Master Protocol: H0P-MC-NP03

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

NCT04707157

Approval Date: 11-Dec-2020

Title Page

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

Protocol Number: H0P-MC-CPMP

Amendment Number: a

Compound: Multi-molecule code LY900028

Study Phase: 2

Short Title: A Master Protocol for Chronic Pain

Acronym: CPMP

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number

IND: 144915

Approval Date:

Protocol amendment (a) 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**
Original Protocol	30 January 2020

Amendment [a]

Overall Rationale for the Amendment:

This amendment addresses

- FDA feedback
- CCI [redacted]
- changes to the schedule of activities
- clarification of use of medications for chronic pain and rescue medication guidelines
- sponsor protocol template updates to provide more trial execution flexibility
- statistical analyses updates, and
- other clarifications throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Secondary objectives – Other Efficacy - change in several endpoints from "greater than" to "greater than or equal to"...	Statistician decision
1.1 Synopsis	Secondary objectives – Other Efficacy - change in several endpoints from "2-point reduction" to "at least 2-point reduction"...	Statistician decision
1.1 Synopsis	Secondary objectives – Other Efficacy - change in several endpoints from "treatment response with a 30%, 50%, and 70% reduction" to "first pain reduction of at least 30%, 50%, and 70%"...	Statistician decision
1.1 Synopsis	Secondary objectives – Other Efficacy - change in several endpoints from "Time to 2-point reduction" to "Time to first pain reduction of at least 2 points"...	Statistician decision
1.1 Synopsis	Updated Overall Design, Visit 2 to clarify the washout period should begin at Visit 2, and the recommended minimum washout is 2 days.	Clarification
1.1 Synopsis	Changed Data Monitoring Committee (DMC) to Assessment Committee (AC)	Correction to more accurately describe committee
1.3 Schedule of Activities	Updated notes for pain medication washout to specify the 'recommended minimum washout duration is 2 days', and if participants are not taking medication for chronic pain at screening,	Clarification

Section # and Name	Description of Change	Brief Rationale
	a washout is not required.	
1.3 Schedule of Activities	Added footnote 'd' to appropriate Visit 2 procedures and removed redundant text from notes	clarification
1.3 Schedule of Activities	Removed vital signs procedures on Visits 3 through 7	Vital sign procedures for these visits will be detailed in the ISAs
1.3 Schedule of Activities	Added respiratory rate to vital signs notes	Based on FDA feedback.
1.3 Schedule of Activities	Removed footnote "d" and added guidance in notes section	Visit 2 procedure should be repeated if >60 days from Visit 1
1.3 Schedule of Activities	Updated notes for rescue medication usage reporting to clarify total quantity from any source	clarification
1.3 Schedule of Activities	Added C-SSRS and associated Self-harm form procedures at Visit 2	correction
1.3 Schedule of Activities	Added B12, methylmalonic acid and homocysteine to labs for Visit 1	Medical decision
1.3 Schedule of Activities	Added alcohol consumption collected at all Visits	Medical decision
1.3 Schedule of Activities	Added recreational drug use collected at Visit 1	For screening purposes
1.3 Schedule of Activities	Added Self-Pain Positioning Questionnaire at Visit 2	Part of the digital biomarkers analysis
CCI		
3.0 Objectives and Endpoints	Secondary objectives – Other Efficacy - change in several endpoints from "greater than" to "greater than or equal to"...	Statistician decision
3.0 Objectives and Endpoints	Secondary objectives – Other Efficacy - change in several endpoints from "2-point reduction" to "at least 2-point reduction"...	Statistician decision
3.0 Objectives and Endpoints	Secondary objectives – Other Efficacy - change in several endpoints from "treatment response with a 30%, 50%, and 70% reduction" to "first pain reduction of at least 30%, 50%, and 70%"...	Statistician decision
3.0 Objectives and Endpoints	Secondary objectives – Other Efficacy - change in several endpoints from "Time to 2-point reduction" to "Time to first pain reduction of at least 2 point"...	Statistician decision
CCI		
4.1.1 Design Outline	Updated Visit 2 to clarify the washout period should begin at Visit 2.	clarification
4.1.1 Design Outline	Added recommended minimum washout duration is 2 days to Visit 2.	clarification
5.1 Inclusion Criteria	Updated Criterion #9 to say… all medications taken for chronic pain conditions…	Clarification that all medications taken for chronic

Section # and Name	Description of Change	Brief Rationale
		pain conditions, not just for condition under study will be discontinued
5.2 Exclusion Criteria	Updated Criterion #23 to say…ideation or behavior occurred within the past 2 months prior to randomization	Clarification of 2 month window prior to randomization
5.2 Exclusion Criteria	Updated criteria #27 and #28 to specify when a participant received at least one dose of investigational intervention	Clarification of situations where a participant may not have received intervention in a study
5.2 Exclusion Criteria	Medical Conditions. Added criterion #32 have fibromyalgia	Medical decision
5.3 Lifestyle Considerations	Added sub-header Study Restrictions. Updated the first bullet to say use of medications for chronic pain conditions. Removed second bullet about modification of pharmacologic therapies for conditions other than chronic pain.	Clarification of information and removal of repeated information already stated in Section 6.5
5.3 Lifestyle Considerations	Added information for caffeine, alcohol and activities	
5.4 Screen Failures	Replaced "operations manual" with the "schedule of activities" in the table	Correction
5.4.1 Participation in Multiple ISAs	Moved one bullet up and added exceptions to 2 other bullets for participants that did not receive intervention	Clarification for participants that were randomized but did not receive intervention
6.2 Preparation/Handling/ Storage/Accountability	Updates to provide additional flexibility for study conduct	Sponsor protocol template updates
6.3 Measures to Minimize Bias: Randomization and Blinding	Removed "case report form" from last bullet of unblinding table. The date and reason that the blind was broken must be recorded in the source documentation of the appropriate ISA.	Correction
6.3 Measures to Minimize Bias: Randomization and Blinding	Updates to provide additional flexibility for study conduct	Sponsor protocol template updates
6.4 Study Intervention Compliance	Updates to provide additional flexibility for study conduct	Sponsor protocol template updates
6.5 Concomitant Therapy	Entire section updated	To provide more clarity for permitted, prohibited, and rescue medication
7.1 Discontinuation of Study Intervention	Changed DMC to AC	Corrected throughout protocol
7.2.1 Discontinuation of Inadvertently Enrolled Participants	Removed "clinical research physician" (CRP) from…the investigator must obtain documented approval from the sponsor…	Documented approval from the sponsor does not need to be from a CRP
7.3 Lost to Follow-up	Updates to provide additional flexibility for study conduct	Sponsor protocol template updates
8.1.1 Screening and Preliminary Data Entry Period	Numeric Rating Scale. Replaced "Exclusion" with "Inclusion" criteria for the PDEP… And updated link to Section 5.1	Correction
8.1.3.4 Sleep Quality	Updated the MOS sleep scale description	Scale update

Section # and Name	Description of Change	Brief Rationale
8.2.3 Electrocardiograms	Evaluating ECGs. Changed "sitting" to "supine"	Collection should occur while participant is supine.
8.2.4 Clinical Safety Laboratory Assessments	Updates to provide additional flexibility for study conduct	Sponsor protocol template updates
CCI	[redacted]	[redacted]
9.3 Populations for Analyses	Updated population description table for Enrolled, Modified ITT, Safety, and Enhanced ITT populations	Based on feedback from the FDA
9.4.1 General Considerations	Updated ISA SAP information for borrowing	Statistician decision
9.4.2 Primary Endpoint and Analysis	Updated the population for the primary efficacy analysis, updated the outcome variable, and removed the continuous fixed covariates in model	Per updates in Section 9.3, feedback from the FDA, and statistician decision, respectively
9.4.2.1 Key Features of the Bayesian Primary Efficacy Analysis Model	Added sub-header for Borrowing Strategy and updated text for the decisions on borrowing of placebo and treatment-effect information	Clarification
9.4.3 Secondary Endpoints and Analysis	Updated outcome variable and removed continuous fixed covariates in model	Per FDA feedback and sponsor decision
9.4.3 Secondary Endpoints and Analysis	Moved the table to Section 9.4.3.1. In the table, updated the outcome variable, removed the continuous fixed covariates in the model, and updated the fixed categorical effects	Statistician decision
9.4.3.1 Continuous Efficacy Analyses	Table from 9.4.3. moved to this section and content updated.	Statistician decision
9.4.3.2 Categorical Efficacy Analyses	Change in several endpoints from "greater than" to "greater than or equal to"... and from "2-point reduction…" to "at least 2-point reduction…"	Statistician decision
9.4.3.2 Categorical Efficacy Analyses	Updated the outcomes from "greater than" to "greater than or equal to…". Updated the outcomes from "a 2-point reduction from baseline" to "at least a 2-point reduction from baseline". Added the model covariates	Statistician decision
9.4.3.3 Time to Event Efficacy Analyses	Updated last 2 bullets to say, "time to first pain reduction of at least 2-points"…	Parallel sentence structure of outcomes
9.4.3.3 Time to Event Efficacy Analyses	Added the "time to event" analyses based on daily NRS score	Statistician decision
9.4.4 Tertiary/Exploratory Endpoints	Added biomarker analysis	Sponsor's decision
9.4.7 Subgroup Analyses	Subgroup analyses model covariates are updated	Statistician decision
9.6 Data Monitoring Committee	Changed DMC to AC and added information for the AC and AC charter.	Correction to more accurately describe committee and its responsibilities
10.1.1 Regulatory and Ethical Considerations	Updates to provide additional flexibility for study conduct. Fourth bullet, …"oversight of	Sponsor protocol template updates

Section # and Name	Description of Change	Brief Rationale
	study conduct for participants under their responsibility…"	
10.1.5 Committees Structure	Changed DMC to AC and updated responsibilities of the SASC	Correction to more accurately describe committee and its responsibilities
10.1.7 Data Quality Assurance	Updates to provide additional flexibility for study conduct	Sponsor protocol template updates
10.1.7 Data Quality Assurance	Added digital biomarker data information	If available, digital biomarker devices will be used in the study
10.1.12 Long-term Sample Retention	Updated terminology in table and changed sample retention from 15 to 7 years for exploratory biomarker sample.	Per updated sponsor guidelines
10.2 Appendix 2: Clinical Laboratory Tests	Added new text for local laboratory testing	Sponsor protocol template updates
10.2 Appendix 2: Clinical Laboratory Tests	Added B12, methylmalonic acid and homocysteine	Per schedule of activities update
10.2 Appendix 2: Clinical Laboratory Tests	Pharmacogenetic and Exploratory Biomarker Sample Collection table, updated terminology and changed plasma to whole blood	Correction per updated sponsor guidelines.
11 References	Added Liang, Zeger 2000 reference	Used in Section 9.4.2.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

Rationale:

The Phase 2 proof-of-concept master protocol is designed to efficiently assess the potential efficacy of novel interventions in multiple chronic pain conditions.

