This study H0P-MC-OA02 (NCT05080660) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

Protocol: H0P-MC-OA02 (a)

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3526318 for the Treatment of Osteoarthritis Pain

NCT05080660

Approval Date: 10-Aug-2021

Title Page

Intervention-Specific Appendix (ISA) for LY3526318: H0P-MC-OA02(a)

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

Master Protocol Number: H0P-MC-CPMP

ISA Title: Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3526318 for the Treatment of Osteoarthritis Pain

ISA Number: H0P-MC-OA02

Amendment Number: a

Compound: LY3526318

Study Phase: 2

Acronym: OA02

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number

LY3526318 IND: 150191

Master Protocol IND: 144915

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

Approval Date: 10-Aug-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	04-Jun-2021

Amendment [a]

Overall Rationale for the Amendment:

This amendment addresses changes in the exclusion criteria in response to FDA feedback based on *in vitro* data currently available.

Section # and Name	Description of Change	Brief Rationale
2.3. Benefit/Risk Assessment	Added sub-section headers.	For clarity.
2.3.1. Risk Assessment	In first paragraph, added text for the effect of LY3526318 on other drugs.	Clarification of the potential of LY3526318 exposure to affect metabolism of other drugs.
2.3.1. Risk Assessment	Updated first bullet to specify CYP3A4, plus minor editorial changes.	For clarity.
2.3.1. Risk Assessment	Added a bullet for CYP3A4 and p-glycoprotein (P-gp) substrates.	Based on in vitro data suggesting a potential for PK interactions.
5.1. Study Population	Updated numbers for inclusion and exclusion criteria.	To align with master protocol and ISA numbering system.
	Updated criterion #1051 to specify drugs taken orally or intravenously.	Topical drugs are allowed.
	Added exclusion criterion #1054 for participants that are taking drugs that are sensitive CYP3A4 substrates with a narrow therapeutic index.	Based on in vitro data suggesting potential CYP3A4 inhibition at the proposed LY3526318 dose.
	Added exclusion criterion #1055 for participants that are taking simvastatin at doses greater than 20 mg/day.	Simvastatin is a sensitive CYP3A4 substrate, with a projected maximal increase in exposure <2-fold in combination with LY3526318. Therefore, doses of 20 mg or less are considered safe.
	Added exclusion criterion #1056 for participants that are taking metformin at doses greater than 1000 mg/day.	Based on limited data related to inhibition of renal transporters.
	Added exclusion criterion #1057 for participants that are taking digoxin.	Based on in vitro data suggesting a potential for LY3526318 to inhibit P-gp.
6.6. Concomitant Therapy	Under Potential Drug-Drug Interactions with LY3526318, added reference to Section 5.2 for concomitant medication restrictions.	Reference to added exclusion criteria.

Section # and Name	Description of Change	Brief Rationale
10.3. Appendix 3: List of Excluded Concomitant Medications	Added reference to Section 5.2 and the Manual of Operations for additional information.	Additional information for excluded concomitant medications are listed in Section 5.2 and the Manual of Operations.
Throughout the protocol	Minor editorial and format changes.	Minor, therefore not described.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Randomized, placebo-controlled, Phase 2 clinical trial to evaluate LY3526318 for the treatment of osteoarthritis pain.

Rationale:

The purpose of this study is to test whether LY3526318 is efficacious in relieving knee pain due to osteoarthritis (OA). LY3526318 is a small molecule that inhibits transient receptor protein ankyrin 1, a calcium permeable nonselective cation channel that is known to be involved in pain and inflammation.

Data will be collected to assess the safety and tolerability of LY3526318 in this study population. Pharmacokinetic properties will also be explored. The totality of data from this proof-of-concept study will assess the benefits and risks associated with LY3526318 and inform decisions for the clinical development of LY3526318.

Objectives and Endpoints:

The primary and secondary objectives and endpoints are stated in the Master Protocol H0P-MC-CPMP (CPMP) and OA disease-state addendum (DSA; H0P-MC-CPMP[1]).

Overall Design:

This is an 8-week, Phase 2, randomized, double-blind, placebo-controlled study that will compare LY3526318 versus placebo in participants with OA in the knee.

Disclosure Statement:

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

Number of Participants:

Approximately 150 participants will be randomly assigned to study intervention CCI) with the assumption that 15% of the participants will drop out prior to the end of the double-blind treatment period.

