I7P-MC-DSAD Statistical Analysis Plan Version 1

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3041658 in Adults with Moderate-to-Severe Hidradenitis Suppurativa

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1. Draft Statistical Analysis Plan for Clinical Studies: I7P-MC-DSAD: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3041658 in Adults with Moderate-to-Severe Hidradenitis Suppurativa

LY3041658 Hidradenitis Suppuruativa

Study I7P-MC-DSAD (DSAD) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of LY3041658 600 mg given intravenously (IV) every 2 weeks (Q2W) in adults with moderate-to-severe HS.

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Protocol I7P-MC-DSAD
Phase 2

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

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to unblinding.

4. Study Objectives

4.1. Primary Objective

Objectives	Endpoints
Primary	
● To test the hypothesis that treatment with LY3041658 is superior to placebo in inducing Hidradenitis Suppurativa Clinical Response (HiSCR) in adult participants with moderate-to-severe hidradenitis suppurativa (HS)	● Proportion of participants achieving HiSCR response at Week 16

4.2. Secondary Objectives

Objectives	Endpoints
Secondary	
● To evaluate the efficacy of LY3041658 compared to placebo with respect to measures of signs and symptoms and pain in adult participants with moderate-to-severe HS	● Mean change from baseline to Week 16 in: ○ Total number of abscesses and inflammatory nodules (AN count) ○ Skin Pain – HS Numeric Rating Scale (NRS)

4.3. Exploratory Objectives

Exploratory
Exploratory objectives and endpoints may include the following: ● To evaluate, at various time points, the efficacy of LY3041658 compared to placebo in inducing improvements in signs and symptoms and quality of life ● To characterize the pharmacokinetics (PK) of LY3041658 and to explore relationships between LY3041658 exposure and select biomarkers and clinical efficacy endpoints ● To assess the potential development of anti-LY3041658 antibodies and their impact on the safety profile and PK of LY3041658

5. Study Design

5.1. Summary of Study Design

Study I7P-MC-DSAD (DSAD) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of LY3041658 600 mg given intravenously (IV) every 2 weeks (Q2W) in adults with HS.

The study duration will be up to approximately 51 weeks over 4 study periods:

Screening: a period lasting up to 35 days before Week 0 (Visit 2, baseline)

Treatment Period 1: a 16-week, 2-group double-blind treatment period:

- At baseline (Visit 2, Week 0), eligible participants will be randomized in a 2:1 ratio to receive either LY3041658 600 mg IV Q2W or placebo IV Q2W, starting at the baseline visit.

Treatment Period 2: a 20-week, single-group open-label extension period:

- Starting at Week 16, all participants, including those previously assigned to placebo, will receive LY3041658 600 mg IV Q2W until the last dosing visit.

Post-treatment follow-up: a period lasting approximately 10 weeks.

- Participants will not receive study drug in this period.
- The last dose of the study drug is given at Visit 19 (Week 34). Thus, participants will have been withdrawn from study drug for a total of 12 weeks at the last post-treatment follow-up visit (Visit 802, Week 46).

Approximately 76 patients will be screened to achieve approximately 51 participants randomized in a 2:1 ratio to one of two treatment groups:

approximately 34 participants randomized to LY3041658, and

approximately 17 participants randomized to placebo.

Unscheduled visits are for participants needing rescue therapy or incision and drainage. The use of concomitant medications, including rescue therapy, is described in Section 6.5 in the protocol.

Participants who permanently discontinue the study drug early (Section 7.1 in the protocol) will undergo early termination procedures, including an early termination visit (ETV) and the post-treatment follow-up visits specified in the Schedule of Activities (SoA) (Section 1.3 in the protocol).

Figure DSAD.5.1 illustrates the study design. The blinding procedure is described in the protocol.

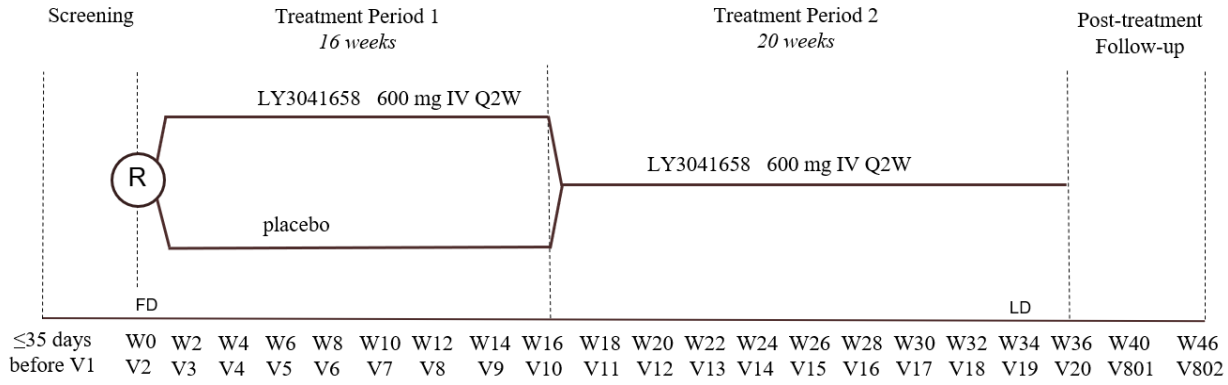

Figure DSAD.5.1. Schema of Study I7P-MC-DSAD, a Phase 2 study to evaluate the efficacy and safety of LY3041658 in adults with moderate-to-severe hidradenitis suppurativa.

