicate procedures, follow the NP03 SoA.

Visit 3

At Visit 3 post randomization

- the site completes the NP03 baseline procedures and sample collection,
- participants receive their first dose of study intervention and instructions for dosing at home,
- the site completes all posttreatment sample collection and safety monitoring, and
- the site instructs participants to continue with study restrictions and Numeric Rating Scale (NRS) diary entries before their visit discharge.

At Visits 4 through 7, the site

reviews available safety data and completes predose procedures and sample collection,
reviews diary compliance,
reviews study intervention compliance,
completes all posttreatment sample collection and safety monitoring, and
instructs participants to continue with study restrictions and NRS diary entries before their visit discharge.

Follow-up Telephone Visit

A follow-up visit to review AEs, will occur 4 to 10 days after last dose of study intervention.

4.2. Scientific Rationale for Study Design

The master protocol describes the overall study design rationale.

Section 2.3.1 describes elements included in this study to further monitor cardiovascular and thyroid function, and the associated rationale.

4.3. Justification for Dose

The dose level of 600 mg twice daily (BID) was determined by current clinical data, efficacy pharmacology, and nonclinical safety data detailed in the IB. A titration scheme is included to maximize tolerability of this target dose.

Safety data from Study LXBA, and the clinical monitoring plan for this ISA, support testing the proposed dose regimen in participants with chronic pain conditions.

The observed LY3556050 exposure following repeated administration of 600 mg BID exceeds the exposure in rats where maximal pharmacological activity was consistently demonstrated across rodent models of neuropathic pain. However, it is not known what exposure is required for efficacy in the target patient population. Therefore, the highest dose (600 mg BID) previously evaluated in Study LXBA was selected for this study as this dosing regimen was observed to be well-tolerated in healthy subjects and supported by an adequate margin of safety, based on both monkey and rat repeated-dose toxicity studies (IB).

4.4. End of Study Definition

A participant is considered to have completed this ISA if he or she has completed all required phases of the study including the last scheduled procedure shown in the ISA SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the ISA SoA for the last participant.

5. Study Population

The master protocol and DPNP DSA provide eligibility criteria that must be followed for this study. LY3556050 specific inclusion and exclusion criteria are listed here.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

[3025] are men or women who abide by the reproductive and contraceptive requirements provided in this ISA Section 10.2, Appendix 2.

Women of childbearing potential (WOCBP) may participate and include those who

are completely abstinent or in a same-sex relationship, as part of their preferred and usual lifestyle, and must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, or must agree to use 1 highly effective method of contraception (less than 1% failure rate), or a combination of 2 effective methods of contraception, for the entirety of the study.

Women not of childbearing potential may participate and include those who

have a congenital anomaly such as Müllerian agenesis
are infertile due to surgical sterilization, or
are postmenopausal.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

[3026] have a history within 2 years prior to Visit 1 or current evidence of syncope, presyncope, uncontrolled vertigo, or postural dizziness, judged to be clinically significant by the investigator

[3027])))) RSQ))))R)))S

[3028] have a non-evaluable PR interval or a PR interval >200 msec at Visit 1 or Visit 2

[3029] have a heart rate <40 bpm at Visit 1 or Visit 2

[3030] have an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at Visit 1 or Visit 2

[3031]))))) H))v) thyroiditis

Prior/Concomitant Therapy

[3032] have been on thyroid replacement therapy or supplements for less than 12 weeks or had a change in thyroid replacement therapy or supplements in the last 12 weeks before Visit 2

[3033] have had a change in beta blocker therapy in the last 12 weeks before Visit 2. This does not include a discontinuation of therapy

[3034] are taking medications that are known MATE1 or OCT2 substrates with the risk for potentially clinically significant drug-drug interactions, such as metformin, dofetilide and dalfampridine

Metformin Exception

Limited dosages of metformin are allowed in this study.

Once daily dosing

Dose levels up to and including 750 mg extended release and 850 mg immediate release may be administered once daily.

Twice daily dosing

Dose levels up to and including 500 mg of an immediate release formulation may be administered twice daily

Additional Considerations for Participants Taking Metformin:

Medical Conditions

[3036] have a history or presence of lactic acidosis

[3037] have history or presence of severe hepatic disease including cirrhosis

[3038] have uncontrolled or unstable congestive heart failure

Prior/Concomitant Therapy

[3039] are taking carbonic anhydrase inhibitors if also taking metformin

[3040] have had a change in metformin therapy in the last 12 weeks before Visit 2.

[3041] have not maintained a stable dose of glucose-lowering agents other than metformin for at least 4 weeks prior to Visit 3.