Intervention Groups and Duration:

This study includes an 8-week double-blind treatment period.

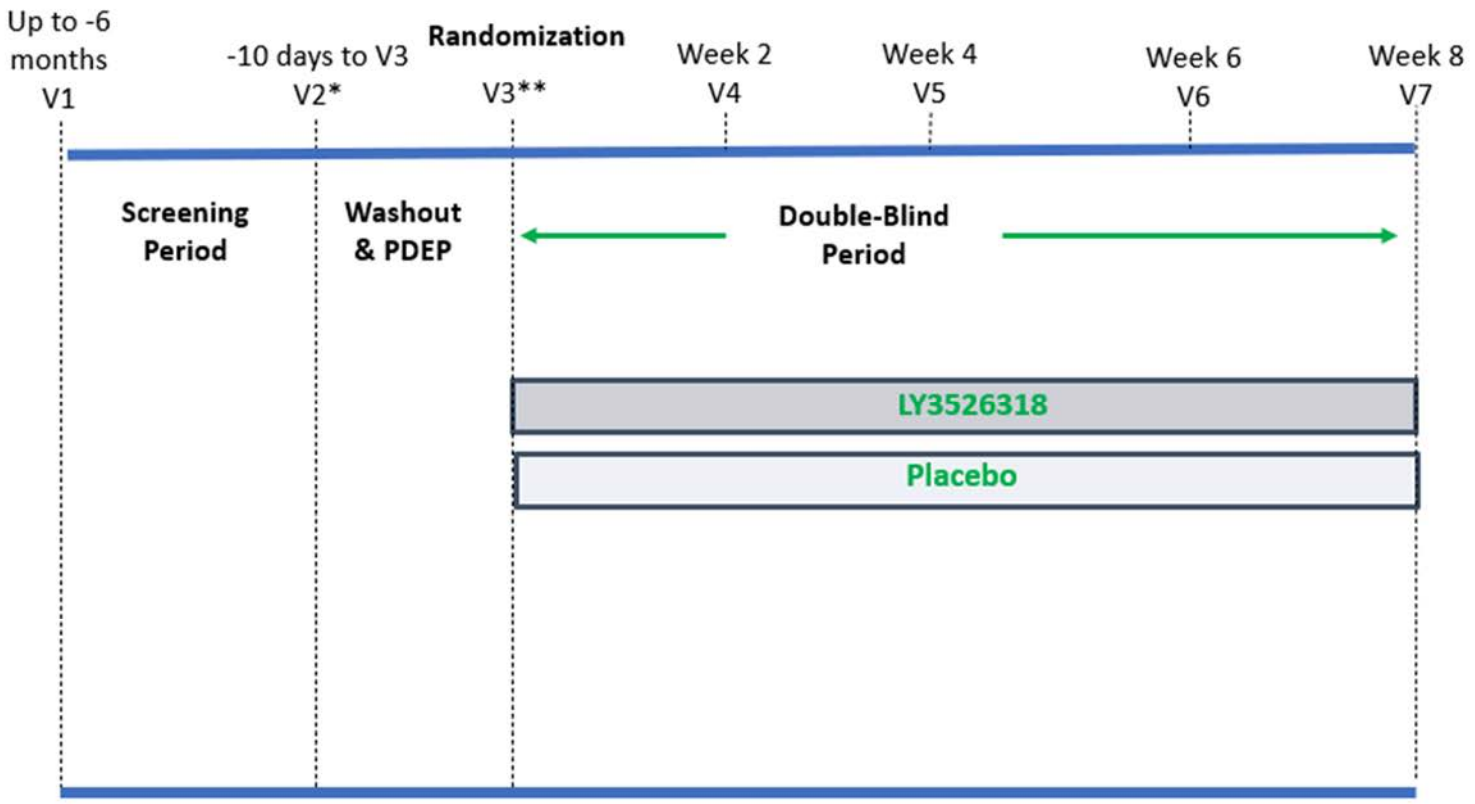
Intervention Name	LY3526318	Placebo
Dosage Level(s)	CCI	Not applicable
Route of Administration and Duration	PO	PO

Abbreviations: PO = by mouth; QD = once daily.

