Clinical Study Protocol Version (a) H0P-MC-OA01

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3016859 for the Treatment of Osteoarthritis

NCT04456686

Approval Date: 27-Mar-2020

Title Page

Intervention-Specific Appendix (ISA) for LY3016859: H0P-MC-OA01(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 LY3016859 for the Treatment of Osteoarthritis

ISA Number: H0P-MC-OA01

Amendment Number: (a)

Compound: LY3016859

Study Phase: 2

Acronym: OA01

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

Master Protocol IND: 144915

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 27-Mar-2020 GMT

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 Food and Drug Administration (FDA) feedback.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Addition of visit window for post-randomization visits	Allows flexibility for participants
Section 1.3. Schedule of Activities	Included details for vital signs and targeted physical examination	Per regulatory feedback
Section 1.3. Schedule of Activities	Included additional urine pregnancy sample collection and updated description of those who would be tested	Per new toxicology data
Section 1.3. Schedule of Activities	Included additional sample collection time for hemoglobin A1c	Sample collection time missed in the original version
Section 2.3.1. Risk Assessment	Removed language for women of childbearing potential and added language for fetal exposure	Women of childbearing potential are now allowed in the study; pregnant or breastfeeding women are not allowed
Section 4 Study Design	Amended post-treatment follow-up period instructions	Updated to maximize data collection in the follow-up period
Section 5.1. Inclusion Criteria	Removed criterion related to women not of childbearing potential	To account for the addition of women of childbearing potential to the study per toxicology data
Section 5.1. Inclusion Criteria	Removed criterion related to supplements and vitamins	Potential to cause unintended screen failures and requirements sufficiently covered in the treatment period through lifestyle restrictions.
Section 5.2. Exclusion Criteria	Addition of language related to ophthalmologic disease	Per regulatory feedback
Section 5.2. Exclusion Criteria	Addition of criterion related to women who are pregnant or breastfeeding	Per regulatory feedback
Section 5.3. Lifestyle Considerations	Removed language about local regulations for contraception use by men	This language is intended for global studies. This study will be conducted in the United States only.
Section 5.3. Lifestyle Considerations	Removed language about supplements	Per removal of related inclusion criterion

Section # and Name	**Description of Change**	**Brief Rationale**
Section 6.1.1. Special Treatment Considerations	Addition of special treatment considerations	Per regulatory feedback
Section 8.1.1. Physical Examinations	New section to include details on targeted physical examination	Per regulatory feedback
Section 10.2, Appendix 2	Addition of definitions and contraceptive guidance related to women of childbearing potential	To account for the addition of women of childbearing potential to the study per toxicology data
Throughout the protocol	Minor editorial and formatting 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 LY3016859 for the treatment of osteoarthritis

Rationale:

The purpose of this study is to test whether LY3016859 is efficacious in relieving knee pain due to osteoarthritis (OA). LY3016859 is a high affinity humanized immunoglobulin G (IgG)4 monoclonal antibody that binds to key residues in the C-terminal regions of transforming growth factor-α (TGF-α) and epiregulin, preventing their binding to the epidermal growth factor receptor (EGFR).

Data will be collected to assess the safety, and tolerability of LY3016859 in this study population. Pharmacokinetic (PK) properties, pharmacodynamic (PD) effects and immunogenicity profile will also be explored. The totality of data from this proof-of-concept study will assess the benefits and risks associated with LY3016859 and inform decisions for the clinical development of LY3016859.

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 a 26-week, Phase 2, randomized, double-blind, placebo-controlled study that will compare LY3016859 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 125 participants will be randomly assigned to study intervention (84 LY3016859 and 41 placebo) 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 26-week study includes an 8-week double-blind treatment period and an 18-week follow-up period.