Objectives and Endpoints

Objective	Endpoint Measure
Primary	
Pain Intensity Efficacy of each study intervention versus placebo	Mean change from baseline assessment to endpoint for average pain intensity as measured by numeric rating scale (NRS)
Secondary	
Physical Functioning Efficacy of each study intervention versus placebo	Mean change from baseline assessment to endpoint for physical functioning measures as described in the disease-state addenda (DSA)
Overall Improvement Efficacy of each study intervention versus placebo	Mean change from baseline assessment to endpoint for overall improvement as measured by Patient's Global Impression of Change
Other Efficacy Efficacy of each study intervention versus placebo	• Mean change from baseline assessment to endpoint for worst pain intensity as measured by NRS • Proportion of participants with a pain reduction from baseline greater than or equal to 30%, 50%, and 70% as measured by the average and worst pain responses on the NRS • Proportion of participants with at least 2-point reduction from baseline as measured by the average and worst pain responses on the NRS • Time to first pain reduction of at least 30%, 50%, and 70% from baseline as measured by the average and worst pain responses on the NRS • Time to first pain reduction of at least 2 points from baseline as

	measured by the average and worst pain responses on the NRS • Mean change from baseline assessment to endpoint on the visual analog scale (VAS) for pain • Proportion of participants with pain reduction from baseline greater than or equal to 30%, 50%, and 70% as measured by VAS • Mean change from baseline assessment to endpoint on the Sleep Scale from the Medical Outcomes Study (MOS Sleep Scale) • Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% on the physical functioning measures as described in the DSA, and • Summary of frequency, timing, and amount of rescue medication used during the treatment phase.
Emotional Functioning Efficacy of each study intervention versus placebo on patient-reported clinical outcomes	Mean change from baseline assessment to endpoint for emotional functioning as measured by the EuroQol-5D 5 level questionnaire (EQ-5D-5L)

Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 2, proof-of-concept master protocol with appendices to compare independent pain interventions versus placebo.

The master protocol

- establishes entry criteria for the master protocol
- establishes an overarching structure for the disease-state addenda (DSA)
- outlines the randomization schema
- tests a common hypothesis across multiple indications and interventions, and
- facilitates advanced statistical modeling and operational efficiencies.

The DSA will contain specific study elements to appropriately define the target population and unique scales for assessment. The chronic pain disease states of interest currently include osteoarthritis, chronic low back pain, and diabetic peripheral neuropathic pain. Disease-state addenda for additional pain conditions may be added as needed.

The master protocol also governs intervention-specific appendices (ISAs). The ISAs

- contain study elements specific to the interventions under study, such as dosing regimen, unique eligibility criteria and assessments, or other requirements
- may start independently of one another as interventions become available for clinical testing, and
- may end independently, either when an intervention has concluded, or as interim analyses show that an intervention's criteria for futility or success have been met.

Screening Period

The investigator determines what DSA the potential participant will be screened for based on the participant's chief complaint.

Visit 1

Interested participants will

1. sign the appropriate informed consent document(s) prior to completion of any procedures
2. complete master protocol screening in advance of or in parallel with screening for any ISA, and
3. participate in screening for all actively enrolling ISAs within the disease-state addendum.

The interactive web-response system (IWRS) will be used to confirm actively enrolling ISAs within the disease state-addendum. Participants may opt to screen for subsequent ISAs that become active prior to Visit 2.

The site determines the half-life of each medication the participant is currently taking for chronic pain to appropriately schedule Visit 2.

Visit 2

The appropriate time to schedule Visit 2 depends on the 5-half-life washout period required for medications taken for chronic pain and the minimum 7-day preliminary data entry period (PDEP) required prior to Visit 3.

The washout period should begin at Visit 2.

If participants are not taking medication for chronic pain during screening, a washout is not required.

The recommended minimum washout duration is 2 days. If a participant is taking a medication that requires a tapered discontinuation that is longer than 5 half-lives, then the medication label instructions for discontinuation should be followed.

The 7-day PDEP is required for all participants regardless of washout duration. The PDEP includes daily participant reporting of pain severity on the numeric rating scale and information on rescue medication use.

The screening period is complete upon investigator confirmation of all screening procedures for the master and all active ISAs.

Visit 3

The appropriate time to schedule Visit 3 is after completion of the washout period and required PDEP. Visit 3 is the common point of randomization within the master protocol for each ISA.

Follow-Up Visit

Visits beyond the 8-week treatment period may be specified in an individual ISA.

Randomization and Blinding

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All participants will be centrally randomized to an ISA and to study intervention within an ISA using an IWRS. The IWRS will be programmed with unblinding instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. However, the investigator should make all attempts to contact the Medical Monitor in advance of unblinding.

Participants

Male and female participants are eligible for inclusion in the study if they have a history of daily pain based on participants' report or medical history.

Disclosure Statement:

This is a master protocol for randomized, investigator- and participant-blind, placebo-controlled, Phase 2 clinical trials of multiple interventions for the treatment of chronic pain.

Number of Participants:

The number of participants will be specified in each respective ISA.

Intervention Groups and Duration:

Information about study intervention is provided in each respective ISA.

Each ISA will have an 8-week double-blind treatment period.

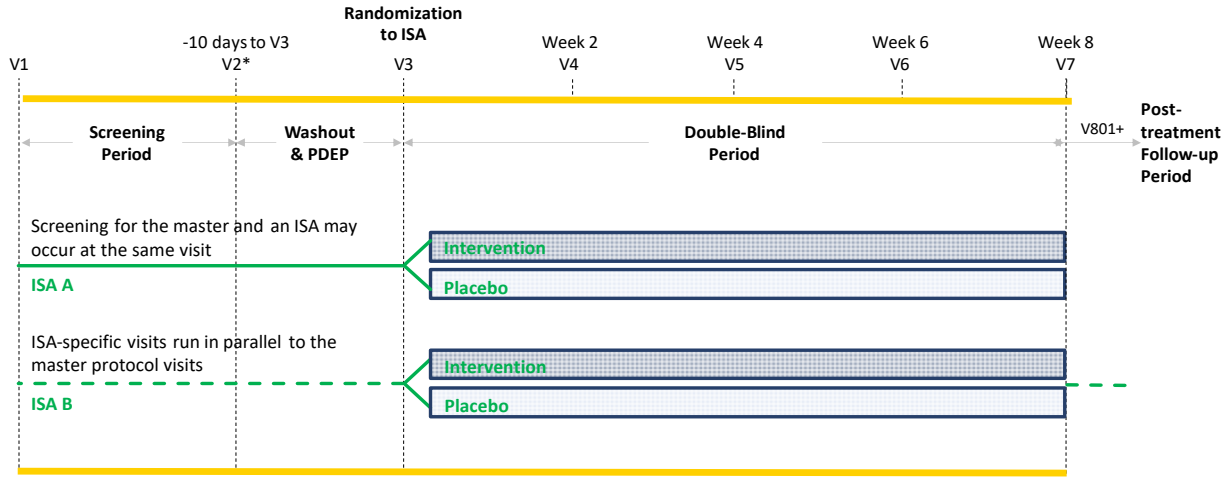
Due to the subjective nature of pain assessments and the desire to mitigate the placebo response seen in clinical studies evaluating pain treatments, ISAs may have an unblinded ethical review board supplement that contains information about study design elements such as active treatment initiation, duration, and termination.

Data Monitoring Committee: Yes

These committees will be established to support the master protocol and ISA teams:

- Assessment Committee
- Internal Steering Committee, and
- Internal Statistical Analysis Subcommittee.

1.2. Schema



*Medication washout and preliminary data entry period begins.
Abbreviations: ISA = intervention-specific appendix; PDEP = preliminary data entry period; V = visit.
Note: Several aspects of the study design are blinded to investigators and clinical staff. Depending on the ISA design, an ethical review board supplement may be used. Optional follow-up periods beyond the 8-week double-blind period may be specified in an individual ISA.

1.3. Schedule of Activities (SoA)

The activities applicable to all disease states and interventions studied under the master protocol are described in the SoA below.

	Screening[a]		Double-Blind Treatment Period						
H0P-MC-CPMP Master Protocol	**Screening Visit for Master**	**Pre-Randomization Screening Visit**	**Randomization to ISA**					**Early Discontinuation**	**Notes**
Visit Number	**V1[b]**	**V2[c]**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	Visits after V7 may be specified in the ISA.
Study Week	Up to -6 months	-10 to -7 days for most participants	0	2	4	6	8		
Procedure/ Assessments									
Informed consent for master protocol	X								
Informed consent for ISA	X								ISA-specific informed consent may occur after other V1 procedures and prior to beginning the medication washout if the ISA is not available at the time of initial screening.
Evaluate master protocol I/E criteria	X	X	X						
Pain medication washout		X							Duration of washout is at least 5 half-lives of the longest half-life medication taken for pain. Recommended minimum washout duration is 2 days. If participants are not taking medication for chronic pain during screening, a washout is not required.
PDEP		X							7-day minimum NRS data and rescue use medication collected daily at home post washout and prior to randomization.
Medical history	X								
Family history	X								

	Screening[a]		Double-Blind Treatment Period						
H0P-MC-CPMP Master Protocol	**Screening Visit for Master**	**Pre-Randomization Screening Visit**	**Randomization to ISA**					**Early Discontinuation**	**Notes**
Visit Number	**V1[b]**	**V2[c]**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	Visits after V7 may be specified in the ISA.
Study Week	Up to -6 months	-10 to -7 days for most participants	0	2	4	6	8		
Demographics	X								Including age, gender, race, and ethnicity
Physical examination	X	X[d]							
Weight	X	X[d]	X	X	X	X	X	X	
Height	X								
Vital signs	X	X[d]							Pulse rate, respiratory rate, blood pressure, and temperature taken with participant in a sitting position.
ECG	X	X[d]	X					X	Triplicate ECGs. Post randomization ECGs are included in each ISA.
AEs		X	X	X	X	X	X	X	Any events that occur after signing the ICF are considered AEs as defined in Section 10.3.
Preexisting conditions	X								Preexisting conditions not identified at V1 and started prior to signing the ICF should be recorded.
Concomitant medications	X	X	X	X	X	X	X	X	
Scales, Questionnaires, and Outcome Measures									
VAS for pain	X	X	X	X	X	X	X	X	V2 procedure should be repeated if >60 days from V1
NRS for pain		X	X	X	X	X	X	X	Collected daily with a take-home device. Compliance reviewed at each clinic visit.

	Screening[a]		Double-Blind Treatment Period						
H0P-MC-CPMP Master Protocol	**Screening Visit for Master**	**Pre-Randomization Screening Visit**	**Randomization to ISA**					**Early Discontinuation**	**Notes**
Visit Number	**V1[b]**	**V2[c]**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	Visits after V7 may be specified in the ISA.
Study Week	Up to -6 months	-10 to -7 days for most participants	0	2	4	6	8		
Rescue medication usage reporting		X	X	X	X	X	X	X	Total quantity from any source, collected daily with a take-home device. Compliance reviewed at each clinic visit. See Section 6.5. for usage guidance.
Pain catastrophizing scale	X								
PGI				X	X	X	X	X	
EQ-5D-5L			X	X	X	X	X	X	
MOS Sleep Scale			X	X	X	X	X	X	
C-SSRS	X	X[d]	X	X	X	X	X	X	At V1, use the C-SSRS Baseline version. All subsequent assessments will use the C-SSRS Since Last Visit version.
Self-Harm Supplement form	X	X[d]	X	X	X	X	X	X	
Self-Harm Follow-Up form	X	X[d]	X	X	X	X	X	X	Complete 1 form for each event identified on the Self-Harm Supplement form.
Clinical Laboratory Tests									
Hematology	X	X[d]	X					X	Post randomization collections will be defined in each respective ISA.