Data Monitoring Committee: Yes

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

1.2. Schema



Abbreviations: PDEP = preliminary data entry period; V = visit.
* Medication washout and PDEP begins.
** Randomization to either LY3526318 or placebo.

1.3. Schedule of Activities (SoA)

This SoA shows visits and procedures unique to the intervention-specific appendix (ISA) H0P-MC-OA02 for LY3526318. Please refer to the CPMP Master Protocol and the OA DSA H0P-MC-CPMP(1) SoAs for additional information.

	Randomization to ISA	Double-Blind Treatment				Early Discontinuation	Notes
	V3	V4	V5	V6	V7	ED	
Study Week	0	2	4	6	8		
Visit Window (days)		±3					
Physical examination	X		X		X	X	Symptom directed physical exam (see Section 8.2.1) at V5, V7, and ED (if applicable).
Vital signs	X	X	X	X	X	X	At V3, vitals should be taken predose and at approximately 2 and 4 hours post dosing. At V4, V5, V6, and V7, vitals should be taken predose. Pulse rate, respiratory rate, blood pressure, and temperature taken with participant in a sitting position.
ECG			X		X	X	Single ECGs at V5, V7, and ED (if applicable).
Study intervention	X	X	X	X	X		See Section 6.1
Intervention compliance		X	X	X	X	X	
Clinical Laboratory Tests and Sample Collection							
Hematology		X	X	X	X		
Chemistry		X	X	X	X		
Lipid panel		X	X	X	X		
Urinalysis					X		
Urine pregnancy	X	X	X	X	X	X	For all WOCBP at V3: collect sample before dosing.
Urine drug screen	X		X		X	X	See Section 5.3.2.
HbA1c	X				X	X	

	Randomization to ISA	Double-Blind Treatment				Early Discontinuation	Notes
	V3	V4	V5	V6	V7	ED	
Study Week	0	2	4	6	8		
Visit Window (days)		±3					
PK sample	X	X	X	X	X	X	At V3, samples should be taken at 2 and 4 hours (±15 minutes) post dosing. At V4, V5, V6 and V7, a sample for PK should be taken before the dose is administered; participants should be asked to refrain from taking their dose on V4-V7 until they have their clinic visit and after the blood sample is taken. The date and time of LY3526318 administration prior to the PK sampling will be recorded, i.e., the dose administered in the clinic at V3 and the last at home dose prior to each of V4, V5, V6, and V7.
CCI							
Participant Device							
Participant returns device					X	X	CCI

Abbreviations: CCI ; ECG = electrocardiogram; ED = early discontinuation; HbA1c = hemoglobin A1c; ISA = intervention-specific appendix; PK = pharmacokinetic; V = visit; WOCBP = women of childbearing potential.

2. Introduction

This intervention-specific appendix (ISA) H0P-MC-OA02 (OA02) is an appendix to the H0P-MC-CPMP (CPMP) Master Protocol and contains unique study elements specific for LY3526318. The master protocol contains the overarching study elements that govern the osteoarthritis (OA) disease-state appendix (DSA) CPMP(1) and this ISA OA02.

2.1. Study Rationale

The purpose of this study is to test whether LY3526318 is efficacious in relieving knee pain due to OA. Data will be collected to assess the safety and tolerability of LY3526318 in this study population. Pharmacokinetic (PK) properties will also be explored. The totality of data from this proof-of concept (PoC) study will assess the benefits and risks associated with LY3526318 and inform decisions for the clinical development of LY3526318.

2.2. Background

The transient receptor potential (TRP) ion channel family comprises a group of 28 nonselective cation channels that are distinct from classical voltage gated ion channels. Among these, transient receptor potential ankyrin 1 (TRPA1) is a calcium-permeable nonselective cation channel, which is expressed in the axons and in both peripheral and central terminals of nociceptors. It is also considered to be important as a chemosensor of nociception (Kovisto et al. 2018; Maatuf et al. 2019; Wang et al. 2019). TRPA1's involvement in pain and inflammation and its localization in sensory neurons are known (Bodkin and Brain 2011; Ückert et al. 2017). Due to its role in evoking pain and eliciting an aversive response, TRPA1 may be a promising target for treating pain (Benemei et al. 2017; Berta et al. 2017; Demartini et al. 2017; Maatuf et al. 2019; Wang et al. 2019).

