This study H0P-MC-BP05 (NCT05630196) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

Protocol H0P-MC-BP05 (a)

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3857210 for the Treatment of Chronic Low Back Pain

NCT05630196

Approval Date: 13-Oct-2022

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 LY3857210 for the Treatment of Chronic Low Back Pain

Brief Title: Phase 2 Clinical Trial to Evaluate LY3857210 for the Treatment of Chronic Low Back Pain
ISA Number: H0P-MC-BP05

Amendment Number: a

Compound: LY3857210

Study Phase: 2

Acronym: BP05

Sponsor Name: Eli Lilly and Company
Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

LY3857210 IND: 156411
Master Protocol IND: 144915

Approval Date: Protocol H0P-MC-BP05 Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-075081

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*21-Sep-2022*

Amendment a

Overall Rationale for the Amendment:

This amendment adds additional physical examinations and exclusion criteria to address regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Added Physical examinations at Visits 5 and 7. Added note, "Complete physical examination, including targeted physical examination specified below, should be performed at V3 and V801 or ED. Targeted examinations for skin, gastrointestinal tract, mammary gland in males, and lymph nodes should also be performed at V5 and V7."	Per regulatory feedback.
5.2. Exclusion Criteria	Modified criterion [2085], "have ~~completed~~ participated in…".	Clarification.
		Per regulatory feedback.
8.2.1. Physical Examinations	Added, "Complete physical examination, including targeted examination specified below, should be performed at V3 and Visit 801 or ED. Targeted physical examinations of skin, gastrointestinal tract, mammary gland in males, and lymph nodes will also be performed at Visits V5 and V7 as described in the SoA. Any clinically significant abnormal physical examination findings will be reported as AEs."	Per regulatory feedback.
	Removed, "…to physical examinations described in the Master Protocol CPMP…"	Editorial.

Table of Contents

1. Protocol Summary 7
1.1. Synopsis 7
1.2. Schema 9
1.3. Schedule of Activities (SoA) 10

2. Introduction 14
2.1. Study Rationale 14
2.2. Background 14
2.3. Benefit/Risk Assessment 14
2.3.1. Risk Assessment 14
2.3.2. Benefit Assessment 15
2.3.3. Overall Benefit Risk Conclusion 15

3. Objectives, Endpoints, and Estimands 16

4. Study Design 17
4.1. Overall Design 17
4.2. Scientific Rationale for Study Design 17
4.3. Justification for Dose 18
4.4. End of Study Definition 18

5. Study Population 19
5.1. Inclusion Criteria 19
5.2. Exclusion Criteria 19
5.3. Lifestyle Considerations 20
5.3.1. Substance Use 20
5.4. Screen Failures 20
5.5. Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention of a Participant 20

6. Study Intervention(s) and Concomitant Therapy 21
6.1. Study Intervention(s) Administered 21
6.2. Preparation, Handling, Storage, and Accountability 21
6.3. Measures to Minimize Bias: Randomization and Blinding 21
6.3.1. Stratification 21
6.4. Study Intervention Compliance 21
6.5. Dose Modification 21
6.6. Continued Access to Study Intervention after the End of the Study 21
6.7. Treatment of Overdose 22
6.8. Concomitant Therapy 22
6.8.1. Permitted Medications 22
6.8.2. Prohibited Medications 22

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 23
7.1. Discontinuation of Study Intervention 23
7.1.1. Liver Chemistry Stopping Criteria 23

7.1.2. Hypersensitivity 24
7.2. Participant Discontinuation/Withdrawal from the Study 24
7.3. Lost to Follow-Up 24

8. Study Assessments and Procedures 25
8.1. Efficacy Assessments 25
CCI [redacted] 25
8.2. Safety Assessments 25
8.2.1. Physical Examinations 25
8.2.2. Electrocardiograms 25
8.2.3. Clinical Safety Laboratory Tests 26
8.3. Adverse Events, Serious Adverse Events, and Product Complaints 26
8.3.1. Pregnancy 26
8.3.2. Hypersensitivity Reactions 27
8.3.3. Adverse Events of Special Interest 27
8.4. Pharmacokinetics 28
8.5. Pharmacodynamics 28
8.6. Genetics 28
CCI [redacted] 28
CCI [redacted] 28
CCI [redacted] 28