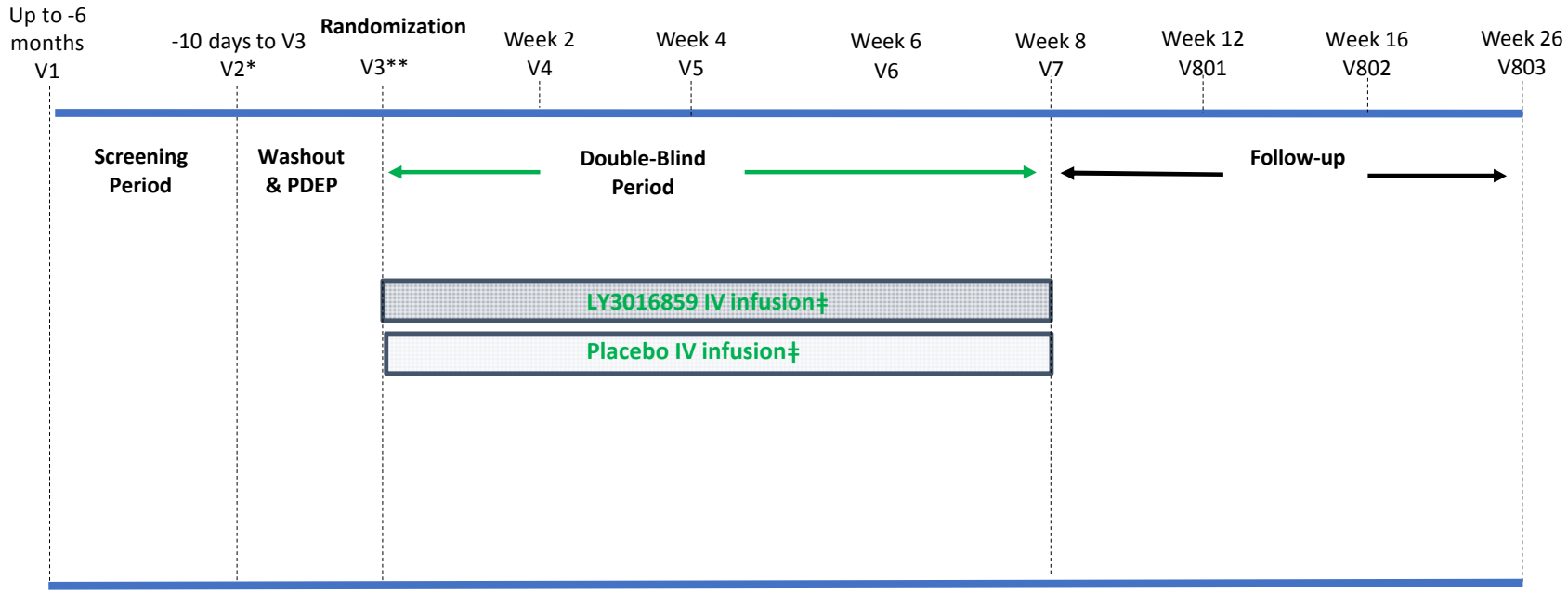
Participants will receive an intravenous (IV) infusion every 2 weeks for a total of 4 infusions.

Intervention Name	LY3016859	Placebo
Dosage Level(s)	750 mg starting dose 500 mg subsequent doses	Not applicable
Route of Administration and duration	1 hour IV infusion	1 hour IV infusion

Participants will be monitored for at least 4 hours after completion of each infusion.

Data Monitoring Committee: Yes

1.2. Schema



* Medication washout and preliminary data entry period begins.
** Randomization to either LY3016859 or placebo.
‡ Each participant receives a 1 hour infusion at Visits 3, 4, 5, and 6.
Abbreviations: IV = intravenous; PDEP = preliminary data entry period; V = visit.

1.3. Schedule of Activities (SoA)

This SoA shows visits and procedures unique to the intervention-specific appendix (ISA) H0P-MC-OA01 (OA01) for LY3016859. Please refer to master protocol H0P-MC-CPMP (CPMP) and the osteoarthritis (OA) disease-state addendum (DSA) H0P-MC-CPMP(1) SoAs for additional information.

H0P-MC-OA01 ISA	Randomization	Double-Blind Treatment				Follow-up			Early Discontinuation	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**V801**	**V802**	**V803**	**ED**	
Study Week	0	2	4	6	8	12	16	26		
Visit Window (days)		±3	±3	±3	±3	±5	±7	±7		Minimal interval between 2 doses cannot be shorter than 11 days.
Physical examination	X	X	X	X	X	X	X	X	X	Targeted exam for skin, eyes, mouth, lungs and GI tract should be performed at each visit, in addition to any symptom driven exam. Full physical exam should be performed at Visit 803 or ED.
Weight								X		
Vital signs	X	X	X	X	X	X	X	X		Includes respiratory rate, blood pressure, temperature and pulse rate. All vital signs are collected before study intervention infusion on V3-6.
ECG			X		X			X		Single safety ECGs
Study intervention IV infusion	X	X	X	X						1 hour IV administration The timing between randomization and the first IV infusion may be up to, but not longer than 2 business days to reduce participant burden.
Adverse events						X	X	X		
Concomitant medication						X	X	X		
Rescue medication usage reporting						X				If the participant discontinues after V801, this assessment is not needed for ED per the CPMP SoA.
NRS						X				If the participant discontinues after V801, this assessment is not needed for ED per the CPMP SoA.
PGI						X				If the participant discontinues after V801, this assessment is not needed for ED per the CPMP SoA.