	Screening[a]		Double-Blind Treatment Period						
H0P-MC-CPMP Master Protocol	**Screening Visit for Master**	**Pre-Randomization Screening Visit**	**Randomization to ISA**					**Early Discontinuation**	**Notes**
Visit Number	**V1[b]**	**V2[c]**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	Visits after V7 may be specified in the ISA.
Study Week	Up to -6 months	-10 to -7 days for most participants	0	2	4	6	8		
Chemistry	X	X[d]	X					X	Post randomization collections will be defined in each respective ISA.
Lipid panel	X	X[d]	X					X	Post randomization collections will be defined in each respective ISA.
Urinalysis	X	X[d]	X					X	Post randomization collections will be defined in each respective ISA.
B12	X								
Methylmalonic acid	X								
Homocysteine	X								
Serum pregnancy	X	X							For women of childbearing potential. V2 test is optional if within 30 days of V1 procedure
FSH	X	X[d]							
Estradiol	X	X[d]							
TSH	X	X[d]							Post randomization collections will be defined in each respective ISA.
Urine drug screen	X								Collected at screening visit for all participants and by investigator discretion after V1.
Alcohol consumption	X	X[d]	X	X	X	X	X	X	

	Screening[a]		Double-Blind Treatment Period						
H0P-MC-CPMP Master Protocol	**Screening Visit for Master**	**Pre-Randomization Screening Visit**	**Randomization to ISA**					**Early Discontinuation**	**Notes**
Visit Number	**V1[b]**	**V2[c]**	**V3**	**V4**	**V5**	**V6**	**V7**	**ED**	Visits after V7 may be specified in the ISA.
Study Week	Up to -6 months	-10 to -7 days for most participants	0	2	4	6	8		
Recreational drug use	X								
HbA1c	X	X[d]							Post randomization collections will be defined in each respective ISA.
HIV	X	X[d]							
Exploratory biomarker samples			X						Post randomization collections will be defined in each respective ISA.
Pharmacogenetic sample			X						
Participant Questionnaire									
Self-pain positioning questionnaire		X							
Participant Device									
CCI									

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L = EuroQol-5D 5 level questionnaire; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; ICF = informed consent form; I/E = inclusion and exclusion; ISA = intervention-specific appendix; MOS = Medical Outcomes Study; NRS = numeric rating scale; PDEP = preliminary data entry period; PGI = Patient Global Impression of Change; TSH = thyroid stimulating hormone; V = visit; VAS = visual analog scale.

[a] Screening assessments may be conducted at other time points prior to randomization if they reduce participant burden.

[b] The site determines the half-life of each pain medication the participant is currently taking to schedule Visit 2. Visit 2 can be scheduled no earlier than 7 days prior to randomization at Visit 3 due to the required 7-day PDEP.

[c] The 5-half-life washout period for pain medications must come before the required 7-day PDEP, resulting in a minimum of 10 days for most participants.

[d] Visit 2 testing is optional for individuals who have completed these assessments within 60 days of Visit 1. If the tests are repeated, the most recent results will be used for I/E purposes.

2. Introduction

Study H0P-MC-CPMP (CPMP) is a master protocol to accelerate the development of novel treatments for chronic pain. This platform trial provides a framework to enable the seamless evaluation of efficacy and safety of interventions as hypotheses emerge.

The master protocol platform design provides an overarching infrastructure that will harness the benefits of operational and statistical efficiencies.

2.1. Study Rationale

This Phase 2 proof-of-concept master protocol is designed to efficiently assess the potential efficacy of novel interventions in multiple chronic pain conditions.

2.2. Background

The master protocol

- establishes entry criteria for the master protocol
- establishes an overarching structure for the disease-state addenda (DSA)
- outlines the randomization schema
- tests a common hypothesis across multiple indications and interventions, and
- facilitates advanced statistical modeling and operational efficiencies.

The disease-state addenda (DSA) will contain specific study elements to appropriately define the target population and unique scales for assessment. The chronic pain disease states of interest currently are osteoarthritis, chronic low back pain, and diabetic peripheral neuropathic pain. Disease-state addenda for additional pain conditions may be added as needed.

The master protocol also governs intervention-specific appendices (ISAs). The ISAs

- contain study elements specific to the interventions under study, such as dosing regimen, unique eligibility criteria and assessments, or other requirements
- may start independently of one another as interventions become available for clinical testing, and
- may end independently, either when an intervention has concluded, or as interim analyses show that an intervention's criteria for futility or success have been met.

2.3. Benefit/Risk Assessment

The overall benefit/risk assessment of each intervention is described in each respective ISA.

Information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of the interventions used in the ISAs may be found in their respective Investigator's Brochures (IBs).

Detailed information about the known and expected benefits and risks of any marketed interventions may be found in the

- Patient Information Leaflet
- Patient Package Insert, or
- Summary of Product Characteristics.

3. Objectives and Endpoints

Objectives and Endpoints

Objective	Endpoint Measure
Primary	
Pain Intensity Efficacy of each study intervention versus placebo	Mean change from baseline assessment to endpoint for average pain intensity as measured by the Numeric Rating Scale (NRS)
Secondary	
Physical Functioning Efficacy of each study intervention versus placebo	Mean change from baseline assessment to endpoint for physical functioning measures as described in the disease state addenda (DSA)
Overall Improvement Efficacy of each study intervention versus placebo	Mean change from baseline assessment to endpoint for overall improvement as measured by Patient's Global Impression of Change
Other Efficacy Efficacy of each study intervention versus placebo	• Mean change from baseline assessment to endpoint for worst pain intensity as measured by NRS • Proportion of participants with a pain reduction from baseline greater than or equal to 30%, 50%, and 70% as measured by the average and worst pain responses on the NRS • Proportion of participants with at least 2-point reduction from baseline as measured by the average and worst pain responses on the NRS • Time to first pain reduction of at least 30%, 50%, and 70% from baseline as measured by the average and worst pain responses on the NRS • Time to first pain reduction of at least 2-point from baseline as measured by the average and worst pain responses on the NRS • Mean change from baseline assessment to endpoint on the visual analog scale (VAS) for pain • Proportion of participants with pain reduction from baseline greater than or equal to 30%, 50%, and 70% as measured by VAS • Mean change from baseline assessment to endpoint on the Sleep Scale from the Medical Outcomes Study (MOS Sleep Scale) • Proportion of participants with reduction from baseline greater

	than or equal to 30%, 50%, and 70% on the physical functioning measures as described in the DSA, and • Summary of frequency, timing, and amount of rescue medication used during the treatment phase.
Emotional Functioning Efficacy of each study intervention versus placebo on patient-reported clinical outcomes	Mean change from baseline assessment to endpoint for emotional functioning as measured by the EuroQol-5D 5 level questionnaire (EQ-5D-5L)

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4. Study Design

4.1. Overall Design

Study Design Overview

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 2, proof-of-concept master protocol with appendices to compare independent pain interventions versus placebo.

The master protocol contains DSA that have specific study elements to appropriately define the target population and unique scales for assessment.

The master protocol also governs ISAs that may start independently of other ISAs as interventions become available for clinical testing.

Anticipated Platform Duration

The master protocol is designed to allow interventions to enter the master protocol for an estimated period of 5 to 7 years.

4.1.1. Design Outline

Screening Period

The investigator determines what DSA the potential participant will be screened for based on the participant's chief complaint.

Visit 1

Interested participants will

1. sign the appropriate informed consent document(s) prior to completion of any procedures
2. complete master protocol screening in advance of or in parallel with screening for any ISA, and
3. participate in screening for all actively enrolling ISAs within the DSA.

The interactive web-response system (IWRS) will be used to confirm actively enrolling ISAs within the DSA. Participants may opt to screen for subsequent ISAs that become active prior to Visit 2.

The site determines the half-life of each medication the participant is currently taking for chronic pain to appropriately schedule Visit 2.

Visit 2

The appropriate time to schedule Visit 2 depends on the washout period required for medications taken for chronic pain and the minimum 7-day preliminary data entry period (PDEP) required prior to Visit 3.

The washout period should begin at Visit 2.

If participants are not taking medication for chronic pain during screening, a washout is not required.

The recommended minimum washout duration is 2 days. If a participant is taking a medication that requires a tapered discontinuation that is longer than 5 half-lives, then the medication label instructions for discontinuation should be followed.

The 7-day PDEP is required for all participants regardless of washout duration. The PDEP includes daily participant reporting of pain severity on the Numeric Rating Scale (NRS) and information on rescue medication use.

The screening period is complete upon investigator confirmation of all screening procedures for the master and all active ISAs.

Visit 3

The appropriate time to schedule Visit 3 is after completion of the washout period and required PDEP. Visit 3 is the common point of randomization within the master protocol for each ISA.

At the time of randomization, the site will confirm

- participant eligibility for the master protocol, DSA, and each active ISA
- adherence with the washout period, and
- adherence with the PDEP data entry per the schedule of activities (SoA) (Section 1.3).

Potential participants will only be randomized to an ISA for which they are eligible.

Participants will be aware of their ISA randomization but not their treatment randomization.

CCI

Follow-Up Visit

Visits beyond the 8-week treatment period may be specified in an individual ISA.

4.2. Scientific Rationale for Study Design

The master protocol construct will

- offer flexibility to continually add different interventions at different time points across different participant populations
- enable efficient testing of multiple promising targets across multiple pain states
- allow direct statistical comparisons of interventions studied within a pain type
- enable borrowing of
    - placebo participants within a pain type, and
    - treatment-effect information across pain types for a given intervention
- facilitate smaller ISA sample sizes as the trial progresses due to the ability to borrow placebo and treatment-effect information
- provide potential site benefit based on multiple therapies offered, and
- offer continuous screening of participants for future interventions.

The proposed design provides many unique operational and statistical challenges as well as opportunities to make the best decisions in advancing molecules through the drug development process.

The primary efficacy analysis is a Bayesian mixed-model repeated measures (MMRM) method that allows the borrowing of placebo information within a DSA and borrowing of treatment difference information between different addendum pain types. The amount of borrowing and the statistical methodology used to accommodate the borrowing (for example, pooling of data, hierarchical modeling), including the specifics of the Bayesian prior distributions, will be specified within each ISA.

The master protocol also allows for adaptations specified within an ISA. The adaptations may include stopping for early futility, stopping for early efficacy, sample size re-estimation, or removal of a dose arm.

Intervention-specific design elements are described in the respective ISA.

Efficacy Assessments

The master protocol contains a core set of assessments based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines (Dworkin et. al. 2005). The recommended domains when designing chronic pain clinical studies are

- pain
- physical functioning
- emotional functioning
- participant ratings of overall improvement
- adverse events (AEs), and
- participant disposition.

The NRS was selected for the primary endpoint based on its demonstrated ability to detect changes in pain and its common use across the disease states under study.

4.3. Justification for Dose

The justification for dose selection of each intervention is described in the respective ISA.

4.4. End of Study Definition

The end of the master protocol will occur when all ISAs are complete and no new ISAs are planned.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

If participants are in the screening phase for 60 or more days, a subset of procedures must be repeated. If participants are in the screening phase for 60 or more days, the most recent values will be used for inclusion and exclusion purposes. Consult the SoA and the Operations Manual for additional guidance.

If participants are in the screening phase of the master protocol for less than 60 days and procedures are not required to be repeated at Visit 2, then the Visit 1 values will be used for inclusion and exclusion purposes unless otherwise specified.

5.1. Inclusion Criteria

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

Age

Age requirements for participation will be specified in the DSA and/or ISAs.

Pain Characteristics

[1] have a visual analog scale (VAS) pain value ≥40 and <95 at Visits 1 and 2

[2] have a history of daily pain for at least 12 weeks based on participant report or medical history

[3] have a value of ≤30 on the pain catastrophizing scale

Weight

[4] have a body mass index <40 kg/m^2 (inclusive)

Gender

[5] are male or female participants

Reproductive and contraceptive requirements will be specified in the ISAs.