9. Statistical Considerations 29
9.1. Statistical Hypotheses 29
9.2. Analyses Sets 29
9.3. Statistical Analyses 29
9.3.1. General Considerations 29
9.3.2. Tertiary Analysis 29
9.3.3. Safety Analyses 30
9.3.4. Exploratory Pharmacokinetic Analyses 30
9.4. Interim Analysis 30
9.5. Sample Size Determination 30

10. Supporting Documentation and Operational Considerations 31
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 31
10.2. Appendix 2: Clinical Laboratory Tests 32
10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event 32
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 34
10.4. Appendix 4: Contraceptive and Barrier Guidance 35
10.4.1. Definitions 35
10.4.2. Contraception Guidance 36
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 38

10.6. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances....39
10.7. Appendix 10: Abbreviations and Definitions....42
11. References....44

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3857210 for the Treatment of Chronic Low Back Pain

Brief Title: Phase 2 Clinical Trial to Evaluate LY3857210 for the Treatment of Chronic Low Back Pain

Regulatory Agency Identifier Numbers:

LY3857210 IND: 156411

Master Protocol IND: 144915

Rationale:

The purpose of this study is to test whether LY3857210 is efficacious in decreasing chronic low back pain (CLBP). LY3857210 is a small molecule receptor antagonist of the P2X7 receptor, an adenosine triphosphate ligand-gated ion channel known to be involved in neuroinflammation and pain.

Data will be collected to assess the safety and tolerability of LY3857210 in this study population. The pharmacokinetics of LY3857210 will also be explored. The totality of data from this proof-of-concept study will assess the benefits and risks associated with LY3857210 and inform decisions for the clinical development of LY3857210.

Objectives, Endpoints, and Estimands:

The primary and secondary objectives and endpoints are stated in the Master Protocol H0P-MC-CPMP (CPMP) and the CLBP disease-state addendum (DSA; H0P-MC-CPMP[2]).

Overall Design:

This is a 10-week, Phase 2, randomized, double-blind, placebo-controlled study that will compare LY3857210 versus placebo in participants with CLBP.

Study Population:

In addition to inclusion and exclusion criteria described in Master Protocol CPMP and DSA CPMP(2), individuals may not take part in the study if they have

- CCI [redacted]
- an eGFR of less than 30 mL/min/1.73 m^2, and
- CCI [redacted]

Number of Participants:

Up to approximately 125 participants will be randomly assigned to study intervention with the assumption that 20% of the participants will drop out prior to the end of the double-blind treatment period.

Intervention Groups and Duration:

This double-blind study includes an 8-week treatment period with a 2-week follow-up visit off treatment.

Intervention Name	LY3857210	Placebo
Dosage Level(s)	45 mg daily	Not applicable
Route of Administration and Duration	PO	PO

Abbreviation: PO = by mouth.