H0P-MC-OA01 ISA	Randomization	Double-Blind Treatment				Follow-up			Early Discontinuation	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**V801**	**V802**	**V803**	**ED**	
Study Week	0	2	4	6	8	12	16	26		
Visit Window (days)		±3	±3	±3	±3	±5	±7	±7		Minimal interval between 2 doses cannot be shorter than 11 days.
WOMAC						X				If the participant discontinues after V801, this assessment is not needed for ED per the CPMP SoA.
C-SSRS						X		X		Use C-SSRS Since Last Visit version.
Self-Harm Supplement Form						X		X		
Self-Harm Follow-up Form						X		X		Required if triggered by the Self-Harm Supplement Form per instructions.
Hematology						X	X	X		
Chemistry		X		X		X	X	X		
Urine Chemistries	X	X	X	X	X	X		X	X	
Urinalysis								X		
Urine pregnancy	X	X	X	X	X			X	X	For all premenopausal females or postmenopausal females <50 years of age V3: collect sample before dosing
Urine drug screen	X		X		X					
Hemoglobin A1c	X				X			X	X	

H0P-MC-OA01 ISA	Randomization	Double-Blind Treatment				Follow-up			Early Discontinuation	Notes
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**V801**	**V802**	**V803**	**ED**	
Study Week	0	2	4	6	8	12	16	26		
Visit Window (days)		±3	±3	±3	±3	±5	±7	±7		Minimal interval between 2 doses cannot be shorter than 11 days.
PK sample	X	X	X	X	X	X	X	X	X	V3-V6: collect samples before IV infusion starts and within 15 minutes after IV infusion is complete. V7 – V803: single sample collected at any time. Obtain PK samples from opposite arm used for IV infusion. Record date and time of collection.
Immunogenicity (ADA) sample	X	X	X		X	X		X	X	V3-6: collect sample before IV infusion starts
Epiregulin sample	X	X	X		X	X	X	X	X	V3-6: collect sample before IV infusion starts. V7-V803: single sample collected at any time to match PK.
CCI										

Abbreviations: ADA = anti-drug antibody; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; GI = gastrointestinal; IV = intravenous; NRS = Numeric Rating Scale for pain; PGI = Patient Global Impression of change; PK = pharmacokinetic; V = visit; WOMAC = Western Ontario and McMaster University Arthritis Index.

2. Introduction

This ISA OA01 is an appendix to the master protocol CPMP and contains unique study elements specific for LY3016859. The master protocol contains the overarching study elements that govern the OA DSA CPMP(1) and this ISA OA01.

LY3016859 is a high affinity humanized immunoglobulin G (IgG)4 monoclonal antibody that binds to key residues in the C-terminal regions of transforming growth factor-α (TGF-α) and epiregulin, preventing their binding to the epidermal growth factor receptor (EGFR). Engagement of LY3016859 results in internalization of the membrane-spanning ligands and neutralization of mature ligand activity *in vitro*.

The EGFR and epiregulin are associated with pain processing (Martin et al. 2017). Epiregulin is increased in blood after nerve injury/insult (Martin et al. 2017). Inhibition of EGFR with clinically available compounds strongly reduces nocifensive behavior in mouse models of inflammatory and chronic pain, including spinal nerve injury and chronic constriction injury (Martin et al. 2017).

TGF-α has also been implicated in some chronic pain conditions, especially with pain in OA. For instance, a single nucleotide polymorphism (SNP) of TGF-α has been associated with increased risk of developing OA of the knee (Cui et al. 2017), and in 1 reported case study (Moryl et al. 2006) a lung cancer patient receiving treatment with the EGFR tyrosine kinase inhibitor gefitinib reported a marked improvement in her OA symptoms. The reported pain relief persisted while on treatment, but painful symptoms returned when treatment was discontinued due to intolerance of EGFR inhibitor associated side effects.

Non-controlled reports show that EGFR inhibition by various oncologic drugs provides rapid relief of pain (Kersten et at. 2013; Kersten et al. 2015; Juhasz et al. 2013); and the pain relief was independent of disease progression (Kersten and Cameron 2012).

2.1. Study Rationale

The purpose of this study is to test whether LY3016859 is efficacious in relieving knee pain due to OA. Data will be collected to assess the safety and tolerability of LY3016859 in this study population. Pharmacokinetic (PK) properties, pharmacodynamic (PD) effects and immunogenicity profile will also be explored. The totality of data from this proof-of concept study will assess the benefits and risks associated with LY3016859 and inform decisions for the clinical development of LY3016859.

2.2. Background

LY3016859 was initially developed for the treatment of diabetic nephropathy (DN) and 2 clinical studies were completed.