Note: Starting at Week 16 participants who received placebo in Treatment Period 1 will receive LY3041658 600 mg IV Q2W.

Abbreviations: FD = first dose; IV = intravenous; LD = last dose; Q2W = every 2 weeks; R = randomization visit; V = visit; W = study week relative to randomization visit.

5.2. Method of Assignment to Treatment

Subjects who meet all criteria for enrollment will be randomized in a 2:1 ratio to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

6. A Priori Statistical Methods

6.1. Statistical Hypotheses

The study will compare LY3041658 with placebo in adults with HS. The primary study objective is to demonstrate superior efficacy of LY3041658 over placebo.

The primary comparison of interest is the proportion of participants achieving HiSCR response at Week 16.

Secondary comparisons include the mean change of AN count and Skin Pain – HS NRS from baseline to Week 16.

Efficacy comparisons will be made without regard to changes to any background therapies. No adjustments for multiplicity will be made across the efficacy assessments. Participants who discontinue the treatment or the study prior to Week 16 will be considered a nonresponder for all relevant analyses.

6.1.1. Estimands

The study will compare LY3041658 with placebo in participants with HS.

The primary comparison of interest is the difference in proportion of participants who achieve HiSCR response at Week 16. The primary objective is to demonstrate superiority of LY3041658 versus placebo.

The primary comparison will be assessed using a composite estimand where the intercurrent events of premature discontinuation and use of prohibited medication are part of the response definition.

6.2. Sample Size Determination

Approximately 76 patients will be screened to achieve approximately 51 participants randomized in a 2:1 ratio to one of two treatment groups:

approximately 34 participants randomized to LY3041658, and

approximately 17 participants randomized to placebo.

For all randomized patients, approximately 45 patients are expected to complete the 16 weeks treatment period to ensure the validity of the study result. This sample size provides at least 80% power to the primary endpoint of HiSCR response. This calculation is a 2-sided test for superiority of LY3041658 compared to placebo on HiSCR response rate with significance level

of 0.05 CCI [redacted]

6.3. General Considerations

Efficacy analyses will be conducted on the Modified Intent-to-Treat (mITT) and Per-Protocol Set Population. The mITT set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants were assigned. The PPS set includes all data from all randomized participants who missed no more than 1 dose of study treatment to which they were assigned up to and including Week 14.

Safety analyses will be conducted on the Safety Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants actually received.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will report the number of participants and incidence as a frequency and as a percentage. All p-values will be rounded up to 3 decimal places.

6.3.1. Analysis Populations

The following populations are defined for this study:

Population	Description
Entered	All participants who sign the informed consent form
Modified Intent-to-Treat (mITT)	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Per Protocol Set (PPS)	All participants randomly assigned to study intervention to which they were assigned at Week 0 and who missed no more than 1 dose of study treatment up to and including Week 14.
Safety	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received within each study period.
Pharmacokinetic (PK) Analysis	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and have PK data available.

6.3.2. Definition of Baseline Measures

The baseline value for Treatment Period 1 is defined as the last nonmissing measurement on or before the date of first study drug administration (expected at Week 0). The baseline value for Treatment Period 2 is the last available value before Visit 10 (Week 16), the visit at which participants who previously received placebo will receive their first dose of LY3041658. Other definitions of the baseline value may be used to conduct additional supporting analyses.

6.3.3. Analysis Methods

The main analysis of categorical efficacy variables and health outcomes variables will use a logistic regression analysis with treatment group in the model. The p-value and 100(1-alpha)% CI for the odds ratio from the logistic regression model are used for primary statistical inference. The difference in percentages and 100(1-alpha)% CI of the difference in percentages using the Newcombe-Wilson without continuity correction will be reported. The p-value from the Fisher's exact test will also be produced as a secondary analysis.

The main analysis for all continuous efficacy and health outcomes variables will use mixed model repeated measures (MMRM) analysis. The model will include treatment, region, baseline disease severity, visit, and treatment-by-visit-interaction as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, the heterogeneous autoregressive [ARH(1)], followed by the heterogeneous compound symmetry (CSH), followed by the heterogeneous Toeplitz (TOEPH) will be used. The Kenward-Roger method will be used to estimate the degrees of freedom. Type III tests for the least-squares means (LSM) will be used for the statistical comparison. The LSM difference, standard error, p-value and 100(1-alpha)% CI will also be reported.