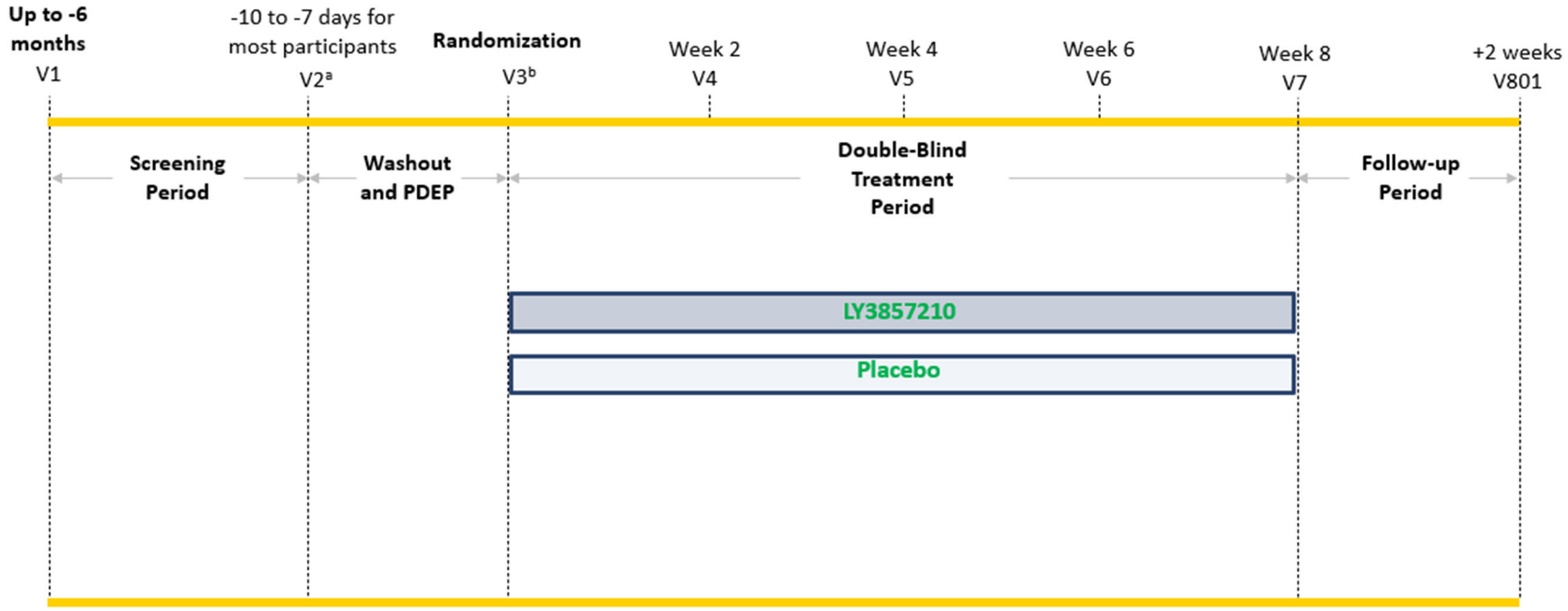
Ethical Considerations of Benefit/Risk:

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with LY3857210 are justified by the anticipated benefits that may be afforded to participants with CLBP.

Data Monitoring Committee: Yes

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

1.2. Schema



Abbreviations: PDEP = preliminary data entry period; V = visit.

[a] Medication washout and PDEP begins.

[b] Randomization to either LY3857210 or placebo.

1.3. Schedule of Activities (SoA)

This SoA shows visits and procedures unique to the intervention-specific appendix (ISA) H0P-MC-BP05 for LY3857210. Please refer to the Master Protocol CPMP and the CLBP DSA CPMP(2) SoAs for additional information.

	Screening		Randomization to ISA	Double-Blind Treatment					F/U	Notes
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	**V801**	
Study Week	Up to -6 month	-10 to -7 days for most participants	0	2	4	6	8		+2	
Visit Window (days)				±3					±3	
Confirm ISA inclusion and exclusion criteria	X	X	X							
Physical examination			X		X		X	X	X	See Section 8.2.1. Complete physical examination, including targeted examination specified below, should be performed at V3 and V801 or ED. Targeted physical examination for skin, gastrointestinal tract, mammary gland in males, and lymph nodes should also be performed at V5 and V7.
Neurological assessment			X	X	X	X	X	X	X	See Section 8.2.1
Prespecified CLBP medical history			X							Includes diagnosis and symptom onset date.
Vital signs			X	X	X	X	X	X	X	At V3, take vitals before dosing. Vitals include pulse rate, respiratory rate, blood pressure, and temperature, taken with participant in a sitting position.
Concomitant medication									X	See footnote a.
AE									X	See footnote a.
ECG (single)					X		X	X	X	