Study	I5V-MC-TGAA (TGAA)
Population	Healthy participants
Study Design	Placebo-controlled, randomized, single-dose escalation
LY3016859 Dose	Intravenous (IV) infusion and subcutaneous: 0.1, 1, 10, 50, 250, and 750 mg
Objectives	Evaluate safety, tolerability, and pharmacokinetics after single IV and subcutaneous dosing.

Study	I5V-MC-TGAB (TGAB)
Population	Participants with diabetic nephropathy
Study Design	2-part, placebo-controlled, randomized, multiple dose escalation and parallel dose study
LY3016859 Dose	Part A: dose range of 10 to 750 mg, administered as a 60-minute IV infusion once every 3 weeks for a total of 2 doses Part B: 60-minute IV infusion once every 3 weeks up to 5 doses, if tolerated Doses did not exceed the maximum tolerated dose from Part A.
Objectives	Evaluate safety, tolerability, and pharmacokinetics and pharmacodynamics. Change from baseline in proteinuria at 16 weeks.

Pharmacokinetics

LY3016859 serum concentration increased more than proportionally with dose; and the terminal half-life increased with dose (approaching 18 days at higher doses), consistent with target-mediated drug disposition.

Pharmacodynamics

LY3016859 demonstrated dose-related target engagement for both TGF-α and epiregulin.

Safety

Intravenous doses of up to 750 mg LY3016859 were safe and reasonably well tolerated.

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3016859 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

The IB provides detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY3016859.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention LY3016859		
Development of treatment-emergent anti-drug antibodies (TE ADA).	Incidence of TE ADA was 50% after a single dose, and up to 57% after multiple doses.	Collect samples up to 20 weeks after last dose to characterize ADA profile.
IV infusion may be associated with infusion reactions and hypersensitivity reactions.	LY3016859 is a monoclonal antibody that will be administered via IV infusion. Hypersensitivity reactions and infusion reactions may occur during treatment with such agents.	Monitor infusion reactions and hypersensitivity reactions. Guidance on management of infusion and hypersensitivity reactions are in Sections 8.2.1. and 8.2.2.
Dermatological adverse reactions similar to EGFR antagonists	One healthy participant who received a single dose of 1 mg LY3016859 experienced a rash that was considered similar to those associated with EGFR antagonists.	Collect dermatological AEs. Stop dosing for severe dermatological AEs.
Changes in eGFR in participants with diabetic nephropathy (DN)	A modest and non-statistically significant decrease in eGFR was observed in participants with DN who received LY3016859 in Part B of Study TGAB, but not in healthy participants in Study TGAA.	Exclude participants with moderate or severe renal impairment in the study. Short dosing duration. Monitor eGFR and stop dosing if necessary. [redacted]
Fetal harm due to in utero exposure	No effects on embryo-fetal development in enhanced pilot embryo-fetal development studies in rats and rabbits. Definitive developmental and reproductive toxicity studies are not yet completed.	Do not enroll women who are pregnant or breastfeeding in studies for LY3016859.
Study Procedures		
Participant may experience increased OA symptoms.	Medications that relieve OA pain will not be allowed until Visit 801.	Rescue medication is permitted. Standard treatment of OA may be restarted after Visit 801 based on investigator discretion.

Abbreviations: ADA = anti-drug antibodies; AE = adverse events; DN = diabetic nephropathy; EGFR = epidermal growth factor receptor; eGFR = estimated glomerular filtration rate; IV = intravenous; OA = osteoarthritis; TE = treatment emergent; TGAA = study I5V-MC-TGAA; TGAB = study I5V-MC-TGAB.

2.3.2. Benefit Assessment

Potential benefits for the study participants include

- study-related medical procedures
    - physical examinations,
    - laboratory tests
    - electrocardiograms (ECGs)
- detailed evaluations of OA
    - knee examinations
    - knee X-rays, and
- OA associated questionnaires that may improve participants understanding their own condition.

As part of Study CPMP, participants to this ISA will report their experience using standard tools that 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 a new treatment with improved safety and efficacy profile compared to standard of care.

2.3.3. Overall Benefit: Risk Conclusion

The measures taken to minimize risk to participants in this study and the potential risks identified in association with ISA OA01 are justified by the anticipated benefits to participants with OA.

3. Objectives and Endpoints

The master protocol CPMP and OA DSA CPMP(1) include objectives and endpoints applicable for this study. This table describes objectives and endpoints specific for LY3016859.

Objectives	**Endpoints**
Tertiary/Exploratory	
Characterize the pharmacokinetics and pharmacodynamics of LY3016859 after multiple intravenous infusions in participants with osteoarthritis	Assessment of serum concentrations of LY3016859 and epiregulin to enable pharmacokinetic and pharmacodynamic evaluations
Characterize immunogenicity of LY3016859	Appearance of anti-drug antibodies and neutralizing antibodies to LY3016859
Explore the effect of LY3016859 on the kidney	Assessment of • urine albumin/creatinine ratio • urine protein/creatinine ratio • eGFR

Abbreviations: eGFR = estimated glomerular filtration rate.