Fisher's exact test will be used for the adverse events (AEs), discontinuation, and other categorical safety data for between-treatment group comparisons. Continuous vital signs, body weight, and other continuous safety variables, including laboratory variables, will be analyzed by an ANCOVA with treatment group and baseline value in the model. The significance of within-treatment group changes from baseline will be evaluated by testing whether or not the treatment group LSM changes from baseline are different from zero; the standard error for the LSM change will also be displayed. Differences in LSM will be displayed, with the p-value associated with the LSM comparison to placebo and a 95% CI on the LSM difference also provided. In addition to the LSMs for each group, the within-group p-value for the change from baseline will be displayed. Treatment-emergent high/low for categorical laboratory safety analyses will also be produced.

6.4. Handling of Dropouts or Missing Data

Missing data on the primary endpoint, HiSCR response, and other dichotomous endpoints will be imputed as nonresponse. As a supplementary analysis, the primary endpoint at week 16 will be imputed using the last observation prior to missingness. For other endpoints, including continuous secondary endpoints, missing data may be imputed using the last observation prior to missingness or other appropriate imputation methods.

6.5. Patient Disposition

A description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as the number and percentage of participants completing the study (participants who receive at least

1 dose of study drug and have at least 1 postbaseline assessment), or discontinuing (overall and by reason for discontinuation). A summary of important protocol deviations will be provided.

6.6. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population. A summary of baseline demographics and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported using descriptive statistics. Other participant baseline characteristics will be summarized by group as deemed appropriate.

6.7. Efficacy and Health Outcome Analyses

6.7.1. Primary Endpoint

The primary comparison of interest is the proportion of participants achieving HiSCR response at Week 16. The HiSCR (Kimball et al. 2014; Kimball et al. 2016b) is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (sum of abscesses and inflammatory nodules [AN count]) with no increase in abscess count (A count) and no increase in draining fistulae count (DF count) relative to baseline.

CCI

The primary comparison to establish superiority of LY3041658 over placebo using a composite estimand where the intercurrent events of premature discontinuation and use of prohibited medication are part of the response definition. The composite endpoint will be analyzed using logistic regression on the mITT and PPS population with treatment group in the model. The treatment difference and 95% CIs will be reported.

6.7.2. Secondary Endpoints

Secondary comparisons of interest are the mean change from baseline to Week 16 for

- total number of abscesses and inflammatory nodules (AN count), and
- Skin Pain – HS NRS.

The Skin Pain – HS Numeric Rating Scale (NRS) is a patient-administered, single-question, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no pain” and 10 representing “pain as bad as I can imagine.” The recall period is 7 days.

An analysis of covariance (ANCOVA) model with proper link function will be used for analysis of these secondary endpoints on the mITT and PPS population. The AN count is a count data and we will use log transformation as the link function.

6.7.3. Exploratory Endpoints

6.7.3.1. Additional HiSCR Response Definitions

The primary endpoint will be assessed using different definitions of HiSCR response at Week 16. Specifically, the needed reduction in AN count will be modified from 50% to 75% and to 90%. The same analysis method used for the primary endpoint will be used for these exploratory analyses. The percentage of responders achieving, HiSCR50, HiSCR75, and HiSCR90, in the mITT and the PPS population will be summarized by visit and by treatment arm to which the patients were randomized at Week 0 (Visit 2). A plot of the percentage of responders over weeks will be provided.

The proportion of visits that a patient achieves HiSCR response out of the total visits the patient attends during study period 1 and 2 (Week 0 to Week 36) will be calculated as follow,

$$\frac{\#\text{ of visits the patient achieves HiSCR response}}{\text{Total }\#\text{ of visits the patient attends}} * 100.$$

The HiSCR response is defined in Section 6.7.1 which is based on a patient's baseline values. The summary statistics of the proportion of visits achieving responses will be summarized by treatment arms to which the patients were randomized at Week 0 (Visit 2).

Moreover, the restricted mean response time (RMRT), a measure of the average time a responder stays a responder within a specified time period, will be provided up for responders at week 16 up (Visit 10) to week 36 (Visit 20) in each treatment arm, respectively. The time to loss of response in HiSCR50 is defined as >= 50% increase in AN compared to the average AN count from the 3 previous visits, and the increase was >= 3 AN from the average AN count of the 3 previous visits. Specifically, the RMRT is calculated as,

$$\sum_{k=10}^{20}\left\{\prod_{v=10}^{k}\left(1-\frac{\delta_v}{R_v}\right)\right\} \times 2\ weeks$$

Where δ_v is the number of patients who are responder at Visit 10 (week 16) but first loss response at Visit v and R_v is the number of patients who are responder at Visit 10 (week 16) and stay reponse before Visit v. The average RMRT will be summarized by treatment arm to which the patients were randomized at Week 0 (Visit 2).

6.7.3.2. Lesion Counts

The mean change from baseline to Week 16 for the total number of abcesses, inflammatory nodules, draining fistulae, and abscess and inflammatory nodule (AN) will be individually summarized and assessed using ANCOVA. Moreover, we will calculate the proportion of patients that achieve 50%, 75% and 90% decreases in AN count at W12 and W16. In addition to AN reduction, the proportion of patients with disease flare will be calculated up to W16, defined as a ≥25% increase in AN count from the baseline and ≥2 in AN count.