LY3526318 is an orally administered, potent, and selective novel antagonist of TRPA1 under development by Lilly.

LY3526318 has been evaluated in 2 completed and 1 ongoing Phase 1 clinical studies.

Completed Study	J2D-MC-CVAA (CVAA)
Population	Healthy participants
Study Design	2-part, placebo-controlled, randomized, single and multiple-dose escalation study.
LY3526318 Dose	CCI [redacted]

Objectives	Part A: To evaluate safety, tolerability, and PK of LY3526318 in healthy participants following a single oral dose. Part B: To evaluate safety, tolerability, and PK of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days.

Completed Study	J2D-MC-CVAB (CVAB)
Population	Healthy female participants
Study Design	Randomized, double-blind, placebo-controlled, 4-way crossover study.
LY3526318 Dose	Each participant was randomly assigned to receive 4 unique doses of study drug in a ratio of 3 LY3526318: 1 placebo, in a crossover manner with at least 14 days of washout between doses. CCI [redacted]
Objectives	To assess target engagement of TRPA1 with cinnamaldehyde (CA)-induced dermal blood flow (DBF) after a single dose of LY3526318.

Ongoing Study	J2D-MC-CVAC (CVAC)
Population	Healthy participants
Study Design	Randomized, double-blind, placebo-controlled, SAD (Part A) and multiple dose (MD; Part B) study.
LY3526318 Dose	CCI [redacted] [redacted]
Objectives	Part A: To evaluate the safety, tolerability, and PK of LY3526318 after a single oral dose administration. Part B: To evaluate the safety, tolerability, and PK of LY3526318 after multiple oral dose administrations.

Pharmacokinetics

CCI [redacted]

[redacted]

Pharmacodynamics

[redacted]

Safety

[redacted]

2.3. Benefit/Risk Assessment

Clinical Safety

In Study CVAA, no clinically significant safety or tolerability concerns were identified at the highest single dose administered (CCI) or the highest multiple dose administered (CCI). Additionally, preliminary data using a new formulation of LY3526318 in Study CVAC showed no clinically significant safety or tolerability concerns at higher exposures following single or multiple doses CCI

Toxicology Studies and NOAEL Exposure

CCI

2.3.1. Risk Assessment

CCI

More information about the known and expected risks, SAEs, and reasonably anticipated AEs of LY3526318 may be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions) of the IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and may be found in Section 5 (Effects in Humans) of the IB.

2.3.2. Benefit Assessment

Potential benefits for the study participants include

- information obtained from study-related medical procedures
    - physical examinations
    - laboratory tests
    - ECGs
- detailed evaluations of OA
    - knee examinations
    - knee X-rays
- OA-associated questionnaires that may improve participants understanding their own condition.

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

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with LY3526318 are justified by the anticipated benefits that may be afforded to participants with OA.

3. Objectives and Endpoints

The CPMP Master Protocol and OA DSA CPMP(1) include objectives and endpoints applicable for this study. This table describes objectives and endpoints specific for LY3526318.

Objectives	Endpoints
Tertiary/Exploratory	
Measure the PK of LY3526318 in participants with OA.	Measure of plasma concentrations of LY3526318 to enable PK evaluations.

Abbreviations: OA = osteoarthritis; PK = pharmacokinetic.

4. Study Design

4.1. Overall Design

The CPMP Master Protocol describes the overall study design and study design rationale. This section describes visits and overall procedures unique to ISA OA02 for LY3526318 in addition to the procedures outlined in CPMP and CPMP(1).

Double-Blind Treatment Period (Visits 3 through 7)

Each visit is an outpatient visit.

At Visit 3

- participants are randomized to LY3526318 or placebo
- the site completes the OA02 baseline procedures and sample collection
- participants receive their oral study intervention
- the site collects participants vitals at 2 and 4 hours after the completion of the oral administration
- the site completes all post-treatment sample collection and safety monitoring, and
- the site instructs participants to continue with study restrictions and Numeric Rating Scale (NRS) diary entries before their visit discharge.

At Visits 4 through 7

- the site reviews available safety data and completes pre-dose procedures and sample collection
- participants continue oral study intervention
- the site completes all sample collection and safety monitoring noted in the Schedules of Activities (SoAs), and
- the site instructs participants to continue with study restrictions and NRS diary entries before their visit discharge.