Other Exclusions

[3035] are pregnant or breastfeeding.

5.3. Lifestyle Considerations

Reproductive and Contraception Requirements

Reproductive requirements and contraceptive guidance are provided in Section 10.2, Appendix 2. Participants should maintain a consistent lifestyle throughout participation as much as possible. Refer to master protocol Section 5.3 for additional details.

Alcohol

In addition to the alcohol restrictions in the CPMP Master Protocol, participants should refrain from binge drinking for the duration of the study as specified below.

Binge drinking is defined as consuming 5 or more units (for males), or 4 or more units (for females), on the same occasion.

One unit of alcohol equals

12 oz or 360 mL of beer
5 oz or 150 mL of wine, or
1.5 oz or 45 mL of distilled spirits.

6. Study Intervention

6.1. Study Intervention(s) Administered

Participants will take capsules orally, BID, approximately every 12 hours, with or without food.

Intervention Name	LY3556050	Placebo
Dose Formulation	capsule	capsule
Unit Dose Strength(s)	200 mg/capsule	not applicable
Dosage Level(s)	CCI mg BID, approximately every 12 hours	placebo to match BID
Route of Administration	oral	oral
Use	experimental	placebo
IMP and NIMP	IMP	IMP and NIMP
Sourcing	LY3556050 from Lilly	Placebo will be packaged, labeled, distributed, and dispensed as IMP by Lilly.
Packaging and Labeling	in bottles	in bottles

Abbreviations: BID = twice daily; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or designee is responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

The pharmacy manual contains further guidance and information for the final disposition of unused study interventions.

6.3. Measures to Minimize Bias: Randomization and Blinding

This ISA contains no additional stratification factors.

6.4. Study Intervention Compliance

A record of the number of LY3556050 or matching placebo capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the case report form (CRF).

6.5. Concomitant Therapy

The master protocol provides details on concomitant therapy. Concomitant therapy use should remain consistent throughout the study unless changes are medically warranted. Please consult the medical monitor for questions.

Potential drug-drug interactions with LY3556050

Please refer to Section 5.2 for exclusion criteria, the IB and Manual of Operations for details on concomitant medication restrictions and dosing information.

Concomitant therapy with metformin

Metformin dosing information

Please refer to Section 5.2 for the allowed metformin dose levels in this study.

To limit the risk of lactic acidosis, the only metformin dosages allowed in this study are those predicted by PK modeling to maintain plasma concentrations below 5 µg/mL (GLUCOPHAGE package insert, 2018).

Requirements for the study site

The study site will ensure participants are aware of lactic acidosis symptoms.

The study site will advise the participants to remain hydrated during the study.

Restrictions for participants taking metformin

Participants taking metformin may not start SGLT2 inhibitors (see the Manual of Operations for details) during the study.

The study site will advise the participant to avoid radiological studies with contrast throughout participation in this study.

6.6. Dose Modification

This protocol allows changes to the dose for individual participants, but the maximum daily dose will not exceed 600 mg BID.

CCI [redacted]

Decisions to change the dose level will be made by the investigator in discussion with the participants based on the adverse events reported for tolerability. The medical monitor should be contacted as needed.

CCI [redacted]


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7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Protocol CPMP provides the reasons and procedures for discontinuation of intervention and participant discontinuation that must be followed for this study. LY3556050-specific information is included here.

7.1. Discontinuation of Study Intervention

Cardiovascular Safety

A participant may be permanently discontinued from study intervention for these clinically significant or symptomatic cardiovascular findings

QTcF >500 msec
PR interval prolongation >240 msec with symptoms
symptomatic sustained tachycardia (>120 bpm) or bradycardia (<45 bpm) at rest
development of a new left bundle branch block, or
Mobitz type II second- or third-degree atrioventricular block.

Thyroid Safety

If thyroid-stimulating hormone (TSH) 10 at 2 consecutive visits, then a participant will be permanently discontinued from study intervention.

If participants have TSH 10 at 2 consecutive visits, then

1. collect thyroid kit samples
2. conduct a thyroid ultrasound approximately 2 weeks after the second laboratory time point, and
3. continue testing until issue resolution.

Metabolic Safety

For participants taking concomitant metformin, please consult the GLUCOPHAGE label for participant management. In event of an elevated anion gap, participants should be contacted immediately for a clinical evaluation and workup. If the participants are on metformin, they should be instructed to hold SSTR4 and metformin dosing.

If lactic acidosis is clinically suspected, LY3556050 and metformin should be discontinued and the patient should be medically evaluated.