6.7.3.3. Modified Sartorius Score (mSS)

The mean percent change from baseline to Week 16 for the total modified Sartorius Score (mSS) will be summarized by treatment group and assessed using MMRM methods.

6.7.3.4. International Hidradenitis Suppurativa Severity Score System (IHS4)

The mean percent change from baseline to Week 16 for the International Hidradenitis Suppurativa Severity Score System (IHS4) will be summarized by treatment group and assessed using MMRM methods.

6.7.3.5. Patient-Reported Outcomes

Categorical variables will be analyzed using logistic regression analyses, whereas the mixed-effects model of repeated measures (MMRM) will be the method of analysis for continuous endpoints. The analyses will be based on the mITT population unless otherwise specified.

The following continuous endpoints from patient-reported outcomes will be assessed:

- Mean change from baseline to Week 16 on the Dermatology Life Quality Index (DLQI)
- Mean change from baseline to Week 16 on the Drainage Numeric Rating Scale
- Mean change from baseline to Week 16 on the Smell Numeric Rating Scale

The following categorical endpoints from patient-reported outcomes will be assessed:

- Proportion of patients responding "no symptoms" on the Patient Global Impression of Severity – 7 Days (Hidradenitis Suppurativa)
- Proportion of patients responding "much better" on the Patient Global Impression of Change – 7 Days (Hidradenitis Suppurativa)
- Proportion of patients responding "much better" or "a little better" on the Patient Global Impression of Change – 7 Days (Hidradenitis Suppurativa)
- Proportion of patients with baseline skin pain NRS≥3 having a decrease in skin pain NRS≥ 30%
- Proportion of patients with baseline drainage NRS≥3 having a decrease in drainage NRS≥ 30%
- Proportion of patients with baseline smell NRS≥3 having a decrease in smell NRS≥ 30%

For patients who meet the criteria at baseline for the presence of inflammatory back pain (IBP), the following endpoints will be assessed using ANCOVA:

- Mean change from baseline to Week 16 on the weekly spinal pain numeric rating scale
- Mean change from baseline to Week 16 on the weekly nightly spinal pain numeric rating scale.

6.7.3.6. Pharmacokinetic Analyses

Plasma concentrations of LY3041658 will be listed by time point using descriptive statistics and displayed graphically. Actual sampling time relative to the last dose and time deviations will be considered to determine exclusions from summary statistics and mean plots.

The data may also be analyzed using a population approach via nonlinear mixed-effects modeling (NONMEM) with the NONMEM software. The PK data from Study DSAD may be combined with data from another study in the clinical development program to improve PK parameter estimation.

6.7.3.7. Immunogenicity

Frequencies and percentages will be tabulated for the following:

- participants with pre-existing ADA, and
- participants who are TE-ADA positive (TE-ADA+) to LY3041658.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE-ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, if assessed, may also be tabulated for the TE-ADA+ participants.

The relationship between the presence of ADA and the LY3041658 concentrations and PD response to LY3041658, including safety and efficacy, may also be assessed.

6.8. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Graphical analyses to explore relationships between LY3041658 exposure and select biomarkers and clinical efficacy endpoints will be performed.

6.9. Safety Analyses

The general methods used to summarize safety data, including the definitions of baseline values, are described in Section 6.3.2.

Safety analyses will include data after rescue unless otherwise stated, and patients will be analyzed according to the investigational product to which they were randomized at Week 0 (Visit 2). Additional analyses may be conducted using data after rescue to systemic therapy for some safety topics such as systemic treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs). Safety analyses will take place using the safety population defined in Section 6.3.1.

Safety topics that will be addressed include the following: AEs, clinical laboratory evaluations, vital signs and physical characteristics.

Unless otherwise specified, by-visit summaries will include planned on-treatment visits. For tables that summarize events (such as AEs, categorical lab abnormalities, shift to maximum value), post-last dose follow-up data will be provided for Treatment Period 1 (Week 0 to Week 16) and Treatment Period 2 (Week 16 to Week 36) separately. For deaths and malignancies, all

available follow-up data up to the end of the study will be included. Listings will include all safety data.

For selected safety assessments, descriptive statistics may be presented for the last measure observed during post-treatment follow-up (up to 30 days after the last dose of treatment including rescue, regardless of the study period).

6.9.1. Extent of Exposure

Duration of exposure (in days) to study drug will be summarized for the safety population in both Period 1 and 2 by treatment group using descriptive statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum).

For subjects without drug interruption, the duration of exposure for each patient is the date of last dose – date of first dose +1. If subjects have drug interruption, the duration of exposure for each patient is the (Treatment end date before drug interruption – date of first dose +1) + (date of last dose – treatment re-start date +1).

6.9.2. Adverse Events

Adverse events are recorded in the eCRFs. Each AE will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of database lock. Severity of AEs is recorded as mild, moderate, or severe.