4.2. Scientific Rationale for Study Design

The master protocol describes the overall study design rationale.

4.3. Justification for Dose

4.4. End of Study Definition

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

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

5. Study Population

The CPMP Master Protocol and OA CPMP(1) DSA provide eligibility criteria that must be followed for this study. LY3526318-specific inclusion and exclusion criteria are listed here.

5.1. Inclusion Criteria

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

[1050] Are men or women who abide by the reproductive and contraceptive requirements provided in OA02 Section 10.2, Appendix 2.

5.2. Exclusion Criteria

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

CCI [redacted]

[1052] Have an eGFR of less than 30 ml/min/1.73 m^2, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at Visit 1 or Visit 2.

[1053] Women who are pregnant or breastfeeding.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of Seville oranges, grapefruit, or grapefruit juice from 5 days before the start of study intervention until after the final dose.

5.3.2. Substance Use

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

5.3.3. Reproductive and Contraception Requirements

Reproductive requirements and contraceptive guidance are provided in Section 10.2, Appendix 2.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

The study intervention will be administered orally, CCI [redacted]

Intervention Name	LY3526318	Placebo
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	CCI [redacted]	[redacted]
Dosage Level(s)	CCI [redacted]	[redacted]
Route of Administration	PO	PO
Use	experimental	placebo
IMP and NIMP	IMP	NIMP

Abbreviations: IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product; PO = by mouth; QD = once daily.

6.2. Preparation, Handling, Storage, and Accountability

The CPMP Master Protocol provides more detail on preparation, handling, storage, and accountability requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

No additional stratification factors are considered for this ISA.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, and documented in the source documents and case report form (CRF).

A record of the number of study intervention capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, will also be recorded in the CRF.

6.5. Treatment of Overdose

In case of suspected overdose, participants should be monitored for any signs or symptoms of adverse reactions or effects, and supportive care should be provided as necessary. There is no known antidote to LY3526318 therapy.

6.6. Concomitant Therapy

All concomitant therapies that are part of routine care for comorbidities other than chronic pain are allowed and may be used during the study, if it is permitted based on the eligibility criteria. The CPMP Master Protocol provides more detail on concomitant therapy.

A list of medications that are prohibited from Visit 2 to Visit 7 for participants randomized to this ISA study will be provided in the Manual of Operations. Participants may return to their standard of care after Visit 7 is completed, as clinically appropriate.

CCI [redacted]

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The CPMP Master Protocol and CPMP(1) DSA provides the reasons and procedures for discontinuation of intervention and participant discontinuation that must be followed for this study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the CPMP Master Protocol, OA CPMP(1) DSA, and ISA OA02 SoAs.

LY3526318-specific assessments and procedures are described here.

8.1. Efficacy Assessments

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Symptom directed physical examinations of skin, eyes, mouth, lungs, and gastrointestinal tract will be performed at each visit as described in the SoA. Any clinically significant abnormal physical examination findings will be reported as AEs.

8.2.2. Electrocardiograms

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

8.2.3. Clinical Safety Laboratory Tests

See OA02 Section 10.1 (Appendix 1) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency for ISA OA02.

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

See the CPMP Master Protocol for additional details.

8.4. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of LY3526318 as specified in the SoA.
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- The date and time (24-hour clock time) of LY3526318 administration prior to the PK sampling will be recorded i.e. the dose administered in the clinic at Visit 3 and the last at home dose prior to each of Visit 4, Visit 5, Visit 6, and Visit 7.

- Samples will be used to evaluate the PK of LY3526318. Samples collected for analyses of LY3526318 plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9. Statistical Considerations

The CPMP Master Protocol and OA DSA CPMP(1) provide statistical considerations. LY3526318-specific considerations are described here.

9.1. Statistical Hypotheses

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

The key secondary null hypothesis is that there is no difference between LY3526318 and placebo on the key secondary endpoint, the mean change from baseline to endpoint for the WOMAC® Pain Subscale Score. CCI [redacted]

9.2. Analyses Sets

The populations are defined in the CPMP Master Protocol.

The PK population includes all randomized participants who received a dose of LY3526318 and have at least 1 evaluable PK sample collected.

9.3. Statistical Analyses

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

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

9.3.1. General Considerations

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

Any borrowing of placebo or treatment effect information will be specified in the ISA SAP. Secondary and tertiary/exploratory endpoints and analyses are described in the CPMP Master Protocol and OA DSA CPMP(1).