Informed Consent and Participant Agreements

[6] are capable of providing informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

[7] are reliable, willing, and able to participate in all required protocol procedures for the duration of the study

[8] are willing to maintain a consistent regimen of any ongoing nonpharmacologic pain-relieving therapies (for example, physical therapy) and will not start any new nonpharmacologic pain-relieving therapies during study participation

[9] are willing to discontinue all medications taken for chronic pain conditions, except rescue medication permitted per protocol (Section 6.5), for the duration of the study

[10] must enter the required daily assessments during the PDEP for at least 5 of the 7 days prior to randomization

5.2. Exclusion Criteria

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

Medical Conditions

[11] have second- or third-degree atrioventricular (AV) heart block or AV dissociation or history of ventricular tachycardia

[12] have had a procedure within the past 6 months intended to produce permanent sensory loss in the target area of interest (for example, ablation techniques)

[13] have surgery planned during the study for any reason, related or not to the disease state under evaluation

[14] have, in the judgment of the investigator, an acute, serious, or unstable medical condition or a history or presence of any other medical illness that would preclude study participation

[15] there is an inability to rule out other causative or confounding sources of pain in the primary condition under study

[16] have had cancer within 2 years of Visit 3, except for cutaneous basal cell or squamous cell carcinoma resolved by excision

[32] have fibromyalgia

Diagnostic Assessments

[17] have substance use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5; American Psychiatric Association)

[18] have congenital QT prolongation or QT interval corrected for heart rate using Fridericia's formula (QTcF) interval measurement >450 msec for male participants, >470 msec for female participants, or >480 msec for participants with bundle branch block

[19] have any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital signs, electrocardiogram (ECG), or clinical laboratory test results that could be detrimental to the participant or could compromise the study

[20] have a positive human immunodeficiency virus (HIV) test result at screening

[21] have central laboratory hepatic results at screening of

- alanine aminotransferase (ALT) ≥2 × the upper limit of normal (ULN)
- aspartate aminotransferase (AST) ≥2 × ULN
- total bilirubin (TBL) ≥1.5 × ULN, or
- alkaline phosphatase (ALP) ≥1.5x ULN.

In asymptomatic individuals with a history of Gilbert's syndrome, use TBL of ≥ 2 × ULN.

[22] are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide

[23] have answered 'yes' to either Question 4 or Question 5 on the 'Suicidal Ideation' portion of the Columbia-Suicide Severity Rating Scale (C-SSRS)

OR

have answered 'yes' to any of the suicide-related behaviors on the 'suicidal behavior' portion of the C-SSRS, and the ideation or behavior occurred within the past 2 months prior to randomization

Prior and Concomitant Therapy/Substance of Abuse

[24] have an intolerance to acetaminophen or paracetamol or any of its excipients

[25] have a history of alcohol, illicit drug, analgesic or narcotic use disorder within 2 years prior to Visit 1

Prior or Concurrent Clinical Trial Experience

[26] are currently enrolled in any other clinical trial involving an investigational intervention or any other type of medical research judged not to be scientifically or medically compatible with this study by the Medical Monitor

[27] have participated within the past 30 days in a clinical study and received at least one dose of investigational intervention, including prior CPMP ISAs

[28] have not completed all prior ISAs within the CPMP master protocol if they received at least one dose of investigational intervention in the assigned ISA

Other Exclusions

[29] are investigator site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[30] are employees of Eli Lilly and Company (Lilly) or partners of employees of Lilly or employees or partners of any third-party organizations involved in the study

[31] have current or pending worker's compensation, litigation, disability, or any other monetary settlement regarding the pain condition, or any closed claim

5.3. Lifestyle Considerations

Study Restrictions

The following are prohibited during the study

- use of medications for chronic pain conditions, except rescue medication permitted per protocol (Section 6.5), for the duration of the double-blind treatment period.
- use of any drugs of abuse, including but not limited to, illicit amphetamine, cocaine, illicit opiates, propoxyphene, methadone, methaqualone, phencyclidine, or barbiturates, and
- initiation of nonpharmacologic pain-relieving procedures such as acupuncture or physical therapy, devices such as transcutaneous electrical nerve stimulation (TENS) units, or garments and braces.

If participants use cannabis or cannabinoids for the treatment of pain, they must discontinue usage for the duration of the study.

If participants use cannabis or cannabinoids for any other use, the usage should remain consistent for the duration of the study.

These restrictions may not apply during follow-up periods in which interventions are not taken. Any modifications to restrictions will be specified in the ISA.

Caffeine and Alcohol

Participants should maintain their usual caffeine intake.

Participants should limit their alcohol consumption for the duration of the study as specified below.

Men up to the age of 65 years should not exceed an average weekly alcohol intake of 21 units per week.

Men over the age of 65 years and women should not exceed an average weekly alcohol intake of 14 units per week.

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.

Activities

Participants are required to maintain similar levels of activity during the double-blind study period. Starting a new exercise program or new strenuous activity is not allowed.

Participants who receive physical therapy should remain on the same therapy program (intensity and frequency).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the master protocol and appropriate ISAs but are not subsequently randomized to any ISA. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this master protocol (screen failure) may be rescreened. This table describes when a participant is considered a screen failure or when a participant may be rescreened.

If…	**Then…**
a participant does not complete screening procedures within 6 months of signing the master informed consent form	participant is considered a screen failure
a participant screen fails for the above reason	participant may be rescreened 1 time
a participant screen fails for the pain intensity criterion (VAS)	participant may not be rescreened for at least 1 year from the date of pain severity assessment
a participant screen fails for the master protocol for reasons other than pain intensity criteria (VAS)	participant may be rescreened no sooner than 3 months from the date of screen failure
more than 60 days have passed between screening for the master protocol and screening for an ISA	a subset of procedures may need to be completed per the Schedule of Activities
a participant screen fails for a specific ISA	participant no longer has to complete the remaining screening procedures specific to that ISA
a participant screen fails for a specific ISA	participant is still eligible under the master protocol for participation in other ISAs

Abbreviations: ISA= intervention-specific appendix; VAS = visual analog scale.

Rescreened participants should be assigned a new participant number. Each time master protocol rescreening is performed, the individual must sign a new master protocol ICF.

Repeating laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

5.4.1. Participation in Multiple ISAs

Interested participants will have the opportunity to participate in multiple ISAs within the same disease state or for different disease states.

Participation in multiple ISAs is allowed if the participant

- meets all inclusion or exclusion criteria for the master protocol, the applicable DSA, and the respective ISA at the time of screening
- has not participated in another ISA with the same intervention
- has completed the 30-day waiting period since participating in another clinical study involving an intervention
    - EXCEPTION – if the participant did not receive intervention, then the participant does not need to complete the 30-day waiting period

- has completed all previous ISAs without early discontinuation
    - EXCEPTION – if the participant discontinues without receiving intervention.

The intervention that the participant received in a previous ISA will have no impact on the randomization of treatment to the current ISA. The number of participants who will participate in multiple ISAs is unknown. Participation in more than one ISA, referred to as 'repeat participation,' will be tracked at the site level, the ISA level, and at the overall master protocol level.

Repeat participation may introduce the potential concern that populations between ISAs may be too homogenous or introduce potential biases into the participant population for future ISAs, such as inflation or deflation of placebo response in repeat participants, or bias of completers in the data set. If these issues occur, edits will be made to future amendments of the Master Protocol or an ISA to address this concern.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered

A multi-molecule code of LY900028 is used for internal purposes. Intervention specific information is defined in each ISA.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm that appropriate storage conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only study personnel may supply, prepare or administer study intervention.
3. 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 study personnel.
4. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the ISAs and corresponding Operations Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

The ISAs will have an 8-week double-blind treatment period in which participants CCI [redacted]

Due to the subjective nature of pain assessments and the desire to mitigate the placebo response seen in clinical studies evaluating potential pain treatments, ISAs may have an unblinded ethical review board (ERB) supplement that contains information about study design elements such as active treatment initiation, duration, and termination.

This table describes how participants will be randomized.

Study using IWRS	• All participants will be centrally randomized or assigned to an ISA and randomized to study intervention within an ISA using an IWRS • Before the study is initiated, the login information and directions for the IWRS will be provided to each site • Study intervention will be dispensed at the study visits as summarized in the ISA • Returned study intervention should not be redispensed to the participants

Abbreviations: ISA = intervention-specific appendix; IWRS = interactive web-response system.

This table describes general procedures for unblinding.

Unblinding (IWRS)	• The IWRS will be programmed with unblinding instructions • In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted • Participant safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the Medical Monitor in advance of unblinding • If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance • The date and reason that the blind was broken must be recorded in the source documentation of the appropriate ISA, as applicable

Abbreviations: ISA = intervention-specific appendix; IWRS = interactive web-response system.

If an investigator, study personnel performing assessments, or participant is unblinded, the investigator must contact the study sponsor as soon as possible to determine if the participant must be discontinued from the study. In cases where there are ethical or other reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor Medical Monitor for the participant to continue in the study.

6.3.1. Stratification

If participants are eligible for more than one ISA, they will be randomly assigned to an ISA using the IWRS. Participation in an ISA is not decided by the site, participant, or physician. CCI [redacted]

Each ISA will include a stratification factor based on the average baseline pain severity score as measured by the NRS.

The definition of the stratification factor is provided as:

severe pain: ≥7 on the baseline NRS average pain score, or

moderate pain: <7 on the baseline NRS average pain score.

Additional stratification factors may be defined in the ISA or DSA.

6.4. Study Intervention Compliance

When required, study intervention will be administered under medical supervision by the investigator or designee. The date and time of each dose administered will be recorded in the source documents and recorded in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed prior to the time of dosing.

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 study intervention per each ISA and documented in the source documents and CRF.

Additional information on intervention compliance will be in the ISA.

6.5. Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the

- reason for use
- dates of administration including start and end dates, and
- dose and frequency.

Permitted Medication

Permitted concomitant therapy should remain stable for dosing and frequency of use throughout the treatment period. The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

Medically required changes to concomitant medication not taken for pain may be considered on a case-by-case basis with the documented approval of the Medical Monitor.

Short-term use of medications such as analgesics or corticosteroids is permitted to treat medical conditions other than chronic pain for no more than a total of 7 days during the treatment phase. For these situations contact the Medical Monitor.

Rescue Medication

Permitted Rescue Medication

Acetaminophen is the **ONLY** allowed rescue medication.

Maximum Daily Acetaminophen Dose

The maximum daily dose is 3000 mg per day.

This maximum amount is inclusive of combination products in which acetaminophen is contained.

General guidelines for acetaminophen use and recording the dose

Beginning at Visit 2, participants will record their use and maximum total dose of acetaminophen daily using a take-home device.

Rescue medication should be used at the lowest effective dose for the shortest duration possible throughout study participation.

During the minimum required 7 days of the PDEP, limit use to no more than 4 days.

This table describes acetaminophen use guidance during the double-blind treatment period.

Acetaminophen Use Guidance during Visit 3 through Visit 7	
Maximum dose per day	3000 mg
Maximum consecutive days	3 days
Maximum total days	14 days

The investigative site should evaluate appropriateness of rescue medication use at each visit. Continued education should be provided as necessary.

Prohibited Medication

Medications for pain other than protocol permitted rescue medication are prohibited after Visit 2.

Any investigational intervention judged to be scientifically or medically incompatible with this study is prohibited.

These restrictions may not apply during follow-up periods in which investigational interventions are not taken. Any modifications to restrictions will be specified in the ISA.

Additional information about concomitant medication use is provided in the respective ISA.

6.6. Dose Modification

This section is not applicable for the master protocol.