A TEAE is defined as an event that either first occurred or worsened in severity after the first dose of study treatment and on or prior to the last visit date during the analysis period. For each event classification term, the number of participants experiencing a TEAE with that classification term will be tabulated. TEAEs will be summarized by treatment period and overall for the study.

Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. For events that are gender-specific, the denominator and computation of the percentage will include only participants from the given gender.

Adverse events are classified based upon the MedDRA PT. The MedDRA Lowest Level Term (LLT) will be used in defining which events are treatment-emergent. The maximum severity for each LLT during the baseline period up to the first dose of the study medication will be used as the baseline. If an event with missing severity is preexisting during the baseline period, and persists during the treatment period, then the baseline severity will be considered mild for determining TEAE (that is, the event is treatment-emergent if the severity is coded moderate or severe postbaseline and not treatment-emergent if the severity is coded mild postbaseline). If an event occurring postbaseline has a missing severity rating, then the event is considered treatment-emergent. The day and time for events where onset is on the day of the first dose of study treatment will both be used to distinguish between pretreatment and posttreatment in order to derive treatment-emergence. Should there be insufficient data for AE start date to make this

comparison (for example, the AE start year is the same as the treatment start year, but the AE start month and day are missing), the AE will be considered treatment-emergent.

In an overview table, the number and percentage of subjects who experienced a TEAE or serious adverse event (SAE), died due to an AE, or discontinued from the study due to an AE will be summarized by treatment.

The frequency and percentages of patients with TEAEs will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. The frequency and percentages of patients with TEAEs by maximum severity will also be summarized by treatment using MedDRA PT nested within SOC.

Fisher's exact test will be performed to compare percentages for each LY3041658 dose group and Placebo at both the SOC and PT levels.

Listings will be presented for all AEs, all SAEs, all AEs leading to death, all AEs leading to study drug temporary interruption, and all AEs leading to discontinuation from the study.

6.9.2.1. Serious Adverse Event Analyses

The number and percentage of patients who experienced an SAE (including the SAEs that led to death) during the study drug period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

6.9.2.2. Other Significant Adverse Events

The number and percentage of patients who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the study drug period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

Fisher's exact test will be performed to compare percentages for each LY3041658 dose group and Placebo at both the SOC and PT levels.

6.9.3. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol. Summaries will be provided in both Système International (SI) and United States (US) conventional (CN) units (when different). Limits from the performing lab will be used to define low and high. Analyses of laboratory values will be produced using the measurements collected at scheduled time points. All unscheduled assessments will appear only in data listings.

- **Box plots for observed values:** Values at each visit (starting at randomization) will be displayed in box plots for patients who have both a baseline and a result for the specified visit. Unplanned measurements will be excluded. Original-scale data will be used for the display. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries. The box plot will be a notched box for each treatment with outliers displayed, individual measurements outside

of reference limits will also be displayed using distinct symbols overlaying the box plot, and descriptive summary statistics will be included in a table below the box plot.

- **Box plots for change values:** Change from baseline to each visit will be displayed in box plots for patients who have both a baseline and a result for the specified visit. Change from baseline to last observation will also be summarized and analyzed for patients who have both baseline and at least 1 postbaseline result. Baseline will be the last non-missing observation in the baseline period. The last non-missing observation in the Dosing Period will be used as the last observation. Unplanned measurements will be excluded. The box plot will be a notched box for each treatment with outliers displayed, change from baseline to last observation will be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot, along with a p-value using the ANCOVA model containing terms for treatment and the continuous covariate of baseline measurement. Type III sums of squares will be used. The significance of within-treatment group changes from baseline will be evaluated by testing whether the treatment group LSMean changes from baseline are different from zero using a t-statistic. In addition to the LSMeans and tests, the SD, minimum, Q1, median, Q3, and maximum will be displayed.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin will not be included in this analysis as different ranges will be used as described in Section 6.9.5.

6.9.4. Vital Signs and Other Physical Findings

Vital signs and physical characteristics include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, weight, and BMI. Original-scale data will be analyzed. When these parameters are analyzed as continuous numerical variables, unplanned measurements will be excluded. When these parameters are analyzed as categorical outcomes and/or treatment-emergent abnormalities, planned and unplanned measurements will be included.

The planned analyses described for the laboratory analytes in Section 6.9.3 will be used to analyze the vital signs and physical characteristics, except for the inclusion of a threshold for change in addition to a limit for the definition of treatment-emergent. defines the low and high baseline values as well as the criteria used to define treatment-emergence based on post-baseline values.

Table DSAD.6.1. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter	Low mmHg	High mmHg
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10

Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg) (Consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease ≥7%	(Gain) increase ≥7%

6.9.5. Special Safety Topics, including Adverse Events of Special Interest

In addition to general safety parameters, safety information on specific topics of special interest will also be presented. Additional special safety topics may be added as warranted.