7.2. Participant Discontinuation/Withdrawal from the Study

If eGFR, based upon CKD-EPI equation from cystatin c, falls below 60 ml/min/1.73 m^2 in a participant taking metformin, the participant should be discontinued from the study.

If a diagnosis of lactic acidosis is confirmed, the subject needs to be discontinued from study participation.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoAs contained in the master protocol CPMP, DPNP DSA, and this ISA.

LY3556050-specific assessments and procedures are described here.

8.1. Safety Assessments

The SoA contains the planned time points for all safety assessments.

8.1.1. Vital Signs

Conduct vital signs measurements for each participant according to the SoA (Section 1.3). Follow the study-specific recommendations included in the Manual of Operations.

8.1.2. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

8.1.3. Clinical Safety Laboratory Assessments

See NP03 Section 10.1, Appendix 1 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

8.2. Adverse Events and Serious Adverse Events

The master protocol provides details on adverse event (AE) and serious adverse event (SAE) collection, evaluation and follow-up, and SAE reporting.

8.3. Treatment of Overdose

There is no known antidote for LY3556050 overdose.

In case of suspected overdose, participants should be monitored for any signs or symptoms of adverse reactions or effects, and supportive care should be provided as necessary.

8.4. Pharmacokinetics

Collect venous blood samples of approximately 2 mL as specified in the SoA.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.

Lilly will provide instructions for the collection and handling of biological samples.

Site personnel will record

the date and time (24-hour clock time) of LY3556050 administration in the morning during both in-clinic and at home dosing, and
the date and time (24-hour clock time) of each PK sample.

Pharmacokinetic samples will be retained for a maximum of 2 years following last subject visit for the study. CCI [redacted]

8.5. Pharmacodynamics

Pharmacodynamic biomarkers have not been identified to date. Data from this study will be used to further evaluate the PD of LY3556050.

9. Statistical Considerations

The master protocol and DPNP DSA provide statistical considerations. LY3556050-specific considerations are described here.

9.1. Statistical Hypotheses

The master protocol describes the primary hypothesis. CCI [redacted]

9.2. Sample Size Determination

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

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

9.3. Populations for Analyses

The master protocol defines the populations for analyses.

The PK population includes all randomized participants who received a dose of LY3556050 and have at least 1 evaluable PK sample.

9.4. Statistical Analyses

Any change to the data analysis methods described in this ISA will require an amendment only if it changes a principal feature of the ISA. Any other change to the data analysis methods described, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The ISA SAP will be finalized prior to unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

The master protocol describes the primary endpoint and analyses.

The master protocol and DPNP DSA describe the secondary and tertiary/exploratory endpoints and analyses.

Any borrowing of placebo or treatment effect information will be specified in the ISA SAP.

9.4.2. Pharmacokinetics and Pharmacodynamics

The observed plasma concentrations for LY3556050 will be reported graphically and descriptively.

Model-based PK and PKPD analyses may be conducted to characterize the PK of LY3556050 in participants with DPNP and to explore exposure-response relationships for various PD measures using suitable population analysis software. 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. Additional details on PK and PKPD analyses will be provided in a separate PKPD analysis plan.

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

9.4.3. Tertiary/Exploratory

All safety analyses will be made on the safety population. Descriptive statistics CCI [redacted] will be conducted as deemed appropriate. Confounding factors, such as beta blocker therapy, may be adjusted in the statistical models for safety analyses. Subgroup analyses of cardiovascular safety endpoints with beta blocker therapy may be conducted accordingly.

9.4.4. Biomarkers

Consistent with the master protocol objectives, exploratory fluid and digital biomarker analyses may be conducted on samples and data collected during the study.

9.5. Interim Analyses

Interim analyses may be conducted for internal decision-making. Unblinding and interim analysis details may be specified in the unblinding plan section of the SAP or in a separate document.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Clinical Laboratory Tests

The master protocol describes tests that may be performed at additional times noted in the SoA for this ISA. This table describes tests unique for ISA 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
Bicarbonate	Free Thyroxine (FreeT4)	Prolactin	LY3556050 concentration
Anion gap (calculation)	Total Thyroxine (T4)	Gastrin	Serum pregnancy test
eGFR calculated by CKD-EPI equation based upon cystatin c		Glucagon	HbA1c
		Insulin	

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; SST = somatostatin; TSH = thyroid-stimulating hormone.

Thyroid Safety Follow-Up

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

Abbreviation: TSH = thyroid-stimulating hormone.