4. Study Design

Master protocol CPMP describes the overall study design and study design rationale. This section describes visits and overall procedures unique to ISA OA01 for LY3016859 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 LY3016859 or placebo
- the site completes the OA01 baseline procedures and sample collection
- participants receive their first dose of study intervention via IV infusion over 1 hour
- the site observes participants in the clinic for at least 4 hours after the completion of the IV infusion
- 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 6

- the site reviews available safety data and completes pre-dose procedures and sample collection
- participants receive an IV infusion over 1 hour
- the site observes participants in the clinic for at least 4 hours after the completion of the IV infusion
- the site completes all post-treatment sample collection and safety monitoring, and
- the site instructs participants to continue with study restrictions and NRS diary entries before their visit discharge.

At Visit 7

- the site completes all procedures and sample collection noted in the SoAs
- no intervention is administered at this visit, and
- the site instructs participants to continue with study restrictions and NRS diary entries before their visit discharge.

Post-treatment Follow-up Period (Visits 801-803)

Participants must complete 3 post-treatment follow-up visits for safety, PK and immunogenicity assessment at Visits 801-803, according to the SoA.

The site schedules Visit 801 approximately 4 weeks after Visit 7.

At Visit 801, participants return the device for NRS diary collection.

At Visit 803, the participants are discharged from the study.

If the participant receives at least one dose of intervention and discontinues during the double-blind treatment period, they should complete early discontinuation procedures per the CPMP Protocol SoA and Visit 801 should be scheduled approximately 30 days after the last dose of study intervention.

4.1. Scientific Rationale for Study Design

The master protocol describes the overall study design rationale.

Efficacy data will be collected up to 6 weeks after the last dose, based on the long PK half-life and potential sustained target engagement of LY3016859.

Safety, PK, PD and immunogenicity samples will be collected up to 20 weeks after the last administration of intervention to characterize the safety and clinical immunogenicity profile.

4.2. Justification for Dose

The proposed dose for proof-of-concept is a 750-mg starting dose followed by 500 mg every 2 weeks IV for a total of 4 doses. The dose level and duration are based on the available toxicology, safety, PK and PD data from the completed studies detailed in the LY3016859 IB.

Briefly, the proposed dose regimen maintains an approximate 10-fold margin of safety (MOS) relative to the no-observed-adverse-effect level (NOAEL) for both rat and monkey repeated dose toxicology studies (Table 4.5 in the IB) and is expected to achieve steady state exposure similar to the 750 mg every 3 weeks dosing regimen tested in Study TGAB. The safety data from the completed TGAA and TGAB studies, and the clinical management plan support testing the proposed dose regimen in participants with various chronic pain conditions.

The PK analyses show a similar PK profile for LY3016859 in healthy participants and patients with various degrees of renal impairment, which is expected for a monoclonal antibody.

While the degree of target-engagement required for analgesic efficacy for LY3016859 has not been established in the clinic, the proposed dosing regimen is expected to reach steady-state within a month[redacted]. If the epiregulin blockade is beneficial for OA pain conditions, then this level of target engagement is expected to enable analgesic efficacy.

4.3. 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 Schedule of Activities.

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 Schedule of Activities for the last participant.

5. Study Population

The master protocol CPMP and OA DSA CPMP(1) provide eligibility criteria that must be followed for this study. LY3016859 specific inclusion and exclusion criteria are listed here.

5.1. Inclusion Criteria

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

[1000] are men or women who abide by the reproductive and contraceptive requirements provided in OA01 Section 10.2, Appendix 2

[1001] are willing to discontinue all pain medications for condition under study except rescue medication permitted until V801 in the follow-up period

[1002] must have venous access in both arms for IV infusion and sample collection.

5.2. Exclusion Criteria

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

Medical Conditions

[1003] have had an intra-articular injection of hyaluronic acid within 24 weeks of Visit 2

[1004] have an eGFR of less than 70 ml/min/1.73m2 based on CKD-EPI formula at Visit 1 or Visit 2

[1005] Have any clinically serious or unstable cardiovascular, musculoskeletal disorder, gastrointestinal, endocrinologic, hematologic, hepatic, metabolic, urologic, pulmonary, dermatologic, immunologic, or ophthalmologic disease within 3 months of Visit 3

Prior/Concomitant Therapy

[1006] have received any antibodies against nerve growth factor (NGF), or antibodies against EGFR, or EGFR tyrosine kinase inhibitors

[1007] have a history of allergic reactions to monoclonal antibodies, or clinically significant multiple or severe drug allergies, including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis

[1008] have a history or presence of uncontrolled asthma, eczema, significant atopy, significant hereditary angioedema or common variable immune deficiency, and

Reproductive

[1009] are women who are pregnant or breastfeeding.