	Screening		Randomization to ISA	Double-Blind Treatment					F/U	Notes
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	**V801**	
Study Week	Up to -6 month	-10 to -7 days for most participants	0	2	4	6	8		+2	
Visit Window (days)				±3					±3	
Placebo response video training (participant)		X								Should view at the beginning of V2.
Study intervention administration			X	X	X	X				See Section 6.1. Instruct participant to NOT take study intervention on the day of V7.
Dispense Study intervention to participant			X	X	X	X				
Participant returns unused study intervention				X	X	X	X	X		Participant to bring study intervention to every visit.
Intervention compliance				X	X	X	X	X		
Scales, Questionnaires, and Outcome Measures										
CCI										
C-SSRS Since Last Visit									X	See footnote a.
Self-Harm Supplement form									X	See footnote a.
Self-Harm Follow-Up form									X	See footnote a. Complete 1 form for each event identified on the Self-Harm Supplement form.
NRS for pain									X	See footnote a. Review eDiary compliance.
Reinforce pain assessment guidelines		X	X	X	X	X	X			Review assessment of pain. See MoO for additional details.

	Screening		Randomization to ISA	Double-Blind Treatment					F/U	Notes
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	**V801**	
Study Week	Up to -6 month	-10 to -7 days for most participants	0	2	4	6	8		+2	
Visit Window (days)				±3					±3	
Rescue medication usage reporting									X	See footnote a.
PGI									X	See footnote a.
Clinical Laboratory Tests and Sample Collection										
Hematology				X	X	X	X		X	
Chemistry				X	X	X	X		X	
Lipid panel				X	X	X	X		X	
Urinalysis							X		X	
Urine pregnancy			X	X	X	X	X	X		For all WOCBP at V3, collect sample within 24 hours prior to dosing.
Urine drug screen			X		X		X	X		See Section 5.3.1.
CCI										
HbA1c			X				X	X		
LY3857210 PK sample			X	X	X	X	X	X		At V3, a PK sample should be taken any time **after** 1 hour post dose and prior to leaving the site. At V4, V5, V6, V7 and ED, a PK sample can be taken at any time during the site visit. The date and time of each PK sample collected will be recorded. The date and time of LY3857210 administration prior to the PK sample collection will be recorded.
CCI										

	Screening		Randomization to ISA	Double-Blind Treatment					F/U	Notes
	V1	V2	V3	V4	V5	V6	V7	ED	V801	
Study Week	Up to -6 month	-10 to -7 days for most participants	0	2	4	6	8		+2	
Visit Window (days)				±3					±3	
CCI										

Abbreviations: AE = adverse event; CCI ; ECG = electrocardiogram; ED = early discontinuation; F/U = follow-up; HbA1c = hemoglobin A1c; ISA = intervention-specific appendix; MoO = Manual of Operations; NRS = numeric rating scale; PGI = patient's global impression of change; PK = pharmacokinetic; V = visit; WOCBP = women of childbearing potential.

a Collect in addition to schedule described in the Master Protocol CPMP.

2. Introduction

This ISA H0P-MC-BP05 (BP05) is an appendix to the Master Protocol H0P-MC-CPMP (CPMP) and contains unique study elements specific for LY3857210. The master protocol contains the overarching study elements that govern the CLBP DSA CPMP(2) and this ISA BP05.

2.1. Study Rationale

The purpose of this study is to test whether LY3857210 is efficacious in relieving CLBP. Data will be collected to assess the safety and tolerability of LY3857210 in this study population. The PK of LY3857210 will also be explored. The totality of data from this proof-of-concept study will assess the benefits and risks associated with LY3857210 and inform decisions for the clinical development of LY3857210.