9.3.2. Exploratory Endpoint Analysis

Exploratory analyses may be described in the ISA SAP.

9.3.3. Safety Analyses

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

9.3.4. Other Analyses

9.3.4.1. Pharmacokinetic and Pharmacodynamic Analyses

The observed plasma concentrations for LY3526318 will be reported graphically and descriptively.

Pharmacokinetic modeling and exposure-response analyses of efficacy measures may be conducted. If conducted, the analyses will be performed using population analysis software, NONMEM®, if data allows. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated, equivalent PK software programs may be used if appropriate, warranted, and approved by Global PK/pharmacodynamic management. Data may be pooled with data from other studies for an integrated PK and/or PK/pharmacodynamic analysis.

A limited number of pre-identified individuals independent of the study team may receive access to unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK and/or exposure-response model development processes. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

9.4. Interim Analysis

An interim analysis may be conducted for internal decision making. Unblinding details would be specified in the unblinding plan section of the SAP or in a separate unblinding document. The SAP will describe any interim analyses in greater detail should they occur.

9.5. Sample Size Determination

Up to approximately 150 participants will be randomized in a CCI ratio to LY3526318 and placebo, respectively. It is expected that approximately 85% of participants will complete the double-blind treatment period of the study. CCI [redacted]

CCI [redacted] If there is no treatment difference between placebo and LY3526318, the probability of passing the efficacy criterion specified above (i.e., false positive) is approximately 0.1. The simulation for the power calculation and sample size determination was carried out in FACTS Version 6.0.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Clinical Laboratory Tests

The CPMP Master Protocol describes tests that may be performed at additional times noted in the SoA for this ISA. This table describes tests unique for ISA OA02.

Other Tests
LY3526318 concentration
Urine pregnancy

10.2. Appendix 2: Contraceptive and Barrier Guidance

10.2.1. Definitions

Word/Phrase	Definition
Women of childbearing potential	Females are considered women of childbearing potential (WOCBP) if • they have had at least 1 cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of childbearing potential	Females are considered women not of childbearing potential (WNOCBP) if • they have a congenital anomaly such as Mullerian agenesis • they are infertile due to surgical sterilization, or • they are post-menopausal. Examples of surgical sterilization include: hysterectomy, bilateral oophorectomy, or tubal ligation.
Postmenopausal state	The post-menopausal state should be defined as: 1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.
Reproductive Toxicology Studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.2.2. Contraception Guidance

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

Must…	Must not…

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

stay in a same-sex relationship without sexual relationships with males	use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

Topic	Condition
Pregnancy testing	Negative urine result at screening followed by a negative serum result within 24 hours prior to treatment exposure.
	Note: Subsequent pregnancy testing is compound specific.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective (less than 1% failure rate)

Examples of different forms of contraception

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	
	Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

Topic	**Guidance**
Contraception for men receiving a genotoxic drug and have a female partner of childbearing potential	• Agree to remain abstinent (if this is their preferred and usual lifestyle), or • use 1 additional effective method of contraception

The table below describes contraception guidance for all men.

Topic	**Guidance**
For all men	should refrain from sperm donation for the duration of the study and for the predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 90 days.
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and • for the predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 90 days
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