5.3. Lifestyle Considerations

Reproductive and Contraception Requirements

Reproductive requirements and contraceptive guidance are provided in OA01 Appendix 2, Section 10.2.

Caffeine and Alcohol

Participants should maintain their usual caffeine intake.

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

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

Men over the age of 65 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 for OA of the index knee should remain on the same therapy program (intensity and frequency) from Visit 3 to Visit 801. New programs may be initiated after Visit 801.

Exposure to Sun

Participants should use sun protection and avoid sunbathing and use of sun beds for the duration of the study. Sun protection may consist of protective clothing or SPF 50 lotion.

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(s) Administered

The study intervention will be administered via a slow IV infusion over approximately 1 hour by blinded site personnel. The infusion rate may be reduced as deemed necessary if an infusion reaction is observed. Participants will be monitored for at least 4 hours after completion of each infusion. Site must have resuscitation equipment, emergency drugs and appropriately training staff available during the infusion and for at least 4 hours after the completion of the infusion. Participants should not use tobacco products from 1 hour before the start of dosing until after collection of the final PK or PD sample after dosing.

Intervention Name	LY3016859	Placebo
Type	Biologic	Not applicable
Dose Formulation	Lyophilized powder reconstituted with sterile water	0.9% Sodium chloride solution
Unit Dose Strength(s)	75 mg/vial	Not applicable
Dosage Level(s)	750 mg starting dose 500 mg subsequent doses	Not applicable
Route of Administration	1 hour IV infusion	1 hour IV infusion
Use	experimental	placebo
IMP and NIMP	IMP and NIMP	IMP and NIMP
Sourcing	LY3016859 from Lilly If needed, saline for reconstitution of IMP will be site sourced.	Placebo will be procured, packaged, labeled, distributed and dispensed as IMP by Lilly
Packaging and Labeling	The lyophilized powder and sterile diluent for infusion will be provided in separate glass vials. Each vial will be labeled as required per country requirement	Placebo will be provided in a glass vial. Each vial will be labeled as required per country requirement

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

6.1.1. Special Treatment Considerations

6.1.1.1. Premedication for Infusions

Premedication for infusions is not planned. However, if an infusion reaction occurs, the study investigator(s) should determine the appropriate premedication for subsequent infusions for that participant.

The investigators and sponsor may decide to use premedication for all participants. They will decide this if the frequency of infusion reactions among participants warrants it.

Any premedications given will be documented as a concomitant therapy (see Section 6.5).

6.1.1.2. Management of Infusion Reactions

All participants should be monitored closely, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness.

Site Needs

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

Management of Infusion Reactions

Investigators should grade the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms.

This table outlines guidance when a mild to moderate infusion reaction occurs.

If…	Then…
a mild to moderate infusion reaction occurs	the infusion rate should be slowed or stopped depending on the symptoms or signs present. For example, reducing the rate by 50% from 2 mL/minute to 1 mL/minute.
the infusion rate is slowed	• the infusion should be completed at the slower rate, as tolerated. • subsequent infusions may be administered at the discretion of the investigator in agreement with the Lilly medical monitor.
the infusion rate is slowed, and subsequent infusions are continued	the infusion rate must be maintained at the slowest tolerated rate used.

The study intervention infusion should be stopped immediately and permanently if it is an infusion reaction

- with systemic involvement, including, but not limited to significant treatment emergent hypotension, bronchospasm, or wide-spread urticaria
- that does not respond to a slower infusion rate or oral medications
- that is determined as clinically significant by the investigator.

If a participant permanently discontinues from study intervention, they should complete AE monitoring and other procedures as stated in Section 4, Study Design, and the CPMP and OA01 SoAs.

6.2. Preparation/Handling/Storage/Accountability

Study intervention and placebo require refrigeration.

Study intervention and placebo will be prepared and verified by unblinded site personnel.

6.3. Measures to Minimize Bias: Randomization and Blinding

No additional stratification factors are considered for this ISA.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each study intervention administered in the clinic will be recorded in the source documents and case report form (CRF). Administration of intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

All concomitant therapies that are part of routine care for other comorbidities besides OA, are allowed and can be used during the study, if it is permitted based on the inclusion and exclusion criteria.

A list of medications that are prohibited from Visit 2 to Visit 801 for participants randomized to this ISA study will be provided. Participants may return to their standard-of-care after Visit 801 is completed, as clinically appropriate.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Protocol CPMP provides the reasons and procedures for discontinuation of intervention and participant discontinuation that must be followed for this study. LY3016859 specific information is included here.