In general, for topics regarding safety in special groups and circumstances, patient profiles and/or patient listings, where applicable, will be provided when needed to allow medical review of the time course of cases/events, related parameters, patient demographics, study drug treatment and meaningful concomitant medication use. In addition to the safety topics for which provision or review of patient data is specified, these will be provided when summary data are insufficient to permit adequate understanding of the safety topic.

6.9.5.1. Abnormal Hepatic Tests

Analyses for abnormal hepatic tests will involve 4 laboratory analytes: ALT, AST, total bilirubin, and ALP. In addition to the analyses described in Section 6.9.3, this section describes specific analyses for this topic.

The central laboratory reference ranges (CLRM reference ranges) will be used for these laboratory assessments (ALT, AST, total bilirubin, and ALP).

Analyses for change from baseline to last observation, change from the baseline value to the minimum value during Period 1 and 2, change from the baseline value to the maximum value during Period 1 and 2, and treatment-emergent high or low laboratory results at any time are described in Section 6.9.3.

The patients with the following abnormal elevations in hepatic laboratory tests at any time will be listed for both Period 1 and 2:

- ALT measurement ≥3 times, ≥5 times and ≥10 times the central laboratory ULN.
- AST measurement ≥3 times, ≥5 times and ≥10 times the central laboratory ULN.
- Total bilirubin measurement ≥2 times the central laboratory ULN.
- ALT or AST measurement ≥3 times the central laboratory ULN and total bilirubin measurement ≥2 times the central laboratory ULN
- ALP measurement ≥2 times the central laboratory ULN.

6.9.5.2. Renal Function Effects

Effects on renal function will be assessed through analysis of elevated creatinine.

The CTCAE will be applied for laboratory tests related to renal effects (Table DSAD.6.2). This CTCAE grading scheme is consistent with both Version 3.0 and Version 4.03 of the CTCAE guidelines.

Shift tables will show the number and percentage of subjects from baseline to maximum during Period 1 and 2, with baseline depicted by highest grade during the baseline period. A shift table summary displaying the number and percentage of subjects with maximum postbaseline results will be presented by treatment group within the following categories:

- Decreased; postbaseline category < baseline category
- Increased; postbaseline category > baseline category
- Same; postbaseline category = baseline category.

Treatment-emergent lab abnormalities related to elevated creatinine occurring at any time during the Dosing Period will be tabulated using the CTCAE grades shown in Table DSAD.6.2. Planned and unplanned measurements will be included.

Treatment-emergence will be characterized using 5 criteria:

- any increase in postbaseline CTCAE grade from worst baseline grade
- increase to Grade 1 or above at worst postbaseline
- increase to Grade 2 or above at worst postbaseline
- increase to Grade 3 or above at worst postbaseline
- increase to Grade 4 at worst postbaseline.

Table DSAD.6.2 Common Terminology Criteria for Adverse Events (CTCAE) Related to Renal Effects

Lab Test	CTCAE Version	Grade	Criteria in SI or CN Units
Elevated creatinine	3.0	0 (normal)	≤ ULN
		1	> ULN and ≤1.5× ULN
		2	>1.5× ULN and ≤3× ULN
		3	>3× ULN and ≤6× ULN
		4	>6× ULN

Abbreviations: CN = conventional (US); CTCAE = Common Terminology Criteria for Adverse Events; SI = Système International; ULN = upper limit of normal.

6.9.5.3. Infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC, with additional terms from the Investigations SOC being used in selected instances, as described below.

Treatment-emergent infections will be analyzed according to various groups of infectious events including:

- all infections
  - all PTs in the Infections and Infestations SOC,
- serious infections
  - all PTs in the Infections and Infestations SOC that are SAEs,

- infections that require therapeutic intervention (antibiotics, antivirals, antifungals, and so on)
    - all PTs in the Infections and Infestations SOC for which there is an antimicrobial concomitant medication associated with that event for that subject,
- herpes zoster
    - specific Lilly-defined PTs from the Herpes Viral Infections high-level term (HLT) in the Infections and Infestations SOC, shown in Appendix 1,
- tuberculosis
    - specific Lilly-defined PTs from the Tuberculous Infections HLT and the Investigations SOC, shown in Appendix 2
- viral hepatitis
    - all PTs from the Hepatitis Viral Infections HLT (HLT code 10057212) in the Infections and Infestations SOC.

For each infection event, the frequency for each PT will be provided, ordered by decreasing frequency in the LY3041658 highest dose group by infection group: all infections, serious infections (overall and on each approach to identifying SAEs), infections that require therapeutic intervention, herpes zoster infections, tuberculosis, and viral hepatitis.

In addition to the incidence of infectious AEs by MedDRA PT as described above, the number and percentage of subjects with treatment-emergent infectious AEs by treatment group will be summarized and listed.

Potential Opportunistic Infections:

Potential opportunistic infections (POIs) will be identified according to 2 different approaches.

POIs are identified from TEAEs based on a Lilly-defined list of MedDRA PTs, shown in the Appendix 3. These PTs are a subset of terms from the Infections and Infestations SOC.