2.2. Background

P2X7 is an adenosine triphosphate (ATP) ligand-gated ion channel that when activated results in Ca^{2+} influx, and cellular activation (for example, caspase 1). For a recent review article, see Zhang et al. 2020. Stimulation of P2X7 plays a key role in the cross talk of the glial cells and neurons at an over-active synapse and in neuroinflammatory conditions (Currò et al. 2020). Thus, inhibition of the P2X7 receptor found on glial cells in the brain and spinal cord is anticipated to decrease synaptic transmission.

LY3857210 is an orally administered small-molecule receptor antagonist of the P2X7 receptor.

CCI

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3857210 may be found in the IB.

2.3.1. Risk Assessment

Study intervention

CCI

Toxicology Studies and NOAEL Exposure

Based on the observed convulsion in the 3-month dog toxicology study (reported in 1 dog) as well as convulsion noted in the rat in vivo micronucleus study (reported in 1 rat), a 10-fold exposure multiple based on the observed AUC and C_{max} associated with the NOEL for convulsions in dog (the most sensitive species) will be maintained in this CCI [redacted]

In addition, neurological examination will be conducted at regular intervals during the study period and AEs related to CNS signs and symptoms will be collected during the study. Participants with a history of seizures will be excluded from the study.

Potential drug-drug interactions

Clinical drug-drug interaction studies have not been conducted with LY3857210. Based on current in vitro data, LY3857210 is a potential inducer of CYP3A4, CYP1A2, CYP2B6, and CYP2C8. To mitigate risk, participants taking sensitive substrates with a narrow therapeutic index are excluded. See Section 5.2 for exclusion criteria and refer to IB for more information.

Information on AEs expected to be related to the study intervention may be found in the IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and may be found in the IB.

2.3.2. Benefit Assessment

Potential benefits for the study participants include

- information obtained from study-related medical procedures
  - physical examinations
  - laboratory tests, and
  - ECGs
- detailed evaluations of low back pain
  - lower back examination, and
  - lumbar X-rays, and
- questionnaires that may improve participants understanding their own condition.

As part of Study CPMP, participants to this ISA will report their experience using standard tools that may contribute to the assessment of novel treatments for CLBP. In addition, data collected from this study may also improve our understanding of CLBP pathogenesis. Both of which may lead to the development of new treatment with improved safety and efficacy profile compared to standard of care.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with LY3857210 are justified by the anticipated benefits that may be afforded to participants with CLBP.

3. Objectives, Endpoints, and Estimands

The Master Protocol CPMP and CLBP DSA CPMP(2) include objectives and endpoints applicable for this study. This table describes objectives and endpoints specific for LY3857210.

4. Study Design

4.1. Overall Design

The Master Protocol CPMP describes the overall study design and study design rationale. This section describes visits and overall procedures unique to ISA BP05 for LY3857210 in addition to the procedures outlined in CPMP and CPMP(2).

Double-blind treatment period (Visits 3 through 7)

Each visit is an outpatient visit.

At Visit 3

- participants are randomly assigned to LY3857210 or placebo
- the site completes the BP05 baseline procedures and sample collection prior to study intervention
- the site collects participants' vitals predose
- participants receive their oral study intervention
- the site completes PK sample collection, and
- the site instructs participants to continue with study restrictions and NRS diary entries before their visit discharge.

At Visits 4 through 7

- the site reviews available safety data and sample collection
- participants continue oral study intervention (not applicable for V7) and bring all study intervention bottles to each visit
- the site completes all sample collection and safety monitoring noted in the SoAs, and
- the site instructs participants to continue with study restrictions, including not using medications for chronic pain, NRS diary entries and wearing of CCI before their visit discharge.

Double-blind post-treatment follow-up period (Visit 801)

Participants must complete 1 post-treatment follow-up visit for safety and efficacy assessment at Visit 801 according to the SoA.

The site schedules Visit 801 approximately 2 weeks after Visit 7 or ED Visit.