6.7. Intervention after the End of the Study

No continued access is planned after completion of each proof-of-concept master protocol ISA, as additional efficacy would be needed to demonstrate continued access criteria.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention.

If study intervention is definitively discontinued, the study participant will not remain in the master protocol or ISA. See the master protocol and ISA SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Additional criteria for discontinuation may be included in each ISA. If an ISA criterion is more restrictive, it should be applied for those participants in the respective ISA.

Participants **may** be discontinued from study intervention if these situations occur:

- based on a specific AE profile, as recommended by the Assessment Committee (AC), the Medical Monitor, or the study sponsor physician/scientist, in discussions with the Principal Investigator
- incorrect enrollment
- severe noncompliance to the study protocol in the judgment of the investigator
- participants answered 'yes' to Question 4 or 5 on the 'Suicidal Ideation' portion of the C-SSRS, or
- participants answered 'yes' to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.
    - a psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant for C-SSRS responses.

Liver Safety

Discontinuation of the intervention should be considered when a participant meets one of the following conditions after consultation with the sponsor-designated Medical Monitor.

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and either TBL >2 × ULN or international normalized ratio (INR) >1.5, or
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

The discontinuation criteria are applicable for participants with no known liver disease and normal or near normal baseline liver tests of

- ALT< 2 × ULN
- TBL <1.5 × ULN, and
- ALP <1.5 × ULN.

Cardiovascular Safety

If a clinically significant finding is identified including, but not limited to, changes from baseline in QTcF after enrollment, the investigator or qualified designee will determine if the study participant can continue in the master protocol or ISA, and if any change in study participant management is needed.

This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the master protocol or ISA:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant
- if enrollment in any other clinical study involving an investigational intervention or enrollment in any other type of medical research judged not to be scientifically or medically compatible with the master protocol or ISA, or
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation should occur prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

If possible, an early discontinuation visit should be conducted at the time of discontinuing from the master protocol/DSA or an ISA. Data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed will be included in the master protocol/DSA and ISA. The participant will be permanently discontinued both from the study intervention and from the master protocol/DSA or ISA at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled in the master protocol/DSA or ISA, then the participant should be

discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment.

If the investigator and the sponsor clinical research physician agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the master protocol or ISA with or without treatment with investigational intervention.

Safety follow-up is outlined in

Section 1.3 (Schedule of Activities [SoA])

Section 8.2 (Safety Assessments), and

Section 8.3 (Adverse Events and Serious Adverse Events).

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Information about the discontinuation of specific sites or of the study are handled as part of the regulatory, ethical, and trial oversight considerations in Appendix 1.

8. Study Assessments and Procedures

Master protocol procedures and their timing are summarized in the SoA (Section 1.3). Additional SoAs are included in the DSA and may also be included in each ISA.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria for the master protocol, DSA, and each active ISA. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Self-reported questionnaires will be administered by either an electronic device or on paper. Participants' self-assessments should be completed before any clinical examinations are performed.

8.1. Efficacy Assessments

The master protocol contains a core set of assessments based on the IMMPACT guidelines (Dworkin et. al. 2005). This table describes the assessments and corresponding measures.

Core Assessment	Measure
Pain intensity	Visual Analog Scale (VAS)* for pain
Pain intensity	Numeric Rating Scale (NRS)* for pain
Participant ratings of overall improvement	Patient Global Impression of Change (PGI)*
Emotional functioning	EuroQol-5D 5 level questionnaire (EQ-5D-5L)*
Quality of sleep	Medical Outcomes Study (MOS) Sleep Scale*
Physical functioning	Described in each disease-state addendum

* = common endpoint measure across all pain types.

8.1.1. Screening and Preliminary Data Entry Period

Visual Analog Scale

The VAS for pain will be used at screening and at each clinic visit. This is a graphic, single-item scale where participants are asked to describe their pain intensity over the past week, in the area under study, on a scale of 0 to 100:

0 = no pain, and

100 = worst imaginable pain.

Participants complete the VAS by placing a line perpendicular to the VAS line at a point that describes their pain intensity. Inclusion criteria are described in Section 5.1.

Numeric Rating Scale

The NRS will be used during the PDEP and daily throughout the study to describe pain severity. This is a numeric, single-item scale where participants are asked to describe their average and worst pain over the past 24 hours, on a scale of 0 to 10:

0 = no pain, and

10 = pain as bad as you can imagine.

Participants complete the NRS daily using a take-home device. Inclusion criteria for the PDEP are described in Section 5.1. Participant compliance is reviewed at each clinic visit.

8.1.2. Primary Efficacy Outcome Measure–Pain Intensity using Numeric Rating Scale

The NRS is used across all disease states to assess pain intensity.

The primary outcome measure is the mean change from baseline to endpoint for average pain intensity as assessed by the NRS item

> 'Please rate your pain by selecting the one number [0-10] that describes your AVERAGE level of [area under study] pain during the past 24 hours.'

This measure was selected based on its demonstrated ability to detect changes in pain and its common use across the disease states under study.

Participants complete the NRS daily using a take-home device. Compliance is reviewed at each clinic visit.

8.1.3. Secondary Efficacy Outcome Measures

8.1.3.1. Numeric Rating Scale

A secondary measure is the mean change from baseline to endpoint for worst pain intensity as measured by the NRS item

> 'Please rate your pain by selecting the one number [0-10] that describes your WORST level of [area under study] pain during the past 24 hours.'

8.1.3.2. Participant Ratings on Overall Improvement

The Patient Global Impression of Change (PGI) is used across all disease states. It captures the participant's perspective of treatment apart from sub-aspects of the general improvement.

This is a numeric scale from 1 to 7:

1 = very much better, and

7 = very much worse.

The participant is asked to

> 'Mark the box that best describes how your pain symptoms are now, compared to how they were before you started taking this medicine.'

8.1.3.3. Emotional Functioning Assessments

The EQ-5D-5L health status questionnaire is used across all disease states.

The EQ-5D-5L is one of the most popular patient-completed instruments to address quality of life (Buchholz et. al. 2018). It is a descriptive system that includes 5 dimensions:

- mobility
- self-care
- usual activities
- pain/discomfort, and
- anxiety/depression.

The participant is asked to 'check the ONE box that best describes your health TODAY,' choosing from 5 options provided under each dimension. The scores on the 5 dimensions can be presented as a health profile or converted to a single summary index number.

The EQ-5D-5L also includes the EQ VAS, which records the participant's self-rated health on a vertical VAS of 0 to 100:

0 = the worst health you can imagine, and

100 = the best health you can imagine.

The instrument used in its EQ-5D-5L version is a short, reliable, validated, easy-to-complete scale with excellent test-retest reliability to address quality of life in relation to pain due to several diseases.

8.1.3.4. Sleep Quality

Sleep disturbance is an important issue in pain research. Among various available instruments, the Medical Outcome Study (MOS) Sleep Scale provides a unique, psychometrically validated score for sleep disturbance.

This scale consists of 12 questions addressing the past week. Participants report how often each sleep symptom or problem is present on a 5-point categorical scale ranging from 'all of the time' to 'none of the time.' The question about time to fall asleep is reported by a 5-point categorical scale and the quantity of sleep is reported as the average number of hours slept each night.

This scale has low administration burden, has been used in different pain studies, and has been validated in patients with neuropathic pain.

8.2. Safety Assessments

Planned time points for safety assessments are provided in the SoA (Section 1.3).

Standard safety assessments include

- physical examination
- vital sign and body weight measurements
- 12-lead ECGs
- clinical laboratory tests
- hepatic safety monitoring (Appendix 6, Section 10.6)
- C-SSRS, and

- spontaneously reported AEs.

8.2.1. Physical Examinations

A complete physical examination will be conducted at Visit 1, as specified in the SoA. Symptom-directed physical examinations may also be conducted at other visits, as determined by the investigator, if a participant presents with complaints.

8.2.2. Vital Signs

Vital signs (blood pressure, pulse rate, body temperature) will be measured with the participant in a sitting position, as specified in the SoA and as clinically indicated. Additional vital signs may be measured during the study visits if warranted, as determined by the investigator, or as detailed in the respective ISAs.

8.2.3. Electrocardiograms

Evaluating ECGs

Triplicate 12-lead ECGs will be collected as specified in the SoA and as clinically indicated using an ECG machine that automatically calculates the heart rate and measures pulse rate, RR, QRS, QT, and QTcF intervals. Post randomization ECGs will be included in the ISA.

The ECGs should be collected

- before any blood draws, procedures, or meals
- after the participant is supine for at least 5 minutes
- while the participant is supine, and
- as closely as possible in succession, approximately 1 minute apart.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more replicates than expected at a particular time point is allowed to ensure high quality records.

A qualified physician (the investigator or qualified designee) at the site will interpret the ECGs as soon after the time of ECG collection as possible and ideally while the participant is still present.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator or qualified designee will

1. assess the participant for symptoms (for example, palpitations, near syncope, syncope)
2. determine if any change in participant management is needed
3. determine if the participant can continue the study, and
4. document the review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Transmitting and Overreading Electrocardiogram Data

Digital ECGs will be transmitted electronically to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory will then conduct a full overread of the replicate ECGs (including all intervals). A report based on data from this overread will be issued

to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

If there are differences in ECG interpretation between the investigator or qualified designee and the cardiologist at the central ECG laboratory, the interpretation by the investigator or qualified designee will be used for study entry and immediate participant management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator or qualified designee must document the review of the final overread ECG report issued by the central ECG laboratory and any alert reports.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with standard collection requirements, the laboratory manual and the SoA.

The investigator must

- review the laboratory results,
- document this review, and
- report any clinically relevant changes occurring during the study as an AE.

The laboratory results must be retained with the source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the master protocol or ISA should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or Medical Monitor.

If such values do not return to normal or baseline within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

If laboratory values from nonprotocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Hepatic Safety Monitoring

Additional monitoring may be included in each ISA. If monitoring is more restrictive in the ISA, then it should be applied for those participants in the respective ISA.

Close Hepatic Monitoring

This table describes when close hepatic monitoring should occur.

If a participant with baseline...	has the following elevations…
ALT or AST <1.5 × ULN ALP <1.5 × ULN TBL <1.5 × ULN	ALT or AST ≥3 × ULN ALP ≥2 × ULN TBL ≥2 × ULN, except for those with Gilbert's syndrome
ALT or AST ≥1.5 × ULN ALP ≥1.5 × ULN TBL ≥1.5 × ULN	ALT or AST ≥2 × baseline ALP ≥2 × baseline TBL ≥2 × baseline, except for those with Gilbert's syndrome

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

The laboratory tests listed in Appendix 6, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated Medical Monitor.

At a minimum, this evaluation should include a physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, seizures) recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol use, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive Hepatic Evaluation

This table describes when a comprehensive evaluation should occur to search for possible causes of liver injury.

If a participant with baseline...	has the following elevations…
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN with hepatic signs/symptoms* OR ALT or AST ≥5 ×ULN
ALP <1.5 × ULN	ALP ≥3 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN, except for those with Gilbert's syndrome
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline with hepatic signs/symptoms* OR ALT or AST ≥3 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL≥1.5 × baseline, except for those with Gilbert's syndrome

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

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time (PT-INR); viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the sponsor's designated Medical Monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatology/gastroenterology consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or liver biopsy.

8.2.5.1. Hepatic Safety Electronic Case Report Form

This table describes when additional hepatic safety data collection in the hepatic safety eCRF should be done.