For the POIs identified from MedDRA PTs, the number and percentage of subjects overall and for each specific PT will be summarized by treatment group, with specific event terms ordered by decreasing frequency in the LY3041658 highest dose.

Association of Infections with Lymphopenia or Neutropenia:

The relationship between the occurrence of lymphopenia and neutropenia with the occurrence of infections will be evaluated based on case reviews. Inferential analyses and/or graphical displays may be conducted if warranted. Infection outcomes considered for this analysis are any infection, any serious infection, infections that require therapeutic intervention (antibiotics, antivirals, antifungals, and so on), tuberculosis, herpes zoster, and viral hepatitis.

6.9.5.4. Allergic Reactions/Hypersensitivities

A search will be performed using the current MedDRA version 20.0 SMQs to search for relevant events, using the following queries:

- Anaphylactic reaction SMQ (20000021)
- Hypersensitivity SMQ (20000214)

- Angioedema SMQ (20000024)

Events that satisfy the queries will be listed, by temporal order within patient ID, and will include SOC, PT, SMQ event categorization including detail on the scope (narrow or broad), reported AE term, AE onset and end dates, severity, seriousness, outcome, etc.

6.9.5.5. 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 adverse event will be recorded, and additional data will be provided to the sponsor in the eCRF. The number and percentage of patients having any ISR, and each Symptoms (erythema, induration, pain, pruritus, and edema) by maximum severity will be summarized by and treatment for Period 1 using the mITT population. Additionally, summaries of ISR and each Symptoms over by treatment will be provided for each visit.

6.9.5.6. Suicidal Ideation and Behavior Risk Monitoring

Responses to the Columbia Suicide-Severity Rating Scale (C-SSRS) will be summarized by treatment and listed for each patient.

6.10. Subgroup Analyses

Subgroup analyses comparing LY3041658 to placebo will be performed on the mITT and PPS population at Week 16 for the following:

- Proportion of participants achieving HiSCR response
- Mean change from baseline to Week 16 in:
    - Total number of abscesses and inflammatory nodules (AN count)
    - Skin Pain – HS Numeric Rating Scale (NRS)

The following subgroups (but not necessarily limited to only these) will be categorized into disease-related characteristics and demographic characteristics will be evaluated:

- Gender: (Male; Female)
- Race: (Asian; Black/African American; White; or Other)
- Ethnicity: (Hispanic or Latino; and Not Hispanic or Latino)
- Region: (United States; and Australia)
- Age (<40,40-65,>65)
- Weight (<60kg, >=60 and <100kg, >=100kg)
- BMI (<25 kg/m^2, >=25 and <40 kg/m^2, >=40 kg/m^2)
- Baseline Hurley stage: II, III

Descriptive statistics will be provided for each treatment and stratum of a subgroup as outlined, regardless of sample size. The subgroup analyses for categorical outcomes will be performed using logistic regression. The model will include the categorical outcome as the dependent variable and treatment, subgroup, and treatment-by-subgroup interaction as explanatory variables. Missing data will be imputed using NRI (Section 6.4). The treatment-by-subgroup interaction comparing treatment groups will be tested at the 0.1 significance level. The p-value

from the logistic regression model will be reported for the interaction test. Response counts and percentages will be summarized by treatment for each subgroup category. The difference in percentages and 100(1-alpha)% confidence interval (CI) of the difference in percentages using the Newcombe-Wilson without continuity correction will be reported. The p-value from the Fisher's exact test will also be produced.

Additional subgroup analyses on efficacy may be performed as deemed appropriate and necessary.

6.11. Protocol Deviations

Protocol deviations will be tracked by the clinical team, and their importance will be assessed by key team members during protocol deviation review meetings. A list of important protocol deviations (IPDs) will be identified.

Potential examples of deviations include patients who receive excluded concomitant therapy, significant non-compliance with study medication (<80% of assigned doses taken, failure to take study medication and taking incorrect study medication), patients incorrectly enrolled in the study, and patients whose data are questionable due to significant site quality or compliance issues. Refer to a separate document for the important protocol deviations.

The number and percentage of patients having IPD(s) will be summarized within category and subcategory of deviation by treatment group for Period 1 using the mITT population. Individual patient listings of IPDs will be provided.

6.12. Interim Analyses and Data Monitoring

Unblinding details are given in a separate unblinding plan.

Analysis for the primary database lock will be conducted when all participants have completed the Period 1 (or discontinued Period 1 treatment).

There are two interim analyses planned for this study:

1. An interim analysis on unblinded safety data will be triggered when approximately 12 patients have completed 8 weeks of treatment.
2. An interim analysis to assess unblinded efficacy and safety data will be triggered when approximately 21 patients have completed 12 weeks of treatment

Other interim analyses may be conducted as needed. All interim analyses will be used to support planning activities associated with the development program. No adjustment of type I error will be performed.

The assessment will be conducted by an internal assessment committee with a limited number of prespecified team members who do not have direct site contact or data entry/validation responsibilities. A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock.

The assessment committee is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data. The analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact or data entry/validation responsibilities.

