Statistical Analysis Plan I1F-MC-RHCG (Version 4)

Multicenter, Open-label, Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Subcutaneous Ixekizumab With Adalimumab Reference Arm, in Children With Juvenile Idiopathic Arthritis Subtypes of Enthesitis-related Arthritis (Including Juvenile-Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis

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1. Statistical Analysis Plan: I1F-MC-RHCG: Multicenter, Open-label, Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Subcutaneous Ixekizumab with Adalimumab Reference Arm, in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-related Arthritis (Including Juvenile-onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis

Ixekizumab (LY2439821)

Study I1M-MC-RHCG (RHCG) is a Multicenter, Open-label, Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Subcutaneous Ixekizumab with Adalimumab Reference Arm, in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-related Arthritis (Including Juvenile-Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis

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Protocol I1M-MC-RHCG
Phase 3

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3. Revision History

SAP Version 1 was approved prior to the first patient visit on 17 December 2020.

Revisions since Version 1

Section	Revision
Entire document	Editorial changes on minor grammatical or formatting changes as needed
Entire document	Updated "CRP (C-reactive protein)" to "hsCRP (high-sensitivity C-reactive protein)" Removed CRP from JIA ACR description
Section 6.1 General Considerations	Added language for success criteria or Bayesian analysis
Section 6.3.3 Modified Nonresponder Imputation (mNRI)	Added language for analysis method for missing visits due to COVID-19
Section 6.6.1 Demographics and Baseline Characteristics	1. Added Country as variable, removed Geographic Region as variable 2. Split "Prior nonbiologic JIA therapy" into 2 variables: a. "Prior csDMARs therapy for JIA" b. "Prior nonbiologic (Non-DMARD) JIA therapy" 3. Split "Number of prior JIA therapy" a. "Number of prior csDMARDs for JIA" b. "Number of nonbiologic (Non-DMARD) JIA therapies" 4. Added row for sulfasalazine 5. Added Biologic JIA therapies "infliximab" and "secukinumab" to abbreviation "c" 6. Added abbreviation "j" to account for csDMARDs therapy category 7. Updated abbreviation "d" 8. Added "including COX-2 inhibitors)" and "systemic glucocorticoids" to abbreviation "d" 9. Removed csDMARDs and MTX from abbreviation "d"
Section 6.9.1 Primary Outcome and Methodology	1. Added success criteria language 2. Added posterior mean, variance, and 95% credible interval equations 3. Changed posterior "distribution" to posterior "probability" 4. Updated number "n=80" in baseyian algorithm 5. Added analyse method for JIA ACR30/50/70/100 response (mNRI) 6. Added analyse method for JIA ACR30 response (Bayesian analysis, mNRI)
Section 6.9.5 Sensitivity Analyses	Added new language for sensitivity analysis
Section 6.15 Interim Analyses and Data Monitoring	Added "evaluable" to number of patients needed before stopping for futility Revised entire second paragraph Added "summary of reasons for missing JIA ACR30 data at Week 16"

SAP Version 2 was approved on 03 March 2021.

Revisions since Version 2

Section	Revision
Section 4.1 Primary Objective	Added a section of estimands for Primary Objective
Section 4.2 Secondary Objectives	Added Secondary objectives for the Long-Term Extension (LTE) Period
Section 4.2 Exploratory Objectives	Updated the analyses window for Long-Term Extension (LTE) Period to include Week 264 instead of Week 156
Section 5.1 Summary of Study Design	Added the LTE period description
Figure RHCG.5.1	Updated the schema diagram to include LTE period and added a footnote sentence for superscript "c" as per the current protocol
Table RHCG.6.1 Analysis Populations	Added LTE Safety Population
Section 6.1.2.1 General Considerations for the OLT Period	Updated the baseline definition to include "on or" before
Section 6.1.2.2 General Considerations for the OLE Period	1. Moved "Additional Population Information" from Section 6.1.2.2 to Section 6.1.2.2.1 2. Added the text "were initially randomized to adalimumab at Week 0 and" under "Additional Population Information"
Section 6.1.2.3 General Considerations for the LTE Period	Added this section to include considerations for the LTE period
Section 6.3.2 Last Observation Carried Forward	Added this under 6.3. Handling of Dropouts or Missing Data to account for the data handling at the component level of JIAACR algorithm
Section 6.5 Patient Disposition	Added the word "LTE" to make the section applicable for the LTE part of the study
Section 6.7 Treatment Compliance	Updated the section for LTE Period Population
Table RHCG.6.3 Number of Injections Prescribed (Assuming adalimumab responders)	Added the column for Long - Term Extension Treatment Period
Section 6.8.2 Concomitant Therapy	Updated the section for LTE Period Population
Table RHCG.6.9 Description and Derivation of Exploratory Efficacy Endpoints	Updated the table to add the exploratory efficacy analyses for LTE Period
Table RHCG.6.10 Description of Analysis Period and Analysis Method of Exploratory Efficacy	Updated the table to add the exploratory efficacy analyses for LTE Period
Section 6.12 Safety Analyses	Updated the whole section to include LTE period details for every subsection.
Section 6.12.1 Extent of Exposure	Added the calculation for The duration of exposure during the LTE Extension
Appendix 1 Algorithm for Determining JIA ACRx Response	Updated as per BARI JIA algorithm Updated "%improvement" to "%change from baseline"
Appendix 2. Algorithm for Calculating Disease Flare	Updated as per BARI Flare algorithm Updated "% improvement" to "% change from baseline"

SAP Version 3 was approved on 20 March 2023.