If a participant with baseline...	has the following elevations…
ALT <1.5 ×ULN	ALT ≥5 × ULN on 2 or more consecutive blood tests
ALP <1.5 × ULN	ALP ≥2 × ULN on 2 or more consecutive blood tests
TBL <1.5 × ULN	TBL ≥2 × ULN, except for cases of known Gilbert's syndrome
ALT ≥1.5 × ULN	ALT ≥3 × baseline on 2 or more consecutive blood tests
ALP ≥1.5 × ULN	ALP ≥2 × baseline on 2 or more consecutive blood tests
TBL ≥1.5 × ULN	TBL ≥2 × baseline

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

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

Additional criteria include

- a hepatic event considered to be an SAE, and
- discontinuation of study intervention due to a hepatic event (Section 7.1).

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Consideration should be given to discontinuing the study intervention in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Suicidal ideation and behavior will be monitored using the C-SSRS and self-harm forms.

C-SSRS and Self-Harm Forms

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group as a counterpart to the Columbia Classification Algorithm of Suicide Assessment (CCASA) categorization of suicidal events.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

The C-SSRS is currently referenced by the US Food and Drug Administration (FDA) (Guidance 2012) as an acceptable scale and is used in clinical trials for neuroscience and non-neuroscience compounds. The C-SSRS is included in the master protocol because prospective collection of suicidal thoughts and behaviors is recommended for compounds reviewed by the FDA's Division of Anesthesiology, Addiction Medicine, and Pain Medicine, as there is often an enhanced risk of depression in the populations under study. As noted in the FDA guidance, prospective questioning will help avoid misclassification of suicidal thoughts and behaviors and ensure that participants who are experiencing suicidal thoughts and behaviors are properly recognized and adequately treated.

The self-harm forms focus only on suicidal and nonsuicidal self-harm behaviors. The Self-Harm Supplement form is a single-question. If a self-harm event is identified, investigators will then complete the Self-Harm Follow-Up form, which provides a description of the behavior.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, that are considered related to the study intervention or study procedures, or that caused the participant to discontinue participation (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention until the follow-up visit.

All AEs will be collected from the signing of the ICF for the master protocol until participation in an ISA or the master protocol has ended, whichever is longest.

Medical occurrences that begin before the start of study intervention but after signing of the ICF will be recorded on the AE CRF.

Although all AEs that occur after signing of the ICF are recorded by the site in the CRF or by electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received study intervention.

If an SAE occurs after signing of the ICF, but prior to receipt of study intervention, then it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3, Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the ISA participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies will be collected in female participants and, if indicated in each ISA, female partners of male participants. The time period for collecting pregnancy information will be detailed in each ISA as applicable.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4, Section 10.4.

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Complaint Handling

Lilly collects product complaints on interventions used in clinical studies to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with an intervention so that the situation can be assessed.

8.4. Treatment of Overdose

In the event of an overdose, the investigator should

1. contact the Medical Monitor immediately
2. closely monitor the participant for any AEs/SAEs and laboratory abnormalities, and
3. document information about the overdose as specified in the ISA.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Additional guidance for the treatment of overdose will be described in the ISA as applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters may be evaluated in the ISAs governed by this protocol. Information on pharmacokinetic sample collection and parameter analysis will be described in the ISA as applicable.

Sample retention is described in Section 10.1.12.

8.6. Pharmacodynamics

Pharmacodynamic parameters may be evaluated in the ISAs governed by this protocol. Information on pharmacodynamic sample collection and parameter analysis will be described in the ISA as applicable.

Sample retention is described in Section 10.1.12.

8.9. Immunogenicity Assessments

Immunogenicity may be evaluated in the ISAs governed by this protocol. Information on immunogenicity sample collection and assessments will be described in the ISA as applicable.

See Section 10.1.12 for sample retention information.

8.10. Health Economics

The EQ-5D-5L is a quality of life assessment that can provide information for health economics assessments.

9. Statistical Considerations

9.1. Statistical Hypotheses

For each ISA in this master protocol, a Bayesian critical success factor (CSF) will be defined in the ISA and used to evaluate whether the ISA met its primary endpoint. The CSF will be evaluated for the primary efficacy endpoint, average pain intensity as measured by the NRS, using the methodology described in Section 9.4.2 and will be calculated at the conclusion of the double-blind portion of each ISA within the master protocol.

The CSF will have the general form of:

- probability (treatment effect < effect of interest) > probability threshold.

The treatment effect will be defined as the LY estimate–placebo estimate of the change from baseline at endpoint. The effect of interest is typically found through a literature search or clinical judgement. The probability threshold is generally set to have a desired level of confidence in the treatment effect or to have the desired operating characteristics under a range of plausible, assumed drug effect scenarios of truth, including a null effect.

Additional hypotheses will include the comparison of each active intervention with placebo for the prespecified objectives and endpoints defined in Section 3.

9.2. Sample Size Determination

The sample size, power, and false positive rate for each ISA within the master protocol will be provided and justified in the ISA.

The sample size and operating characteristics of each ISA within the master protocol will be evaluated by simulation. The simulations will include various assumed effect sizes and/or treatment differences and prior distribution specifications. Also provided will be a justification of how missing data are accounted for, if and how placebo or treatment-effect information is borrowed from other ISAs, and other key information needed to conduct a simulation study. Both sample size and operating characteristics may vary by ISA. The false positive rate is defined as the percentage of times the CSF is met, assuming that the treatment effect is 0 at all postbaseline visits and may vary by ISA.

An ISA that enters the master protocol later in calendar time may potentially randomize fewer participants, since there may be a bolus of placebo participants or treatment-effect information that can be borrowed and used in the primary efficacy analysis. Operating characteristics may also vary for the ISAs that enter later in calendar time for the same reason.

Each ISA will randomize to both the active intervention(s) and placebo [redacted]. Multiple intervention arms may be included in the ISA [redacted]

9.3. Populations for Analyses

This table describes the populations that will be used for statistical analyses within each ISA of the master protocol. Additional intervention-specific populations for analyses may be described in the ISAs.

Population	Description
Entered	All participants who sign the ICF for an ISA
Enrolled (ITT)	All participants randomly assigned to an ISA
Modified ITT (mITT)	All enrolled participants who take at least 1 dose of study intervention within an ISA. Participants will be analyzed according to the intervention they are randomly assigned.
Safety	All enrolled participants who take at least 1 dose of study intervention within an ISA. Participants will be analyzed according to the intervention they receive.
Enhanced ITT	This population includes all participants from the modified ITT population and participants from the supplementary ISAs that are used to borrow placebo/treatment effect information for the ISA of interest
Biomarker Evaluable	All participants within the subset of participants from the biomarker of interest from whom a valid assay result has been obtained within an ISA
Per-Protocol	Some ISAs may define this population, and details will be provided in the ISA or ISA SAP. Generally, participants will be required to have a certain level of compliance with the master protocol and ISA to be included in the population

Abbreviations: ICF = informed consent form; ISA = intervention-specific appendix; ITT = intention to treat; SAP = statistical analysis plan.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of the master protocol and ISAs will be the responsibility of the sponsor or its designee.

Multiple statistical analysis plans (SAPs) will be defined and used throughout the duration of the entire master protocol. A single master protocol SAP will be developed, as well as an ISA SAP, for each ISA.

The master protocol SAP describes the statistical analyses that are common across the entire master protocol, and the analyses will be conducted within each ISA. The analyses in the master protocol SAP will include

- disposition reports
- AE analyses
- laboratory analyses
- vital signs analyses, and
- efficacy analyses that do not specify borrowing of placebo or treatment-effect information from other ISAs.

A DSA SAP will not be developed. The DSA-specific analyses will be provided in the ISA SAP.

The ISA SAP will contain the statistical analyses unique for each ISA and will include

- the proposed strategy of borrowing placebo and/or treatment-effect information from other ISAs
- if borrowing of placebo or treatment effect information is implemented, the Bayesian model and exact prior distributions used for the primary efficacy analysis and other Bayesian secondary analyses, and
- details of analyses that are unique to the ISA or analyses that may differ from what is specified in the master protocol SAP.

If there is a discrepancy between the master protocol SAP and the ISA SAP, the methodology in the ISA SAP will be used.

Changes to the master protocol data analysis methods will require an amendment only if they change a principal feature of the master protocol. Any other change to the data analysis methods, and the justification for making the change, will be described in the respective SAP and the clinical study report for each respective ISA. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The master protocol SAP will be finalized prior to the unblinding of the first ISA. Any updates to the master protocol SAP will be finalized prior to the unblinding of the respective ISA.

The ISA SAP will be finalized prior to the first unblinding of the respective ISA.

The specific baseline definitions for each analysis will be provided in the master protocol SAP.

No adjustments for multiplicity will be performed unless specified in the ISA SAP.

If the primary efficacy analysis dataset for an ISA includes data from repeat participants, all available data for the repeat participants will be included and used in the model. A participant by ISA-specific random effect (or other appropriate adjustments) will be added to the primary efficacy analysis model to account for the repeat participants. Specific details will be provided in each ISA SAP.

9.4.1.1. Missing Data

The NRS value of average pain and worst pain over the past 24 hours will be collected daily for each participant. For the statistical analyses, the average NRS value of the average and worst pain over the past 24 hours will be calculated for both weekly intervals and biweekly intervals.

The average of the weekly intervals for the NRS will result in 8 postbaseline observations, and the average of the biweekly intervals will result in 4 postbaseline observations for each participant if a participant completes the placebo-controlled portion of the study.

The average of the weekly intervals for the NRS will be used in the primary efficacy analysis and other analyses described below, unless otherwise specified in the SAP.

A participant must have 50% or greater of the daily NRS values during the prespecified time interval to calculate the average NRS value; otherwise, the average NRS value for that visit will be considered missing.

Missing data for other variables and analyses will be described in the master protocol SAP.

For all Bayesian analyses, the missing values will be accounted for naturally using the Bayesian imputation of missing values.

9.4.2. Primary Endpoint and Analysis

The primary efficacy measure will be the same across all disease states and ISAs.

The primary efficacy analysis for an ISA will be conducted when all participants randomized to the ISA have completed the placebo-controlled portion of the ISA. The follow-up period may vary by ISA. Therefore, the primary efficacy analysis may be conducted prior to conclusion of the ISA and the collection of all follow-up data.

The primary efficacy analysis will be performed using a Bayesian MMRM method where the baseline information is modeled as a dependent variable. The baseline estimated means will be constrained to be the same between treatment groups due to randomization (Liang and Zeger, 2000). The primary efficacy analysis of the ISA of interest will be conducted on either the modified intention to treat (mITT) population or enhanced ITT population (see Section 9.3). The enhanced ITT population includes participant level data from ongoing ISAs and/or ISAs that have completed. Participants from ongoing ISAs must have had the opportunity to complete the placebo-controlled portion of the ISA to be included in the primary efficacy analysis for the ISA of interest. The ISA SAP will define the exact participant population included in the primary efficacy analysis.

The Bayesian CSF for the primary efficacy analysis will be defined in the ISA SAP for each respective ISA. The 95% credible intervals will be provided for the key parameters of interest.

This table describes information related to the primary efficacy measure.

Primary Efficacy Measure	Mean change from baseline to endpoint for average pain intensity as measured by the NRS. The exact endpoint for each ISA will be defined in the ISA SAP and may be defined, for example, as the last time point, the average of the last 2 time points, etc.
Data Collection	The NRS average pain will be collected daily. Average scores will be calculated over weekly and biweekly time intervals and will be available for analysis. The average of the weekly time-interval will be used for the primary efficacy analysis.
Primary Analysis	Efficacy of the active treatment(s) compared with placebo
Analysis Method	Bayesian MMRM analysis
Outcome Variable	The raw baseline and postbaseline values will be included in the response vector when fitting the statistical model. The change from baseline will be assessed via the statistical model.
Fixed Categorical Effects in Model	• Time interval • Interaction of treatment by time interval without the baseline • Average baseline pain severity category (moderate or mild vs severe), defined by baseline NRS <7 vs baseline NRS ≥7 • Pooled investigative site
Additional Covariates in Model	Any stratification variable used for randomization of the ISA of interest will also be included in the model. Additional covariates may also be specified at an ISA level.

