Statistical Analysis Plan Version 3 H0P-MC-BP01

# Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3016859 for the Treatment of Chronic Low Back Pain

NCT04529096

Approval Date: 06-Dec-2021

# 1. Statistical Analysis Plan: H0P-MC-BP01: Intervention-Specific Appendix (ISA) for LY3016859



Epiregulin/TGFα (LY3016859) Pain for the Treatment of Chronic Low Back Pain

This is a randomized, placebo-controlled, phase 2 clinical trial to evaluate LY3016859 for the treatment of chronic low back pain.


Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol H0P-MC-BP01
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 06-Dec-2021 GMT

# 2. Table of Contents

**Section** **Page**

## Table of Contents

**Appendix** **Page**

# 3. Revision History

SAP Version 1 was approved prior to unblinding data for H0P-MC-BP01.

SAP Version 2 was approved prior to unblinding H0P-MC-BP01 data for PoC lock. The following updates were made.

- Section 6.1, the estimand for this ISA was described.
- Section 6.10.3, the details for the constrained model for the key secondary endpoint were added.
- Section 6.17, section added to describe the safety totality of evidence analysis.

SAP Version 3 was approved prior to the final lock. The following updates were made.

- Section 6.11, bioanalytical and pharmacokinetic/pharmacodynamic analysis was updated.
- Section 6.12.2, definition for post-treatment-emergent adverse events was updated.
- Section 6.12.4, the analysis for renal function assessment was updated.
- Section 6.12.5, immunogenicity analysis was added.
- Section 6.14, 'violations' is replaced with 'deviations' for consistency across CPMP documents, and the list of IPDs is referenced in the trial issue management plan. The prohibited medications and drugs of abuse list was moved to the CPMP SAP because it applies across all ISAs, and acetylsalicylic acid was added to the list of prohibited medications.
- Section 7, text on maintaining the blind for assessment committee review was deleted from BP01 SAP V3 since it is covered in H0P-MC-CPMP SAP Version 5.
- Section 8, additional analyses for the double-blinded treatment and safety follow-up period combined was added for the final lock.

# 4. Study Objectives

## 4.1. Primary Objective

The primary objective of this ISA is stated in the H0P-MC-CPMP (a) protocol. For H0P-MC-BP01, endpoint is defined as 8 weeks post initial treatment administration.

## 4.2. Secondary Objectives

Secondary objectives applicable to all ISAs are listed in the H0P-MC-CPMP SAP Version 5.

Additional secondary endpoints specific to H0P-MC-BP01 are listed below.

| Objective | Endpoint Measure |
|---|---|
| **Other Secondary** | |
| **Physical Functioning**<br>Efficacy of LY3016859 versus placebo | • Mean change from baseline to endpoint for the Roland-Morris Disability Questionnaire (RMDQ) total score<br>• Proportion of participants with reduction from baseline of at least 3.5 points on RMDQ total score across all time points<br>• Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% on the RMDQ total score across all time points<br>• Time to first treatment response with at least 30%, 50%, and 70% reduction from baseline in RMDQ total score |

## 4.3. Exploratory Objectives

The following exploratory objectives and endpoints are specific to H0P-MC-BP01.

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

Abbreviations: eGFR = estimated glomerular filtration rate.

# 5. Study Design

## 5.1. Summary of Study Design

The H0P-MC-CPMP SAP Version 5 provides a summary of the overall study design for the chronic pain master protocol. This section describes ISA-specific study design components.

**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 Schedule of Activities (SoA).

The site schedules Visit 801 approximately 4 weeks after Visit 7, Visit 802 approximately 8 weeks after Visit 7, and Visit 803 approximately 18 weeks after Visit 7.

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

## 5.2. Determination of Sample Size

Approximately 150 participants will be randomized in a 2:1 ratio to LY3016859 and placebo, respectively. It is expected that approximately 128 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 less than 0.05. The simulation for the power calculation and sample size determination was carried out in FACTS Version 6.0.

## 5.3. Method of Assignment to Treatment

The method of treatment assignment is described in the H0P-MC-CPMP SAP Version 5.

# 6. A Priori Statistical Methods

## 6.1. General Considerations

The estimand for the primary clinical question of interest has been described in the H0P-MC-CPMP SAP Version 5.

Other general considerations for analyses are described in the H0P-MC-CPMP SAP Version 5.

## 6.2. Adjustments for Covariates

The general adjustment strategy has been described in the H0P-MC-CPMP SAP Version 5.

Randomization into H0P-MC-BP01 is stratified by the presence of neuropathic pain as defined by the painDETECT score.