10.2. Appendix 2: Definitions of Reproductive Requirements and Contraceptive Guidance

Women

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman not of Childbearing Potential (non-WOCBP)

Women in the following categories are not considered WOCBP:

premenarchal
premenopausal female that is infertile due to surgical sterilization, or
postmenopausal.

Surgical sterilization examples include

hysterectomy
bilateral oophorectomy, or
tubal ligation.

Postmenopausal is defined as either

a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL,
a woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or
a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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records, medical examination, or medical history interview.

Participation in the Study

Women not of childbearing potential and of childbearing potential may participate in this study.

Women not of childbearing potential include those who

have a congenital anomaly such as Müllerian agenesis
are infertile due to surgical sterilization, or
are postmenopausal.

At least 6 weeks must have passed after surgical bilateral oophorectomy with or without hysterectomy, or after tubal ligation.

Women of childbearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

Women of childbearing potential who are completely abstinent or in a same-sex relationship, as part of their preferred and usual lifestyle, must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males.

All other women of childbearing potential must agree to use 1 highly effective method of contraception (less than 1% failure rate), or a combination of 2 effective methods of contraception, for the entirety of the study.

Abstinence or contraception must continue for 3 days after the last dose of intervention.

Acceptable Methods of Contraception

Highly effective methods of contraception (less than 1% failure rate) comprise, but are not limited to

combination oral contraceptive pill and mini-pill
implanted or injectable contraceptives
contraceptive patch (only for women <198 pounds or 90 kg)
total abstinence
vasectomy if they are the only sexual partner
fallopian tube implants if confirmed by hysterosalpingogram
combined contraceptive vaginal ring, or
intrauterine devices.

Effective methods of contraception comprise but are not limited to

Male or female condoms with spermicide
diaphragms with spermicide or cervical sponges
barrier method with use of a spermicide
- condom with spermicide
- diaphragm with spermicide, or
- female condom with spermicide.

Note: the barrier method must include use of a spermicide to be considered effective.

Not Acceptable Methods of Contraception

Ineffective methods of contraception comprise of

Spermicide alone
Immune-contraceptives
Periodic abstinence
Fertility awareness
- Calendar method

- Temperature method
- Combination of calendar and temperature method
- Cervical mucus, or
- Symptothermal

Withdrawal
Post coital douche, or
Lactational amenorrhea.

Men

Men are not required to use contraception during study participation.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3556050.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours)))) N

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at 20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in the master protocol CPMP

Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study and will follow the standard discontinuation process.

10.3. Appendix 3: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor.

Exceptional circumstances

Exceptional circumstances are rare events may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor)) H)) implement changes if permitted by local regulations.

Ethical Review Boards (ERBs) and regulatory bodies will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before communication to ERBs and regulatory bodies. Lilly will report all changes as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, the site must retain confirmation of this approval in the study records.

Additional written guidance will be provided by the sponsor in the event written approval is granted for changes in study conduct.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are

Good Clinical Practice compliance, and
minimization of risk to study integrity.

Such changes are intended to

mitigate risks of participants missing visits,
allow participants to continue safely in the study, and
maintain the data integrity of the study.

Informed Consent

If these circumstances occur, additional consent from the participant will be obtained, if applicable, for:

participation in remote visits,
additional study intervention dispensed to a participant during an extended visit window, or

alternate delivery of study intervention and ancillary supplies, as well as provision for their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations. Missing data will be captured as protocol deviations.

Remote visits

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.

Assessments to be completed in this manner include, but are not limited to, individual safety follow-up.

Mobile healthcare: Healthcare visits may be performed at locations other than the study)A) H) B))))) te due to an exceptional circumstance. Such visits will be performed by a mobile healthcare provider.

Procedures performed at such visits include, but are not limited to, collection of blood samples, physical examinations, ECGs, vital signs, intervention accountability and compliance, AE collection, and collection of health information.

Other local procedures: Laboratory draws may be done at an alternate location in exceptional circumstances.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Every effort should be made to enable participants to return to onsite visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local Laboratory Testing

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

If local testing is used, PK and exploratory biomarker sample collection may not occur.

Investigational Product and Ancillary Supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal onsite visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
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) Hand
arranging delivery of study supplies.

Alternate delivery of investigational product should be performed in a manner that does not compromise treatment blinding and ensures product integrity.

The existing protocol requirements for product accountability remain unchanged, including verification of participa)))) N

When delivering supplies to a location other than the study site, the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

Instructions should be provided to the participant on how to return any unused or completed study supplies.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid study intervention interruption and maintain overall integrity of the study.