At Visit 801, participants return CCI

After Visit 801, medications for chronic pain may be restarted.

4.2. Scientific Rationale for Study Design

The Master Protocol CPMP describes the overall study design rationale.

4.3. Justification for Dose

4.4. End of Study Definition

A participant is considered to have completed this ISA if they have 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 CPMP and CLBP DSA CPMP(2) provide eligibility criteria that must be followed for this study. LY3857210-specific inclusion and exclusion criteria are listed here.

5.1. Inclusion Criteria

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

Sex and contraceptive/barrier requirements

[2075] Males and females may participate in this trial.

No male contraception is required except in compliance with specific local government study requirements.

WOCBP and WNOCBP may participate in this trial. See Section 10.4 for definitions and additional requirements related to contraception.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

5.2. Exclusion Criteria

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

[2077] Have an eGFR of <30 mL/min/1.73 m2, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at Visit 1 or Visit 2.

[2078] Have known allergies to LY3857210, related compounds or any components of the formulation, or history of significant atopy.

[2079] Women who are pregnant or breastfeeding.

5.3. Lifestyle Considerations

See the Master Protocol CPMP for lifestyle considerations.

ISA-specific lifestyle considerations are provided below.

5.3.1. Substance Use

Positive urine drug screen will not be considered illicit use if it is a prescribed concomitant medication for a known preexisting condition.

5.4. Screen Failures

Screen failures are described in the Master Protocol CPMP.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention of a Participant

This section is not applicable to this study.

6. Study Intervention(s) and Concomitant Therapy

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3857210	Placebo
Dosage Level(s)	45 mg daily	N/A
Route of Administration	PO	PO

Abbreviations: N/A = not applicable; PO = by mouth.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

Preparation, handling, storage, and accountability are described in the Master Protocol CPMP.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are described in the Master Protocol CPMP.

6.3.1. Stratification

There are no additional stratification factors for this study.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned capsules, and documented in the source documents and CRF. A record of the number of study intervention capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, will also be recorded in the CRF.

6.5. Dose Modification

Dose modification is not permitted.

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.7. Treatment of 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. There is no known antidote to LY3857210 therapy.

6.8. Concomitant Therapy

6.8.1. Permitted Medications

All concomitant therapies that are part of routine care for comorbidities other than chronic pain are allowed and may be used during the study, except as indicated in Section 6.8.2.

The Master Protocol CPMP provides more detail on concomitant therapy.

6.8.2. Prohibited Medications

A list of medications that are prohibited from Visit 2 to Visit 801 for participants randomly assigned to this ISA study will be provided in the Manual of Operations. Participants may return to their routine care after Visit 801 is completed, as clinically appropriate.

Potential drug-drug interactions with LY3857210

Please refer to Section 5.2, IB, and Manual of Operations for details on concomitant medication restrictions.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

The Master Protocol CPMP and DSA CPMP(2) provide the reasons and procedures for discontinuation of intervention and participant discontinuation that must be followed for this study.

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study intervention based on elevated liver tests

The study drug should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.5. of the Master Protocol CPMP) if 1 or more of the conditions in this table occur.

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL > 2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA 2009 and other consensus guidelines, with minor modifications.	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal.

Resuming study intervention after elevated liver tests

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited, non-drug etiology is identified. Otherwise, the study intervention should be discontinued.

7.1.2. Hypersensitivity

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

For laboratory samples to be obtained at the time of a systemic hypersensitivity event, see Section 10.2.1.

7.2. Participant Discontinuation/Withdrawal from the Study

See the Master Protocol CPMP.

7.3. Lost to Follow-Up

See the Master Protocol CPMP.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the Master Protocol CPMP, CLBP DSA CPMP(2), and ISA BP05 SoAs.

LY3857210-specific assessments and procedures are described here.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoAs.

See the Master Protocol CPMP and DSA CPMP(2) for additional information on efficacy assessments.