The following stratification factor will be included in the models for the primary, secondary, and some exploratory outcomes.

| **Neuropathic pain** | **painDETECT score** |
|---|---|
| Positive presence | ≥19 |
| Unclear or negative | <19 |

## 6.3. Handling of Dropouts or Missing Data

The missing data strategy has been described in the H0P-MC-CPMP SAP Version 5.

## 6.4. Multiple Comparisons/Multiplicity

There is no plan to formally adjust for multiplicity.

## 6.5. Use of an "Efficacy Subset" of Participants

There are no plans to use a modified efficacy subset.

## 6.6. Participant Disposition

The summary of participant disposition has been described in the H0P-MC-CPMP SAP Version 5.

## 6.7. Participant Characteristics

The general summary of participant characteristics has been described in the H0P-MC-CPMP SAP Version 5.

ISA-specific considerations are described below.

- painDETECT ≥19 (i.e., Positive for neuropathic pain)
- Roland Morris Disability Questionnaire (RMDQ) Total Score at baseline

## 6.8. Treatment Compliance

To assess the impact of compliance to the protocol specified dosing schedule, the number of days between each infusion will be summarized and reported by treatment arm. The summaries will include descriptive statistics (sample size at visit, mean, SD, median, minimum, maximum). No inferential statistics will be reported.

## 6.9. Concomitant Therapy

The summary and reporting of concomitant therapy has been described in the H0P-MC-CPMP SAP Version 5. No additional covariates will be considered in the models of weekly rescue medication use.

## 6.10. Efficacy Analyses

### *6.10.1. Primary Outcome and Methodology*

The analysis of the primary outcome has been described in the H0P-MC-CPMP SAP Version 5. The longitudinal model will include average NRS during the preliminary data entry period (PDEP) period and within each nominal week of the double treatment period as a longitudinal outcome. As noted in Section 4.1, endpoint for the primary analysis is defined as 8 weeks post initial treatment administration.

### *6.10.2. Additional Analyses of the Primary Outcome*

There are no additional analyses planned for the primary outcome.

### *6.10.3. Secondary Efficacy Analyses*

Secondary efficacy analyses common to all ISAs within H0P-MC-CPMP have been described in the H0P-MC-CPMP SAP Version 5. H0P-MC-BP01 will also consider the following secondary analyses.

The RMDQ is a simple, sensitive, and reliable method to measure disability in patients with back pain. The RMDQ consists of 24 statements relating to the person's perceptions of back pain and associated disability based on

- physical ability/activity
- sleep/rest
- psychosocial
- household management
- eating, and
- pain frequency.

Participants are asked if they feel the statement is descriptive of their own circumstance on that day. The total score is obtained by counting the number of ''Yes'' responses, ranging from:

0 = no disability to 24 = maximal disability.

A Bayesian longitudinal mixed-effect model repeated measures (MMRM) analysis will be performed to evaluate the change from baseline to each postbaseline visit for the RMDQ total score. The model will utilize the constrained cell means model so that a common mean is estimated at the baseline. More details on this approach are provided in the H0P-MC-CPMP SAP Version 5.

This table describes information included in the model.

| | |
|---|---|
| **Categorical effects** | • the interaction of treatment and timepoint (constrained to estimate a common mean at baseline across treatments)<br>• average baseline pain severity category (baseline NRS < 7, baseline NRS >= 7)<br>• presence of neuropathic pain (painDETECT ≥19, painDETECT <19)<br>• pooled investigative site |
| **Continuous covariates** | • none |

### Other Secondary Analysis

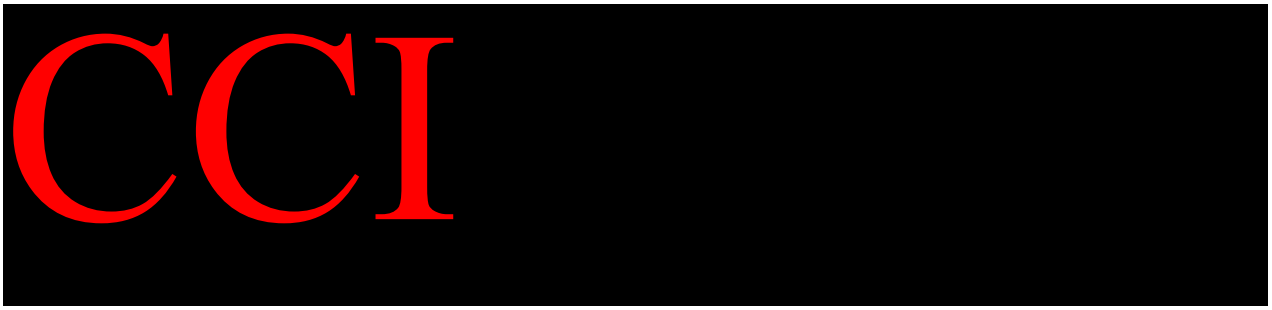
The proportion of participants in each treatment group meeting prespecified binary efficacy outcomes will be calculated for each post baseline time point and will be used to compare treatment groups. The prespecified binary efficacy outcomes include the proportion of participants:

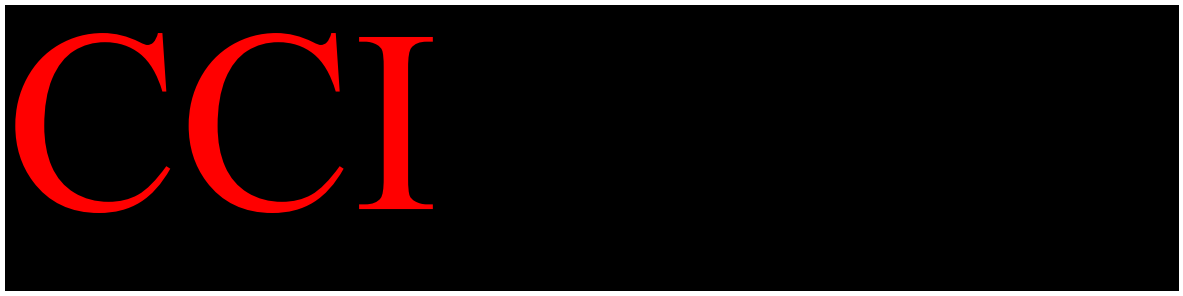
- with a reduction greater than or equal to 30%, 50%, and 70% from baseline as measured by the RMDQ score, and
- with at least a 3.5 point reduction from baseline in the RMDQ score.

A Bayesian pseudo-likelihood-based categorical repeated measures regression model that includes all post baseline observations will be used to estimate the probability of achieving the response level in each treatment group and will be used to compare treatment groups.

The model will include the categorical and continuous covariates described for the secondary analysis of RMDQ total score.

In addition, time to first treatment response from baseline based on the prespecified binary thresholds above will be assessed. Analyses will be conducted according to the time to event analyses specified in the CPMP SAP Version 5.






## 6.12. Safety Analyses

The general analysis of safety has been described in the H0P-MC-CPMP SAP Version 5. However, additional ISA-specific safety considerations are described in the sections below.

### *6.12.1. Extent of Exposure*

The cumulative dosage taken during the double-blind treatment period will be summarized. In addition, the distribution of the number of doses received during the double-blind treatment period will be summarized by reporting the number and percent of participants in the safety population who received 1, 2, 3, or 4 infusions during the double-blind treatment period.

Duration of exposure to study drug (defined as the time since first injection of the study treatment in days) will be summarized by treatment group using descriptive statistics; the summary will also include the total exposure in patient years.

Duration of exposure (days):
*= Date of last study visit (scheduled or unscheduled) during the double blind treatment period – Date of first injection of the study treatment + 1*

Total exposure in patient years will be calculated as follows:
*Total exposure in patient years = Sum of duration (days) of exposures for all patients in the treatment group/365.25*

### *6.12.2. Adverse Events*

The general analysis of adverse events has been described in the H0P-MC-CPMP SAP Version 5.

This ISA will also consider post-treatment-emergent adverse events due to the long follow-up period.

A post-treatment-emergent adverse events (PTEAE) is defined as an event that first occurs or worsens in severity after treatment discontinuation and on or before study discontinuation. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in the post-treatment-emergent computation. The maximum severity for each LLT during the treatment period will be used as a reference.

The baseline of PTEAE is from the first dosing date to the treatment disposition in the double-blind treatment phase. The post-treatment follow-up period will be included as postbaseline for this analysis. While unusual, it is possible to have a missing severity for events. Events with a

missing severity during the post-treatment period will be treated as "severe" and post-treatment period emergence will be determined by comparing with treatment period. All events occurring after the day of treatment discontinuation will be treated as post-treatment period.

PTEAEs will be summarized by preferred term and by preferred term within system organ class in participants who received LY3016859.

### *6.12.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events*

The general summary of adverse of events is described in the H0P-MC-CPMP SAP Version 5.