Abbreviations: ISA = intervention-specific appendix; MMRM = mixed-model repeated measures; NRS = numeric rating scale; SAP = statistical analysis plan.

9.4.2.1. Key Features of the Bayesian Primary Efficacy Analysis Model

The primary efficacy analysis will be a Bayesian longitudinal MMRM analysis conducted on the NRS average pain score. The model will include the categorical effects and covariates described in Section 9.4.2. The change from baseline to each postbaseline time interval will be assessed.

The primary efficacy analysis model includes these key features:

- ability to borrow placebo information from other ISAs within the DSA using a suitable choice of informative prior on the key parameters
- ability to borrow treatment-effect information from other ISAs between DSA for the same intervention using a suitable choice of informative prior on the key parameters
- ability to update and tune the model parameters as more ISAs are added to the master protocol and more data become available
- flexibility for each ISA to define the amount of borrowing that will occur by specifying the prior distributions of key parameters in the ISA SAP
- ability to define which data from additional ISAs are included in the model
- flexibility to include additional covariates for each ISA as needed, and
- option to specify informative priors on some model parameters based on external data sources, for example, utilization of Bayesian Augmented Control for placebo parameters and data to inform other key parameters.

The ISA SAP will contain the exact specification of the model and parameters for the respective ISA.

Borrowing Strategy

Each ISA will define the specific decisions on the borrowing of placebo and treatment-effect information, including if borrowing will be implemented and, if so, how much information to borrow and the specific methodology used to borrow. These decisions may vary over the course of the master protocol, as some borrowing strategies may perform better than others as more data are available to borrow.

Specific differences between ISAs, for example, method of administration or additional inclusion or exclusion criteria, may impact the borrowing strategy for an ISA. Adjustments may also be made to the primary analysis model to incorporate the difference in placebo response in different time periods to facilitate efficient borrowing between the placebo participants.

The current borrowing strategies considered across the master protocol for each ISA include

- pooling of placebo data between ISAs within a disease state
    - note: pooling is not being considered for borrowing treatment-effect information for an intervention studied in multiple disease states
- use of a hierarchical model with an appropriate prior on the between-study standard deviation (SD) (or variance) term that influences the amount of borrowing
- commensurate priors with different mixture probability weights
- mixture priors
- meta-analytic predictive prior or meta-analytic combined prior, and
- model fit with respective ISA data only (no utilization of information from other ISAs).

9.4.3. Secondary Endpoints and Analysis

The secondary efficacy measures will be the same across all disease states and ISAs.

9.4.3.1. Continuous Efficacy Analyses

This table describes information related to the continuous secondary efficacy measures and analyses.

Key Secondary Measures	• NRS worst pain • VAS for pain • PGI • MOS Sleep Scale • EQ-5D-5L • Physical functioning–described in the DSA
Data Collection	The NRS worst pain will be collected daily. The scores for the other secondary measures will be collected at each visit as described in the visit schedule.
Analyses	Efficacy of active treatment(s) compared with placebo
Analysis Method	Same as primary efficacy analysis
Outcome Variable	The raw baseline and postbaseline values will be included in the response vector when fitting the

	statistical model. The change from baseline will be assessed via the statistical model
Fixed Categorical Effects in Model	• Time interval (or visit) • Interaction of treatment by time interval (or visit) without the baseline • Average baseline pain severity category (moderate vs severe), defined by baseline NRS <7 vs baseline NRS ≥7 • Pooled investigative site
Additional Covariates in Model	Additional covariates may also be specified at an ISA level.

Abbreviations: DSA = disease-state addenda; EQ-5D-5L = EuroQol-5D 5 level questionnaire; ISA = intervention-specific appendix; MOS = Medical Outcomes Study; NRS = numeric rating scale; PGI = Patient Global Impression of Change; VAS = visual analog scale.

In addition to the primary efficacy analysis of the NRS average pain score, the change from baseline to each postbaseline time interval (or visit) will be analyzed using a similar Bayesian MMRM method as the primary efficacy analysis for select scales. A similar participant population and borrowing strategy of the primary efficacy analysis for the ISA will be implemented for each scale. The ISA SAP will contain the exact specification of the model and parameters for each scale. The model will be fit for the following scales:

- NRS worst pain with weekly average values
- VAS, and
- physical functioning scales described in each DSA (note: direct treatment-effect borrowing will not be available for the physical functioning scales, since they are only collected within a DSA).

Similar borrowing and modeling may be considered for other efficacy scales. The ISA SAP will contain the exact specification of the model and parameters for each scale.

Additional analyses will be conducted using data only from the respective ISA, which do not utilize any borrowing of placebo and/or treatment information. A Bayesian MMRM analysis will be used to evaluate the change from baseline to each postbaseline time interval (or visit) and the comparison of treatment groups within an ISA for

- NRS average pain
- NRS worst pain
- VAS
- physical functioning scales described in each DSA
- PGI
- EQ-5D-5L, and
- MOS Sleep Scale multi-item scores of sleep disturbance, somnolence, sleep adequacy, and the sleep problems index.

The Bayesian models will include the categorical effects and covariates described in Section 9.4.3, unless otherwise noted in the ISA SAP.

9.4.3.2. Categorical Efficacy Analyses

The proportion of participants in each treatment group meeting prespecified binary efficacy outcomes will be estimated for each postbaseline visit. The estimates will be provided from a longitudinal Bayesian model that includes all postbaseline observations. The average weekly score for the NRS will be computed and used in the comparison between treatment groups within an ISA.

The prespecified binary efficacy outcomes include the proportion of participants

- with a pain reduction greater than or equal to 30%, 50%, and 70% from baseline as measured by the NRS average pain scale
- with a pain reduction greater than or equal to 30%, 50%, and 70% from baseline as measured by the NRS worst pain scale
- with a pain reduction greater than or equal to 30%, 50%, and 70% from baseline as measured by the VAS
- with at least 2-point reduction from baseline on the NRS average pain scale
- with at least 2-point reduction from baseline on the NRS worst pain scale, and
- with an improvement in physical function greater than or equal to 30%, 50%, and 70% from baseline as measured by the physical functioning scales defined in the DSA.

The models will include treatment, time interval (or visit), interaction between treatment by time interval (or visit), average baseline pain severity category (moderate vs severe) as defined by baseline NRS less than 7 versus baseline NRS greater than or equal to 7 and pooled investigative site, unless otherwise noted in the ISA SAP. The ISA SAP will contain the exact specification of the model and parameters for the respective ISA.

9.4.3.3. Time to Event Efficacy Analyses

A Kaplan-Meier analysis will be conducted for these outcomes:

- time to first pain reduction of at least 30%, 50%, and 70% from baseline as measured by the NRS average pain scale
- time to first pain reduction of at least 30%, 50%, and 70% from baseline as measured by the NRS worst pain scale
- time to first pain reduction of at least 2-points from baseline on the NRS average pain scale, and
- time to first pain reduction of at least 2-points from baseline on the NRS worst pain scale.

For the time to event analyses, participants who do not have the event of interest by the end of the treatment phase will be treated as a right censored observation.

For these analyses, the average score over a weekly interval for the NRS will be computed and used in the analysis. In addition, time to event analyses will also be performed using the daily NRS scores.

The ISA SAP will contain the exact specification of the model and parameters for the respective ISA.

9.4.4. Tertiary/Exploratory Endpoints

A cumulative distribution function of percent change from baseline to endpoint for the NRS average and worst pain scales and the VAS will be provided for each treatment group. No statistical comparisons will be made between the groups.

Appropriate statistical methods will be used to understand the relationship of the biomarker endpoints to other clinical endpoints in terms of treatment effect. Any intervention-specific tertiary/exploratory analyses will be described in the respective ISA.

9.4.5. Treatment Group Comparability

9.4.5.1. Participant Disposition

Participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported for each ISA. A detailed description of participant disposition and the reasons for discontinuation will be summarized by treatment group for each ISA at the end of the study. Intervention-specific analyses will be detailed in each respective ISA.

9.4.5.2. Participant Characteristics

Participant characteristics and baseline clinical measures will be summarized for each treatment period. For all participant characteristics, the summaries will include descriptive statistics for continuous measures (sample size, mean, SD, median, minimum, and maximum) and for categorical measures (sample size, counts and percentages).

Additional intervention-specific analyses will be specified in each respective ISA.

9.4.5.3. Concomitant Therapy

Concomitant medications used during the study will be listed and summarized for each ISA.

The average intake (in milligrams) per day of the approved pain rescue therapy acetaminophen will be summarized by weekly intervals for each treatment group. The average intake per day over the entire placebo-controlled phase will also be compared and summarized between treatment groups.

9.4.5.4. Treatment Compliance

Treatment compliance with the study intervention will be summarized by treatment for each ISA. Intervention-specific analyses will be described in the respective ISAs.

9.4.6. Safety Analyses

All safety analyses will be conducted on the Safety Population for each ISA.

9.4.6.1. Vital Signs Analyses

The mean change from baseline in pulse rate, systolic and diastolic blood pressure, temperature, and weight will be summarized for each treatment group. The incidence of treatment-emergent abnormal high and low vital signs and weight will be summarized by treatment group.

9.4.6.2. Electrocardiogram Analyses

The mean change from baseline will be summarized by treatment group for the following ECG parameters: heart rate, PR interval, QRS duration, QT interval, and QTcF interval. All analyses of corrected QT will be carried out using Fridericia's correction factor [$QTcF=QT/RR^{0.333}$]). The incidence of treatment-emergent abnormal high and low changes in heart rate, PR interval, QRS duration, and QTcF interval will be summarized.

The number and percentage of participants with a QT interval greater than 500 msec and the percentage with a QTcF greater than 500 msec will be summarized for each treatment group. The percentage of participants who experienced a treatment-emergent increase from the maximum baseline in QTcF interval of greater than 30 msec, 60 msec, or 75 msec at any time will also be summarized.

9.4.6.3. Laboratory Assesment Analyses

The mean change from baseline laboratory assessments will be summarized for each treatment group. The incidence of treatment-emergent abnormal high and low laboratory assessments will be summarized by treatment group. In addition, listings of abnormal findings for laboratory analyte measurements, including qualitative measures, will be provided.

9.4.6.4. Adverse Events

Adverse events will be classified by system organ class and preferred term as defined by the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity after baseline and on or before the date of the last visit within the dosing period.

All conditions existing prior to randomization at Visit 3 will be used as baseline. The postbaseline visits during the placebo-controlled phase will be included as the postbaseline period for analysis.

For events that are gender specific, the denominator and computation of the percentage will only include participants of the given gender.

All AEs will be summarized by

- number and percentage of participants who experience TEAEs
- TEAEs by maximum severity
- TEAEs related to study intervention
- follow-up emergent AEs
- AEs leading to discontinuation of intervention
- AEs leading to discontinuation from the study
- SAEs, and
- deaths.

All AEs, including preexisting conditions, will be listed by

- participant
- visit
- preferred term

- treatment group
- severity (mild, moderate, or severe), and
- possible relationship to the study intervention.

Adverse events of special interest will be defined in the ISA.