7.1. Discontinuation of Study Intervention

If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction or a serious infusion reaction has occurred related to study intervention administration, the participant should be permanently discontinued from the study intervention.

A participant should be discontinued from study intervention if they experience a dermatological adverse reaction, such as acneiform rash, that is related to study intervention, **and** is either mild to moderate and does not respond to topical treatment **or** is severe. The participant may continue in the study at the discretion of the investigator in consultation with the medical monitor or study sponsor physician/scientist.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the protocol CPMP, OA DSA CPMP(1), and ISA OA01 SoAs.

LY3016859 specific assessments and procedures are described here.

8.1. Safety Assessments

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

8.1.1. Physical Examinations

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

8.1.2. 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 pulse rate, QRS, QT, and QTc.

8.1.3. Clinical Safety Laboratory Assessments

See OA01 Appendix 1 (Section 10.1) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency for ISA OA01.

8.2. Adverse Events and Serious Adverse Events

8.2.1. Infusion Site Reactions

Symptoms of a local infusion site reaction may include erythema, induration, pain, pruritus, and edema. If an infusion site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the CRF.

Additional blood and urine samples should be collected as described in OA01 Section 10.3, Appendix 3, "Recommended Laboratory Testing for Hypersensitivity Events". Laboratory results are provided to the sponsor via the central laboratory.

8.2.2. Hypersensitivity Reactions and Infusion-related Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. Drugs administered via IV infusion may lead to a systemic infusion-related reaction. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the CRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic reaction be treated per the local standard of care.

In the case of generalized urticaria or anaphylaxis, or moderate to severe infusion-related reactions, additional blood and urine samples should be collected as described in OA01

Section 10.3, Appendix 3, "Recommended Laboratory Testing for Hypersensitivity Events". Laboratory results are provided to the sponsor via the central laboratory.

8.2.3. Adverse Events of Special Interest

Dermatological adverse reactions

EGFR antibodies or EGFR-associated tyrosine kinase inhibitors are associated with various dermatological AEs, including acneiform rashes, xerosis, pruritis, and photosensitivity. Secondary infection can also develop.

Participants should use sun protection during the study period. Dermatological adverse reactions should be managed by the investigator according to standard of care. Discontinuation of treatment may be considered if these AEs do not respond to topical treatment or are widespread (>30% body surface area) or are severe.

If any of these AEs are reported, sites will be prompted to provide additional information.

Renal Function

Changes in eGFR were observed in participants with diabetic nephropathy in Study TGAB (Section 2.2). Such changes were reversible and were not associated with increase in proteinuria. Blood and urine samples will be collected to characterize the effects of LY3016859 on renal function and eGFR will be monitored during the study.

8.3. 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.

8.4. Pharmacokinetics

Venous blood samples of approximately 4 mL will be collected for measurement of LY3016859 concentrations as specified in the SoA. Samples will be used to evaluate the PK of LY3016859.

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.

Instructions for the collection and handling of biological samples will be provided by Lilly.

Site personnel will record

- The date and time (24-hour clock time) of LY3016859 administration (start and end of infusion), and
- The date and time (24-hour clock time) of each PK sample.

It is essential that the times are recorded accurately.

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

8.5. Pharmacodynamics

Venous blood samples of approximately 4 mL each will be collected for the measurement of epiregulin as specified in the SoA. Any remaining blood samples may be used to test other potential PD endpoints, including, but not limited to TGF-α.

Instructions for the collection and handling of biological samples will be provided by Lilly.

8.7. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA, predose venous blood samples will be collected to determine antibody production against LY3016859. The actual date and time (24-hour clock time) of each sample collection will be recorded.

If the immunogenicity sample at the last scheduled assessment or discontinuation visit is treatment-emergent (TE) anti-drug antibody (ADA) positive (as defined in Section 9.4.2.1), additional samples may be taken until the signal returns to baseline (i.e., no longer TE-ADA positive) or for up to 1 year after last dose.

To aid interpretation of these results, a predose blood sample for PK analysis will be collected at the same time points.

Sample collection, handling, and use

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

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3016859 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3016859.

Sample retention

Sample retention is described in protocol CPMP, Appendix 1, Section 10.1.12.

9. Statistical Considerations

The master protocol and OA DSA provide statistical considerations. LY3016859 specific considerations are described here.

9.1. Statistical Hypotheses

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

The key secondary null hypothesis is that there is no difference between LY3016859 and placebo on the key secondary endpoint, the mean change from baseline to endpoint for the WOMAC® Pain Subscale Score. CCI [redacted]

9.2. Sample Size Determination

Approximately 125 participants will be randomized in a 2:1 ratio to LY3016859 and placebo, respectively. It is expected that approximately 107 participants will complete the double-blind treatment period of the study. CCI [redacted]

CCI [redacted] If there is no treatment difference between placebo and LY3016859, 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.