Details of the planned interim data analyses and the assessment committee data review process are included in an assessment committee charter.

6.13. Annual Report Analyses

Annual report analyses, such as the Development Update Safety Report (DSUR), will be documented in a separate document.

6.14. 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 a summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AE are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE 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 patients/patients 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.

Similar methods will be used to satisfy the European Clinical Trials Database (EudraCT) requirements.

7. References

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8. Appendices

Appendix 1. Lilly-Defined MedDRA Preferred Terms for Herpes Zoster

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Herpes zoster	10019974
Ophthalmic herpes zoster	10030865
Herpes zoster infection neurological	10061208
Herpes zoster oticus	10063491
Herpes zoster disseminated	10065038
Genital herpes zoster	10072210
Herpes zoster pharyngitis	10074245
Herpes zoster meningoencephalitis	10074248
Herpes zoster meningomyelitis	10074251
Herpes zoster meningitis	10074259
Herpes zoster cutaneous disseminated	10074297
Varicella zoster virus infection	10075611

Appendix 2. Lilly-Defined MedDRA Preferred Terms for Tuberculosis

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Adrenal gland tuberculosis	10001358
Bone tuberculosis	10056377
Bovine tuberculosis	10006049
Choroid tubercles	10008779
Congenital tuberculosis	10010657
Conjunctivitis tuberculous	10010754
Cutaneous tuberculosis	10011684
Disseminated tuberculosis	10013453
Ear tuberculosis	10014027
Epididymitis tuberculous	10015004
Erythema induratum	10015213
Extrapulmonary tuberculosis	10064445
Female genital tract tuberculosis	10061150
Immune reconstitution inflammatory syndrome associated tuberculosis	10072797
Interferon gamma release assay positive	10072866
Intestinal tuberculosis	10075268
Joint tuberculosis	10056367
Latent tuberculosis	10065048
Lupus vulgaris	10025143
Lymph node tuberculosis	10025183
Male genital tract tuberculosis	10061234
Meningitis tuberculosis	10027259
Mycobacterium tuberculosis complex test positive	10070325
Oesophogeal tuberculosis	10030200
Pericarditis tuberculous	10055069
Peritoneal tuberculosis	10053583
Prostatitis tuberculous	10064743
Pulmonary tuberculoma	10066927
Pulmonary tuberculosis	10037440
Renal tuberculosis	10038534
Salpingitis tuberculous	10039463
Silicotuberculosis	10068876
Spleen tuberculosis	10041640
Thyroid tuberculosis	10043774
Tuberculin test positive	10044728
Tuberculoma of central nervous system	10052883
Tuberculosis	10044755
Tuberculous abscess central nervous system	10052884
Tuberculosis bladder	10044758
Tuberculosis gastrointestinal	10061390

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Tuberculosis liver	10058120
Tuberculosis of central nervous system	10061391
Tuberculosis of eye	10044819
Tuberculosis of genitourinary system	10044828
Tuberculosis of intrathoracic lymph nodes	10044846
Tuberculosis of peripheral lymph nodes	10044965
Tuberculosis ureter	10045026
Tuberculous endometritis	10071559
Tuberculous laryngitis	10045072
Tuberculous pleurisy	10045104
Tuberculous tenosynovitis	10059161

Appendix 3. Lilly-Defined MedDRA Preferred Terms for Potential Opportunistic Infections

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Candida pneumonia	10053158
Respiratory moniliasis	10038705
Gastrointestinal candidiasis	10017938
Oesophageal candidiasis	10030154
Coccidioides encephalitis	10054214
Coccidioidomycosis	10009825
Cutaneous coccidioidomycosis	10068747
Meningitis coccidioides	10027207
Cryptococcal cutaneous infection	10054216
Cryptococcal fungaemia	10067112
Disseminated cryptococcosis	10013439
Gastroenteritis cryptococcal	10011485
Meningitis cryptococcal	10027209
Neurocryptococcosis	10068368
Biliary tract infection cryptosporidial	10067319
Gastroenteritis cryptosporidial	10017899
Cytomegalovirus colitis	10048983
Cytomegalovirus duodenitis	10049014
Cytomegalovirus enteritis	10049074
Cytomegalovirus enterocolitis	10049015
Cytomegalovirus gastritis	10049016
Cytomegalovirus gastroenteritis	10051349
Cytomegalovirus gastrointestinal infection	10052817
Cytomegalovirus gastrointestinal ulcer	10075619
Cytomegalovirus hepatitis	10011830
Cytomegalovirus mucocutaneous ulcer	10065036
Cytomegalovirus myelomeningoradiculitis	10065621
Cytomegalovirus myocarditis	10056261
Cytomegalovirus oesophagitis	10049018
Cytomegalovirus pancreatitis	10049566
Cytomegalovirus pericarditis	10056721
Cytomegalovirus proctocolitis	10049019
Cytomegalovirus urinary tract infection	10051350
Disseminated cytomegaloviral infection	10049075
Encephalitis cytomegalovirus	10014586