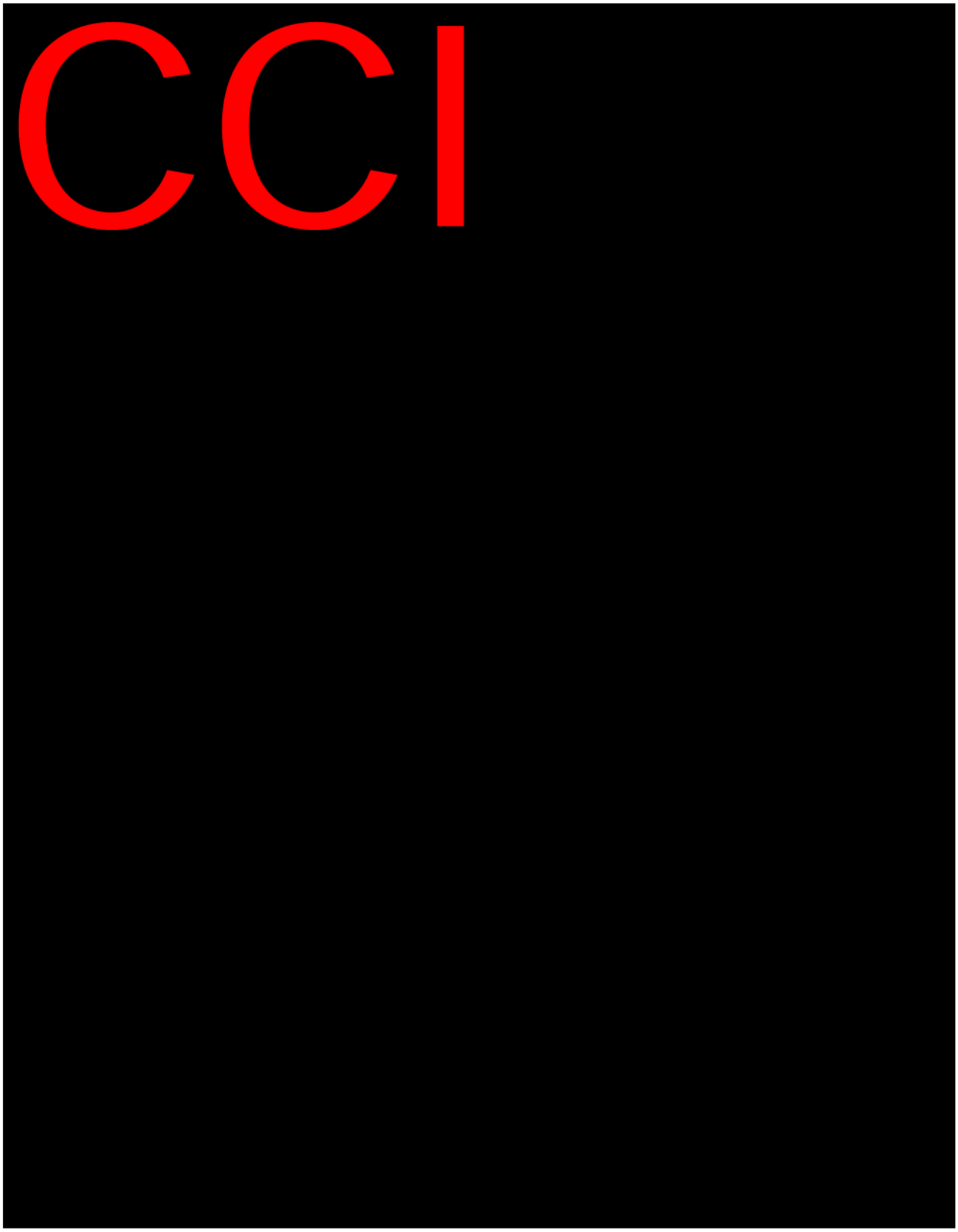
Examples of highly effective, effective, and unacceptable methods of contraception can be found below