9.3. Populations for Analyses

The populations are defined in protocol CPMP.

The pharmacokinetic population includes all randomized participants who received a full dose of LY3016859 at Visit 3 and have at least 1 evaluable PK sample collected prior to dosing at or after Visit 4.

9.4. Statistical Analyses

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

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

9.4.1. General considerations

The primary endpoint and analyses have been described in protocol CPMP.

Any borrowing of placebo or treatment effect information will be specified in the ISA SAP. Secondary and Tertiary/Exploratory endpoints and analyses are described in protocol CPMP and DSA CPMP(1).

9.4.2. Other Analyses

9.4.2.1. Immunogenicity

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADA and who are TE-ADA positive (TE-ADA+) to LY3016859 will be tabulated.

If neutralizing antibodies are assessed, the distribution of titers and frequency of neutralizing antibodies for the TE-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, PD response, safety or efficacy to LY3016859, may also be assessed. Additional details may be provided in the SAP.

9.4.2.2. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic and pharmacokinetic-pharmacodynamic (PKPD) analyses may be conducted to explore the exposure-response relationships for various pharmacodynamics measures. 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 PKPD management. Data may be pooled with data from other studies for an integrated PKPD analysis. The observed serum concentrations for LY3016859 and epiregulin will be reported graphically and descriptively.

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 PKPD model development processes. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

9.5. Interim Analyses

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.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Clinical Laboratory Tests

The master protocol CPMP describes tests that may be performed at additional times noted in the SoA for this ISA. This table describes tests unique for ISA OA01.

Chemistry	Urine Chemistries	Other Tests
Cystatin-C	Albumin	Immunogenicity
	Creatinine	Epiregulin
	Albumin/creatinine ratio (ACR)	LY3016859 concentration
.	Protein	Urine pregnancy
	Protein/creatinine ratio (PCR)	

Refer to Section 10.3, Appendix 3 for recommended laboratory testing for hypersensitivity events.

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

Women

Women of child-bearing potential may participate in this study.

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

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

All other women of child-bearing potential must agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study.

Abstinence or contraception must continue for 90 days after the last dose of intervention.

Acceptable Methods of Contraception

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

- combination oral contraceptives
- implanted contraceptives, or
- intrauterine devices.

Effective methods of contraception comprise but are not limited to diaphragms with spermicide or cervical sponges.

Not Acceptable Methods of Contraception

Use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Women not of childbearing potential may participate and include those who

- have a congenital anomaly such as Mullerian agenesis
- are infertile due to surgical sterilization, or
- are post-menopausal.

Surgical sterilization examples include

- hysterectomy
- bilateral oophorectomy, or
- tubal ligation.

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

Post-menopausal is defined as either

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

Men

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with non-pregnant women of child bearing potential partners for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 6 months after the last dose.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure to the fetus, predicted to be 6 months after the last dose.

Acceptable Methods of Contraception

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

- combination oral contraceptives
- implanted contraceptives, or
- intrauterine devices.

Effective methods of contraception comprise but are not limited to diaphragms with spermicide or cervical sponges.

Men and their partners may choose to use a double–barrier method of contraception that must include use of a spermicide.

Other Guidance

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 6 months after the last dose.

Men who are in exclusively same sex relationships, as their preferred and usual lifestyle, are not required to use contraception.

10.3. Appendix 3: Recommended Laboratory Testing for Hypersensitivity Events and Infusion-related Reactions

Recommended laboratory tests should be performed at the time of a systemic hypersensitivity event. The management of the adverse event may warrant laboratory testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a Systemic Hypersensitivity Event is performed to

- help characterize and classify systemic hypersensitivity reactions
- meet regulatory expectations, and
- improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis.

If anaphylaxis is suspected or generalized urticaria is present, then

1. obtain a sample within 1 to 2 hours of the event.
    a. samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time
2. record the time at which the sample was collected, and
3. obtain a follow up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

Laboratory Tests for Hypersensitivity Events

Test	Details
Tryptase	If a tryptase sample is obtained more than 2 hours after the event (i.e. within 2 to 12 hours),or is not obtained because more than 12 hours have lapsed since the event, then obtain urine for *N*-methylhistamine (NMH) testing. For tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
Anti-drug antibody (ADA)	ADA testing should include drug specific IgE or the basophil activation test (BAT). The BAT requires a serum sample
LY3016859 pharmacokinetic concentration	
Complement	C3a, C5a
Cytokines	IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

All tests will be performed by a Lilly-designated central laboratory.

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