8.2. Safety Assessments

Planned time points for all efficacy assessments are provided in the SoAs.

See the Master Protocol CPMP and DSA CPMP(2) for additional information on safety assessments. Additional Study BP05-specific assessment information is provided below.

8.2.1. Physical Examinations

Complete physical examination, including targeted examination specified below, should be performed at V3 and Visit 801 or ED. Targeted physical examinations of skin, gastrointestinal tract, mammary gland in males, and lymph nodes will also be performed at Visits V5 and V7 as described in the SoA. Any clinically significant abnormal physical examination findings will be reported as AEs.

In addition, a directed neurological assessment will be performed by the investigator or designee at the time points specified in the SoA. If abnormalities are noted at these time points, additional examinations should be performed as clinically necessary. The examiner should be familiar with the participant's baseline examination.

Elements of the neurological assessment include inspection for tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

8.2.2. 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, RR, QRS, QT, and QTcF

intervals. Refer to Section 7.1. of the Master Protocol CPMP for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

Additional details related to ECG are provided in the Master Protocol CPMP.

8.2.3. Clinical Safety Laboratory Tests

See BP05 Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency for ISA BP05.

Additional details are provided in the Master Protocol CPMP.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of AEs, SAEs, and PCs can be found in Appendix 3 of the Master Protocol CPMP.

See the Master Protocol CPMP Section 8.3 for additional details.

8.3.1. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator
  - will obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

  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, regardless of gestational age, 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 post-study 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 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.2. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

8.3.3. Adverse Events of Special Interest

Convulsion is an AE of special interest for LY3857210 and will be subject to enhanced surveillance activities. Additionally, convulsion will be analyzed for presentation in the Clinical Study Report in accordance with the SAP.

If a seizure or convulsion is reported, then contact the medical monitor as soon as possible. Additional evaluation or follow-up may be requested.

8.4. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of LY3857210 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. The timing of PK samples may be altered during the course of the study based on newly available data to ensure appropriate data collection.

Instructions for the collection and handling of PK samples will be provided by the sponsor.

The date and time (24-hour clock time) will be recorded for

- LY3857210 administration prior to the PK sample collection, and
- PK sample collection.

PK samples may also be used to evaluate safety or efficacy measures related to concerns arising during or after the study.

8.5. Pharmacodynamics

Pharmacodynamic assessments will not be evaluated in this study.

8.6. Genetics

See the Master Protocol CPMP for details related to genetic sampling.

9. Statistical Considerations

The Master Protocol CPMP and CLBP DSA CPMP(2) provide statistical considerations. LY3857210-specific considerations are described here.

9.1. Statistical Hypotheses

The Master Protocol CPMP describes the primary hypothesis. CCI [redacted]

9.2. Analyses Sets

The populations are defined in the Master Protocol CPMP.

The PK population includes all randomly assigned participants who received a dose of LY3857210 and have at least 1 evaluable PK sample collected.

9.3. Statistical Analyses

If the primary analysis approach needs to be changed, the updated approach will be provided in the SAP and should not lead to modification of this protocol. Any other change to the data analysis methods described, and the justification for making the change, will be described in the 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 more technical and detailed descriptions of the statistical analyses described in this section.

9.3.1. General Considerations

The primary and secondary endpoint and analyses have been described in the Master Protocol CPMP.

Any borrowing of placebo or treatment effect information will be specified in the ISA SAP. Secondary and tertiary/exploratory endpoints and analyses are described in the Master Protocol CPMP and CLBP DSA CPMP(2).

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.2. Tertiary Analysis

Exploratory analyses may be described in the ISA SAP.

9.3.3. Safety Analyses

Safety analyses have been described in the Master Protocol CPMP. Additional ISA-specific safety analyses may be described in the ISA SAP.