Treatment emergent adverse events of special interest will be reported separately by preferred term. These events include

- infusion site reactions (preferred MedDRA term)
- hypersensitivity and infusion-related reactions
    - Anaphylatic reaction (SMQ)
    - Anaphylatic/anaphylactoid shock conditions (SMQ)
    - Angioedema (SMQ)
    - Hypersensitivity (SMQ)
    - Infusion-related reaction (preferred MedDRA term)
- dermatological adverse events
    - Severe cutaneous adverse reactions (SMQ)
    - Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)
- abnormal renal function
    - Renal function analyses (MedDRA HLT)
    - Renal failure and impairment (MedDRA HLT)


CCI


CCI


### *6.12.6. Vital Signs and Other Physical Findings*

The analysis of vital sign parameters is described in the H0P-MC-CPMP SAP Version 5.

### *6.12.7. Electrocardiograms*

The analysis of electrocardiograms parameters is described in the H0P-MC-CPMP SAP Version 5.

## 6.13. Subgroup Analyses

General subgroup analyses are described in the H0P-MC-CPMP SAP Version 5.

There are no additional subgroup analyses planned.

## 6.14. Protocol Deviations

Paticipants with study important protocol deviations will be summarized by type of deviation and listed by treatment and investigative site.

Important protocol deviations for the study are described in the H0P-MC-CPMP SAP Version 5

and H0P-MC-BP01 Trial Issue Management Plans.

## 6.15. Interim Analyses and Data Monitoring

Interim analyses may be conducted under the auspices of an Assessment Committee according to the specifications set forth in the protocol. These analyses will be at the CPMP level and will consider data from all ongoing ISAs. Details are provided in the H0P-MC-CPMP SAP Version 5.

There are no additional interim analyses planned for H0P-MC-BP01.

## 6.16. Planned Exploratory Analyses

In addition, a cumulative distribution function of percent change from baseline to endpoint for the RMDQ total score will be provided for each treatment group. However, no statistical comparisons will be made between the groups.

## 6.17. Totality of Evidence for Safety

The totality of evidence for safety analysis has been briefly described in the H0P-MC-CPMP SAP Version 5. The key safety events to be considered for H0P-MC-BP01 are listed below by domain:

**General Adverse Event Information**

- Serious adverse events related to study treatment
- Study discontinuation due to adverse event
- Treatment discontinuation due to adverse event

**Cardiovascular**

- QTc prolongation: > 60 msec increase
- Serious cardiac disorders adverse event

**Liver function**

- Hy's Law case: Serum total bilirubin ≥ 2 and ALT ≥ 3 for at least one visit during the double-blind treatment period

**Metabolic function**

- Serious hypoglycemia adverse event
- Treatment emergent HbA1c: Shift from low/normal at baseline to high at least once during the double-blind treatment period

**Renal function**

- Treatment emergent abnormal eGFR: Shifts
    - Mild at baseline to moderate/severe during the double-blind treatment period
    - Moderate at baseline to severe during the double-blind treatment period

**Dermatological**

- Serious or severe dermal reactions

**Hypersensitivity**

- Moderate to severe infusion site reactions
- Serious or severe hypersensitivity reactions

## 6.18. Annual Report Analyses

Analyses will be produced as needed for the purposes of providing periodic safety reviews to regulatory agencies (e.g. Development Safety Update Reports.) Data from this ISA will be combined with data from other clinical studies that investigated LY3016859. In all analyses, a combined LY arm will be created which includes participants assigned to any dose of LY3016859 in the included studies, including LY-combination regimens.

The following data will be summarized by treatment group.

- Enrollment (ongoing and completed)
- Demographics (Race, ethnicity, and gender)
- Exposure
    - Cumulative number of subjects exposed to LY3016859
    - Cumulative number of subjects exposed to LY3016859 by age
    - Cumulative number of subjects exposed to LY3016859 by sex
    - Cumulative number of subjects exposed to LY3016859 by race
- Cumulative summary of serious adverse events

The following listings will be provided.

- List of serious adverse events during the reporting period
- List of subjects who died
- Cumulative list of subjects who discontinued due to an adverse event (discontinued from treatment or study)
- List of subjects who discontinued due to an adverse event during the reporting period

Additional analyses may be added or omitted at the time of report submission as needed.

## 6.19. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset, which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- A serious adverse event is an adverse event that is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term

  - the number of events experienced.

- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

A summary of a baseline characteristics XML file will be provided.

# 7. Unblinding Plan

The general unblinding plan is described in the H0P-MC-CPMP SAP Version 5. Unblinding considerations specific to H0P-MC-BP01 are provided below.