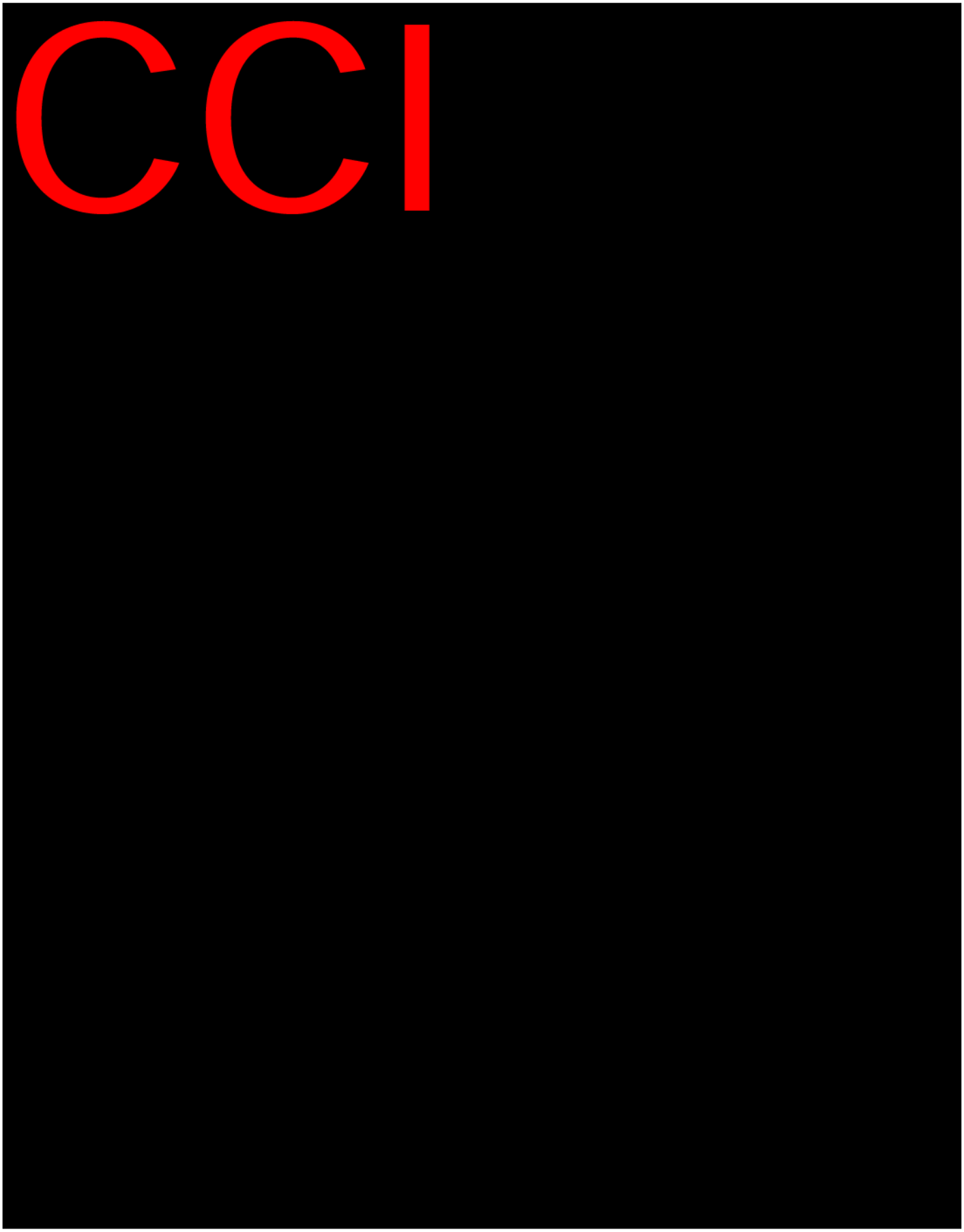
Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	
	Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche, or • lactational amenorrhea

10.3. Appendix 3: List of Excluded Concomitant Medications

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10.4. Appendix 4: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

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

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

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

The following changes in study conduct will not be considered protocol deviations.

Remote visits

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

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor.

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

Other alternative locations: Laboratory draws may be done at an alternate location in exceptional circumstances.

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

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

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

Local laboratory testing option

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

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Study intervention and ancillary supplies (including participant diaries)

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

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.

- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities as described in the CPMP Master Protocol, CPMP(3) DSA, and NP02 ISA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

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

Documentation

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.5. Appendix 5: Abbreviations

Term	Definition
AE	adverse event
AITC	allyl isothiocyanate
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 subjects are aware of the treatment received.
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum serum/plasma concentration
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, and applicable regulatory requirements.
CRF	case report form
CV%	percent coefficient of variation
CYP3A	cytochrome P450 enzymes 3A
DDI	drug-drug interaction
data monitoring committee	A data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DSA	disease-state addendum
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
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.
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
IMP	Investigational Medicinal Product

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.
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.
investigational product	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 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.
ISA	intervention-specific appendix
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NRS	Numeric Rating Scale
OA	osteoarthritis
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK	pharmacokinetics
PO	by mouth
PoC	proof-of-concept
OA	osteoarthritis
QD	once daily
QTc	corrected QT interval
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
$t_{1/2}$	elimination half-life

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.
t_{max}	time to maximum plasma concentration
TRP	transient receptor potential
TRPA1	transient receptor potential ankyrin 1
WOCBP	women of childbearing potential

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Approver: PPD [redacted]

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Signature meaning: Approved

Approver: PPD [redacted]

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Signature meaning: Approved