9.3.4. Exploratory Pharmacokinetic Analyses

Plasma concentrations for LY3857210 will be reported graphically and descriptively. Model-based PK and exposure-response relationships for various efficacy and safety measures may be conducted.

9.4. Interim Analysis

An interim analysis may be conducted for internal decision making. The potential reasons for interim analyses could include futility analyses, early efficacy analyses, safety analyses, PK analyses or other analyses needed for key business decisions and planning. Unblinding details would be specified in the unblinding plan section of the SAP or in a separate unblinding document. The SAP will describe any interim analyses in greater detail should they occur.

9.5. Sample Size Determination

Up to approximately 125 participants will be randomly assigned to LY3857210 and placebo. It is expected that approximately 80% of participants will complete the double-blind treatment period of the study. CCI [redacted] CCI [redacted] CCI [redacted] If there is no treatment difference between placebo and LY3857210, the probability of meeting the primary objective specified above (that is, false positive) is ≤0.05.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

See the Master Protocol CPMP for regulatory, ethical, and study oversight considerations.

10.2. Appendix 2: Clinical Laboratory Tests

The Master Protocol CPMP describes tests that may be performed at additional times noted in the SoA for this ISA. This table describes tests unique for ISA BP05.

Other Tests	Assayed by Lilly-designated laboratory
LY3857210 concentration	Results will not be provided to the investigative sites

CCI

CCI

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up pre-dose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

Timing	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase
	complements (C3, C3a, and C5a)
	cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines)

Abbreviation: IL = interleukin.

a All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

See the Master Protocol Appendix 3 for information related to AE and SAE.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the Master Protocol CPMP and the BP05 Schedule of Activities for subsequent pregnancy testing requirements.
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These forms of contraception must be used for the duration of the study.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide
Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

See the Master Protocol CPMP Appendix 6 for liver safety: suggested actions and follow up assessments.

10.6. Appendix 9: 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 in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that 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's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

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 compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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.

Remote visits

> ***Telemedicine:*** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.
> ***Mobile healthcare:*** Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor.
> Procedures performed at such visits include, but are not limited to, collection of blood samples, symptom directed physical examinations, ECGs, vital signs, intervention accountability and compliance, AE collection, and collection of health information.
> ***Other alternative locations:*** Laboratory draws may be done at an alternate location in exceptional circumstances.

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.

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

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

Local laboratory testing option

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

CCI [redacted]

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site 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
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention 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 participant's receipt of study supplies.

- When delivering supplies to a location other than the study site (for example, participant's home), 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 may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities as described in the Master Protocol CPMP , CPMP(2) DSA, and BP05 ISA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

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

Documentation

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study 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 investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.7. Appendix 10: Abbreviations and Definitions

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the curve
AST	aspartate aminotransferase
CLBP	chronic low back pain
CNS	central nervous system
CPMP	chronic pain master protocol
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CCI	
DSA	disease-state appendix
ECG	electrocardiogram
ED	early discontinuation
eGFR	estimated glomerular filtration rate
IB	Investigator's Brochure
ISA	intervention-specific appendix
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
MAD	multiple-ascending dose
MoO	Manual of Operations
NOAEL	No observed adverse effect level
NOEL	no observable effect level
NRS	numeric rating scale
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK	pharmacokinetics

CCI	
QTc	corrected QT interval
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
WNOCBP	Women not of childbearing potential
WOCBP	Women of childbearing potential

11. References

Currò D, Navarra P, Samengo I, Martire M. P2X7 receptors exert a permissive effect on the activation of presynaptic AMPA receptors in rat trigeminal caudal nucleus glutamatergic nerve terminals. *J. Headache Pain*. 2020;21(1):83. https://doi.org/10.1016/j.pain.2005.01.002

Zhang WJ, Zhu ZM, Liu ZX. The role and pharmacological properties of the P2X7 receptor in neuropathic pain. *Brain Res Bull*. 2020;155:19-28. https://doi.org/10.1016/j.brainresbull.2019.11.006