9.4.6.5. Columbia Suicide-Severity Rating Scale

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (CSSRS [WWW]).

9.4.7. Subgroup Analyses

Subgroup analyses will be conducted for the primary efficacy measure of NRS average pain. The subgroup analyses will be provided for the following subgroups using data from the respective ISA only:

- baseline pain severity: baseline pain severity category (moderate vs severe) defined by baseline NRS average pain <7 versus baseline NRS average pain ≥7
- gender, and
- pooled investigative site.

For the subgroups of baseline pain severity and gender, the Bayesian MMRM method described in Section 9.4.2 will be utilized, with the relevant terms added for subgroup, subgroup-by-treatment, subgroup-by-time interval without the baseline, and subgroup-by-treatment-by time interval interactions without the baseline. For the pooled investigative site subgroup analysis, the change from baseline to endpoint will be evaluated using a Bayesian model with terms for pooled investigative site, baseline pain severity, and treatment-by-pooled investigative site interaction.

9.4.8. Sensitivity Analysis

Sensitivity analyses of the primary efficacy analysis will be conducted to evaluate the impact of the borrowing of placebo and treatment-effect information, as well as the impact of missing data.

A tipping point analysis will also be conducted to evaluate the impact of missing data for the primary efficacy analysis.

The details of the sensitivity analyses will be provided in the ISA SAP.

9.5. Interim Analyses

The master protocol will not require or specify interim analyses for a specific ISA. If an interim analysis is planned for an ISA, the details (for example, timing, rationale, use of participants in other ISAs) will be provided in the ISA or ISA SAP. The potential reasons for interim analyses could include futility analyses, early efficacy analyses, safety analyses, or other analyses needed for key business decisions and planning.

Unblinding details will be specified in the unblinding plan section of the respective ISA SAP or in a separate unblinding plan document.

9.6. Data Monitoring Committee

The AC will provide oversight for safety by reviewing unblinded data for each ISA. The structure and the responsibilities of the AC will be detailed in the AC charter.

Safety analyses for review will be detailed in each ISA SAP and in the AC charter.

The AC may evaluate additional objectives that are specific to an individual ISA, for example, assessing futility or early efficacy. If this is requested, details will be specified in the AC charter.

The committees that will be established to support the master protocol and ISA teams are described in Appendix 1, Section 10.1.5.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - applicable International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an ERB by the investigator and reviewed and approved by the ERB before the study is initiated.
- Any amendments to the protocol will require ERB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - providing written summaries of the status of the study to the ERB annually or more frequently in accordance with the requirements, policies, and procedures established by the ERB
  - notifying the ERB of SAEs or other significant safety findings as required by ERB procedures, and
  - providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the ERB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests for the master protocol and each ISA in which the investigator participates and for 1 year after completion.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the master protocol and eligible ISAs.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the ERB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the master protocol and ISA, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

These committees will be established to support the master protocol and ISA teams:

- Assessment Committee (AC), and
- Internal Steering Committee, including a Statistical Analysis Subcommittee (SASC).

The AC will routinely (for example, quarterly) evaluate safety for all ISAs within the master protocol. The safety reports will be provided for an ISA only and, as appropriate, for the aggregate data of an intervention if it is studied in multiple disease states.

The Internal Steering Committee will be established to support the strategic and technical integration of the master protocol to achieve Lilly's overarching clinical development needs.

The Internal Steering Committee will function as a resource group to provide oversight of the master protocol including consultation, advice, analysis, and feedback to clinical teams and other

interested parties during the study. It will be composed of cross-functional representatives from departments such as medical, statistics, clinical operations, and project management.

The SASC will be a small cross-functional group that will function as an expert panel for consultation, advice, and feedback to the Internal Steering Committee and the ISA teams. One of the primary roles of the SASC is to generate the master protocol level integrated datasets, which include data from completed and ongoing ISAs. Thus, the SASC will be unblinded to data from both ongoing and completed ISAs. The SASC will

- provide the AC with unblinded safety reports,
- be responsible for communication with the AC, and
- generate analysis reports for ongoing or completed ISAs based on the integrated datasets..

10.1.6. Dissemination of Clinical Study Data

A clinical study report will be provided for each ISA.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on a printed or electronic case report form (CRF), unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, ERB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study and each ISA must be retained by the investigator for 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, electronic clinical outcome assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant into a provisioned hand-held device. The eCOA data will serve as the source documentation, and the investigator does not maintain a separate written or electronic record of these data. Authorized study personnel will monitor participant compliance with eCOA entry and re-educate participants on the importance of compliance as necessary. Some eCOA data values may be blinded to the site during the study to minimize any potential rating bias.

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Data collected via the sponsor-provided data capture systems will be stored at a vendor selected by the sponsor. The investigator will have continuous access to the unblinded data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of all eCOA data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

- failure of the investigator to comply with the protocol, the requirements of the ERB or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator, or
- discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ERB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of the ISAs conducted as a part of this master protocol or other relevant learning materials may be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers at qualified clinical trial sites and with experience in the treatment of chronic pain will participate as investigators in this clinical trial.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of the intervention or after the intervention becomes commercially available.

*Retention periods may differ locally.

The sponsor has the right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the study site. Slides and tissue samples collected during the study will not be returned.

10.2. Appendix 2: Clinical Laboratory Tests

The clinical laboratory tests will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

If the sponsor approves local laboratory testing in lieu of central laboratory testing, the local laboratory must be qualified in accordance with applicable local regulations.

Pregnancy testing will be done prior to randomization as noted in the SoA, Section 1.3. Additional testing will be detailed in each ISA.

Investigators must document their review of laboratory safety results.

Clinical Laboratory Tests

Chemistry	Hematology and Differential	Urinalysis	Urine Drug Screen	Other Tests
Sodium	Hemoglobin	Specific gravity	Antidepressants	**Hormones (female)**
Potassium	Hematocrit	pH	Opiates	Pregnancy test (serum, urine)
Chloride	Erythrocyte count (RBC)	Protein	Cocaine	FSH
Bilirubin, total	MCV	Glucose	Benzodiazepines	Estradiol
Bilirubin, direct	MCH	Ketones	Barbiturates	TSH
ALP	MCHC	Bilirubin	Amphetamines	**Other**
ALT	Leukocytes (WBC)	Urobilinogen	Cannabinoids	HbA1C
AST	**Differential (absolute)**	Blood	Methadone	HIV
Urea nitrogen (BUN)	Neutrophils	Nitrite	Phencyclidine	
Creatinine, enzymatic	Bands	Leukocyte esterase	Propoxyphene	
Protein	Lymphocytes	Microscopic examination of sediment		
Albumin	Monocytes			
Calcium	Eosinophils			
Glucose	Basophils			
Cholesterol	Platelets			
Triglycerides	Cell morphology (RBC, WBC)			
eGFR calculated by CKD-EPI equation				
B12				
Methylmalonic acid				
Homocysteine				
Lipid Panel				
HDL-C				
LDL-C				

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HbA1C = hemoglobin A1C; HDL = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells.


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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE, unless it is an intentional overdose taken with possible suicidal/self-harming intent. Report such overdoses regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been admitted to the hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

- **Results in persistent disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In these cases, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A 'reasonable possibility' of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in the assessment. • For each AE/SAE, the investigator **must** document in the medical notes that they reviewed the AE/SAE and provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee. • The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information. • If a study participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data

collection tool to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE data collection tool or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the Operations Manual.

SAE Reporting to via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Operations Manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Definitions of woman of childbearing potential (WOCBP) and woman of nonchildbearing Potential (WONCBP) will be provided in each ISA.

Contraception Guidance:

Contraception guidance will be provided in each ISA.

Collection of Pregnancy Information:

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male study participant is in this trial. This applies only to male study participants who receive intervention.

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 of learning of the partner's pregnancy. 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 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 up 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 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 <22 weeks gestational age) or still birth (occurring at >22 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 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.


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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Samples for selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required during follow-up with participants in consultation with the clinical research physician of the sponsor or sponsor's designee.

This table describes hepatic-specific monitoring tests.

Hepatic Evaluation Testing Central testing required, except for microbiology. Local testing may be performed in addition to central testing when required for immediate participant management.	
	Comments:
Hematology	
Hemoglobin	
Hematocrit	
Erythrocytes (RBC)	
Leukocytes (WBC)	
Differential:	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Basophils	
Eosinophils	
Platelets	
Cell morphology (RBC and WBC)	
Coagulation	
Prothrombin time, INR (PT-INR)	
Clinical Chemistry	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Creatine kinase (CK)	

Other Chemistry	
Acetaminophen	
Acetaminophen protein adducts	
ALP isoenzymes	
Ceruloplasmin	
Copper	
Haptoglobin	
Immunoglobulin A (IgA) (quantitative)	
Immunoglobulin G (IgG) (quantitative)	
Immunoglobulin M (IgM) (quantitative)	
Phosphatidylethanol (PEth)	
Urine Chemistry	
Drug Screen	
Ethyl glucuronide (EtG)	
Serology	
Hepatitis A virus (HAV) testing:	
HAV total antibody	
HAV IgM antibody	
Hepatis B virus (HBV) testing:	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B surface antibody (anti-HBs)	
Hepatitis B core total antibody (anti-HBc)	
Hepatitis B core IgM antibody	
Hepatitis B core IgG antibody	
HBV deoxyribonucleic acid (DNA)	
Hepatis C virus (HCV) testing:	
HCV antibody	
HCV ribonucleic acid (RNA)	
Hepatitis D virus (HDV) testing:	
HDV antibody	
Hepatitis E virus (HEV) testing:	
HEV IgG antibody	
HEV IgM antibody	
HEV RNA	

Other Serology	
Anti-nuclear antibody (ANA)	
Anti-smooth muscle antibody (ASMA)	This is not required if anti-actin antibody is tested.
Anti-actin antibody	This is not required if ASMA is tested.
Epstein-Barr Virus (EBV) testing:	
EBV antibody	
EBV DNA	
Cytomegalovirus (CMV) testing:	
CMV antibody	
CMV DNA	
Herpes simplex virus (HSV) testing:	
HSV (type 1 and 2) antibody	
HSV (type 1 and 2) DNA	
Liver kidney microsomal type 1 (LKM-1) antibody	
Microbiology	Assayed by investigator-designated local laboratory ONLY; no central testing available.
Culture:	
Blood	
Urine	

Abbreviations: INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

10.7. Appendix 7: Abbreviations

Term	Definition
AC	Assessment Committee
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) intervention, whether or not related to the medicinal (investigational) intervention.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CCASA	Columbia Classification Algorithm of Suicide Assessment
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSF	critical success factor
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DPNP	diabetic peripheral neuropathic pain
DSA	disease-state addenda
eCOA	electronic clinical outcome assessment
EDC	electronic data capture
ECG	electrocardiogram

enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol-5D 5 level questionnaire
ERB	ethical review board
ERCP	endoscopic retrograde cholangiopancreatography
FDA	US Food and Drug Administration
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
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.
intervention	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way that is different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ISA	intervention-specific appendix

ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MOS	Medical Outcomes Study
MCRP	magnetic resonance cholangiopancreatography
NIMH	National Institute of Mental Health
NRS	numeric rating scale
participant	Equivalent to CDISC term 'subject': an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control.
PDEP	preliminary data entry period
PGI	Patient's Global Impression of Change
PT	prothrombin time
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SASC	Statistical Analysis Subcommittee
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.
SD	standard deviation
SoA	schedule of activities
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TENS	transcutaneous electrical nerve stimulation

ULN	upper limit of normal
VAS	visual analog scale

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