Adjustments to Visit Windows

Participants should complete the SoA as described in the master protocol CPMP, DSA CPMP(3) and this ISA whenever possible and safe to do so. To maximize the possibility that visits are conducted at the clinical site, the visit windows may be adjusted to minimize missing data and preserve the intended conduct of the study. Adjustments to the visit windows will be discussed with, and approved by, the sponsor prior to any changes.

Documentation

Changes to study conduct will be documented.

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances.

Dispensing and shipment records of intervention and relevant communications, including delegation, should be filed with site study records.

Source documents generated at a location other than the study site should be part of the
))))))))))in a secure and timely manner.

The study site should capture specific explanations for any missing data and other protocol deviations in source documents.

Although protocol deviations may be unavoidable in an exceptional circumstance, documentation of protocol deviations and missing data will be important for data analysis and reporting.

10.4. Appendix 4: Abbreviations

Term	Definition
AE	adverse event
BID	twice daily
DPNP	diabetic peripheral neuropathic pain
DSA	disease-state addendum
eGFR	estimated glomerular filtration rate
ERB	Ethical Review Board
FACTS	Fixed and Adaptive Clinical Trial Simulator software tool
ISA	intervention-specific appendix
PD	pharmacodynamic
PK	pharmacokinetic
PKPD	pharmacokinetic-pharmacodynamic
PR interval	During an ECG, the period, measured in milliseconds, that extends from the beginning of the P wave until the beginning of the QRS complex.
QRS	During an ECG, a combination of the Q wave, R wave and S wave, representing ventricular depolarization.
QT	During an ECG, the QT interval is the time from the start of the Q wave to the endo of the T wave.
QTcF	)))t))
SAE	serious adverse event
SAP	statistical analysis plan
SST	somatostatin
SSTR	somatostatin receptor
TSH	thyroid-stimulating hormone
WOCBP	woman/women of childbearing potential

10.5. Appendix 5: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [a] 12 March 2021

Overall Rationale for the Amendment:

This amendment introduces a dose titration scheme for participants. The starting dose level is 200 mg and decisions to change the dose level will be made by the investigator, in discussion with the participants, based on adverse events reported for tolerability. The changes for dose titration affect sections throughout the ISA. Additional updates were made according to emerging data and changes to the master protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updates made to Number of Participants Intervention Groups and Duration, and Data Monitoring Committee	Sample size and study intervention text updated for new dose titration scheme r))))) n))))) master CPMP protocol
1.2 Schema	Updated schema to show dose titration	New dose titration scheme for participants
1.3 Schedule of Activities (SoA)	Added telephone visits and updated study intervention notes to include a link to the new dose modification section	To implement new dose titration scheme
1.3 Schedule of Activities (SoA)	Updates were made to ECG and Vital signs	Corrections for clarity
1.3 Schedule of Activities (SoA)	Replaced Urinalysis with Urine drug screen.	Urinalysis was only for Visit 3, so removed. Urine drug screen added and performed according to investigator discretion
1.3 Schedule of Activities (SoA)	Added window for PK sample collection	Adding flexibility
1.3 Schedule of Activities (SoA)	Added participant digital biomarker device for Visit 7 and ED	To indicate when the participant needs to return the device.
2.2 Background	Updated information for the 2 Phase 1 clinical studies	Both studies are completed
4.1 Overall Design	Updated and added text to describe the new dose titration scheme	New dose titration scheme for participants
4.3 Justification for Dose	Added text for the titration scheme)))) beginning of second paragraph	New dose titration scheme for participants Study LXBA is now completed
5.2 Exclusion Criteria	Updated Criteria #3028	Clarifications based on clinical experience and emerging pharmacokinetic/metabolism data

Section # and Name	Description of Change	Brief Rationale
5.3 Lifestyle Considerations	Removed text that is already in the master CPMP	Master protocol updates for CPMP amendment (a)
6.1 Study Intervention(s) Administered	Updated text and table	New dose titration scheme for participants. Emerging data allow participants to take capsules with or without food
6.5 Concomitant Therapy	Removed text that is duplicated in CPMP Added sub-header for drug-drug interactions	Consistency across ISAs
6.6 Dose Modification	New section	New dose titration scheme for participants
8.2 Adverse Events and Serious Adverse Events	Added text to refer to the master	Master protocol contains AE and SAE information
9.2 Sample Size Determination	Updated sample size	New dose titration scheme for participants
9.3 Populations for Analyses	))) n „	The master protocol defines the populations for analyses
10.2 Appendix 2	Updated the acceptable and ineffective methods of contraception text	Updates to internal Lilly guidance
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

11. References

Metformin [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2018.

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