**Immunogenicity Analysis Planning**
To support the assessment committee's evaluation of immunogenicity, a limited number of preidentified individuals may also gain access to the unblinded data. The project statistician will work with the clinical immunogenicity scientist and clinical lab data scientist to determine an appropriate amount of ISA-level data to support this objective. The timing of the transfer of treatment assignment and immunogenicity data will be based on this collaboration. 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.

# 8. Reports to be Generated at Final Database Lock

The following analysis will be performed for final database lock.

- Patient disposition - the analysis of patient disposition conducted in POC lock will be conducted for double-blind treatment and safety follow-up period combined (DB plus FU).
- eCOA compliance - the overall eCOA compliance analysis conducted in POC lock will be summarized for PDEP period plus at each nominal week up to Visit 801.
- Concomitant therapy – the analysis conducted in POC lock will be repeated in DB plus FU period (may also include PDEP) except the listing of rescue medication use above protocol specified limits.
- Efficacy endpoint – The weekly average pain intensity via NRS will be calculated with extension to week 12 (Visit 801). The following analysis will be conducted across all time points in DB plus FU period based on the same model conducted in DB treatment period. Nominal weeks 9-12 in the follow-up period will be derived in a similar way as described in section 6.12.1 of the H0P-MC-CPMP SAP Version 5, except that the days between V7 and V801 are split across 4 weeks.
    - Change from baseline in average pain intensity measured by weekly average of NRS
    - Change from baseline in worst pain intensity measured by weekly average of NRS
    - Change from baseline in DSA-specific physical functioning measures
    - Proportion of participants with a pain reduction from baseline greater than or equal to 30%, 50%, and 70% as measured by the average pain responses on the NRS
    - Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% on DSA-specific physical function subscale
    - Overall improvement as measured by Patients' Global Impression of Change

  A frequentist MMRM analysis will be conducted as a sensitivity analysis for the primary and some secondary endpoints.

  A Bayesian MMRM subgroup analysis of baseline pain severity (<7, >=7) will be also evaluated for the primary endpoint. A frequentist MMRM analysis will be performed as a sensitivity analysis for subgroup analysis.
- Safety analyses for TEAEs – the following analysis will be repeated in DB plus FU period unless otherwise specified.
    - Overview of adverse event, a listing of AE (also include PDEP)
    - SAE and a listing of SAE
    - TEAE and post-treatment-emergent adverse event (PTEAE) by PT, by PT within SOC, and PT by maximum severity. A listing of TEAE and PTEAE will be provided.

  - Post-treatment-emergent AE by PT, by PT within SOC for safety follow-up period only
  - Adverse event of special interest (ISA specific)
- Laboratory measures – some analysis conducted in POC lock will be repeated in DB plus FU period. The additional analysis will be included but not limited to
  - Summary of laboratory measures with box plot for observed value and change from baseline by visit, and shifts to high/low.
  - The shift table of eGFR at baseline vs. postbaseline by minimum, maximum and last observed eGFR result will be summarized.
  - Summary of hepatic function laboratory maximum observed result at baseline and any postbaseline will be presented.
- Vital signs – some analysis conducted in POC lock will be repeated for combined DB plus FU period.
- ECG - some analysis conducted in POC lock will be repeated for combined DB plus FU period. Additionally, a summary of ECG measures and boxplot will be provided as well as a listing of out of range of ECGs.
- Protocol deviations - summary of important protocol deviation will be conducted in DB plus FU period.

# 9. References

Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22(10):1911-1920.

Inker L.A., Schmid C. H., Tighiouart H., Eckfeldt J.H., Feldman H.I., Greene T., Kusek J.W., Manzi J., Van Lente F., Zhang Y., Coresh J., and Levey A.S. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. N Engl J Med. 2012; 367: 20-29.

Levey A.S., Coresh J., Greene T., Stevens L.A., Zhang Y., Hendriksen S., Kusek J.W., and Van Lente F. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. Ann Intern Med. 2006; 145: 247-254.

# 10. Appendices

# Appendix 1. Planned Laboratory Analytes and Direction of Interest

The H0P-MC-CPMP SAP Version 5 describes tests that may be performed broadly for the Chronic Pain Master Protocol. This table describes additional tests in H0P-MC-CPMP.

| Chemistry | CCI | Other Tests |
|---|---|---|
| Cystatin-C | | Immunogenicity |
| | | Serum Epiregulin |
| | | LY3016859 concentration |
| | | Urine pregnancy |
| | | |

**Leo Document ID = 10f50551-87b2-4a58-a289-175366533963**

**Approver:** PPD

**Approval Date & Time: 06-Dec-2021 21:18:26 GMT**

**Signature meaning: Approved**