Revisions since Version 3

Section	Revision
Table RHCG.6.3.Number of Injections Prescribed	Updated the start of LTE period to "104" and number of injections for Ixe OLE to 23 and added a note for number of OLE injection,
Table 6.9.Description and Derivation of Exploratory Efficacy Endpoints :	Added the analysis variable for "Time to inactive/low disease status" for JADAS-27 endpoint.
Table 6.10 Table RHCG.6.10. Description of Analysis Period and Analysis Method of Exploratory Efficacy	Specified the analyses period details for time to inactive/low status
	Specified missing data handling

4. Study Objectives

4.1. Primary Objective

Table RHCG.4.1. Primary Objective and Endpoint

Objectives	Endpoints
Primary • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the JIA ACR30 response	Percentage of patients meeting the JIA ACR30 response criteria at Week 16

Abbreviations: ACR = American College of Rheumatology; ERA = Enthesitis-related Arthritis; JIA = Juvenile Idiopathic Arthritis; JoAS = Juvenile-Onset Ankylosing Spondylitis; JPsA = Juvenile Psoriatic Arthritis.

In compliance with International Conference on Harmonisation (ICH) E9(R1) guidelines, a study should be clear in defining an estimand framework, which includes 4 attributes:

- the population of interest: the patients targeted by the scientific question
- the variable (or endpoint) of evaluation that is obtained for each patient, that is required to address the scientific question
- the population-level summary of the variable, a basis for treatment evaluation, and
- the specification of how to account for intercurrent events to reflect the scientific question of interest.

In particular, for Study RHCG, the estimand is defined by:

- **population of interest**: children from 2 to less than 18 years of age, with juvenile idiopathic arthritis (JIA) subtypes of enthesitis-related arthritis (ERA) defined through appropriate inclusion/exclusion criteria to reflect the targeted participant population. Analysis populations are defined in Section 6.1.1.
- **variable (or endpoint) of evaluation**: JIA American College of Rheumatology (ACR) 30 response at Week 16 in the ixekizumab arm
- **population-level summary**: The primary quantity of interest will be the percentage of patients in the ixekizumab arm meeting the JIA ACR30 response criteria at Week 16. Details are given in Section 6.9.1.
- **intercurrent event strategy**: The analysis population will be based on patients who have had the chance to complete the visits. In the estimand framework, for primary variable, the composite estimand strategy will be applied and non-responder imputation will be used to support this strategy. Patients will be considered non-responders for the nonresponder imputation (NRI) analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point of interest. All nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as non-responders for the NRI analysis at Week 16.

4.2. Secondary Objectives

Table RHCG.4.2. Secondary Objective and Endpoint

Objectives	Endpoints
Secondary for the Open Label Treatment (OLT) and Open Label Extension (OLE) Periods	
• To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the other clinical responses, disease activity, and physical function measures • To evaluate the efficacy of adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on JIA ACR30 and the other clinical responses, disease activity, and physical function measures	The following outcomes will be assessed at each regular study visit[a]: • Percentage of patients meeting the JIA ACR30/50/70/90/100 response criteria • Changes from baseline in each of the 6 individual components of the JIA ACR core set variables as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the Childhood Health Assessment Questionnaire (CHAQ) o Acute-phase reactant (high-sensitivity C-reactive protein [hsCRP]) and erythrocyte sedimentation rate (ESR) • Change from baseline in Psoriasis Area and Severity Index (PASI) for JPsA patients with at least 3% Body Surface Area (BSA) at baseline • Change from baseline in Leeds Enthesitis Index (LEI) for patients with enthesitis at baseline • Proportion of patients with disease flare (flare defined as worsening of ≥30% from baseline in at least 3 of the 6 JIA ACR core set criteria and an improvement of ≥30% in no more than 1 of the criteria)
• To characterize ixekizumab pharmacokinetics (PK) in children with JIA subtypes of ERA (including JoAS) and JPsA	• Trough concentrations of ixekizumab in patients with JIA subtypes of ERA (including JoAS) and JPsA

Objectives	Endpoints
• To evaluate the potential development of anti-ixekizumab antibodies and their impact on the efficacy and safety of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	• Percentage of patients with anti-ixekizumab antibodies
• Describe the safety of ixekizumab in patients with JIA subtypes of ERA (including JoAS) and JPsA	• Adverse events (AEs) including serious adverse events (SAEs) • Safety parameters including but not limited to infections, injection site reactions, and laboratory data including B-, T-cell, and natural killer (NK)-cell levels, white blood cell (WBC) count, red blood cell (RBC) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST)
Secondary for the Long-Term Extension (LTE) Period	
• To evaluate the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	The following outcomes will be assessed at each regular study visit: • AEs including SAEs and adverse events of special interest (AESIs) • Safety parameters including but not limited to infections, injection site reactions, and laboratory evaluations (including chemistry and hematology) • Permanent and temporary discontinuations of the study intervention • Vital signs, growth, and development

Abbreviations: ACR = American College of Rheumatology; ERA = Enthesitis-related Arthritis; JIA = Juvenile Idiopathic Arthritis; JoAS = Juvenile-Onset Ankylosing Spondylitis; JPsA = Juvenile Psoriatic Arthritis.

[a] During the OLE period, regular visits and assessments will occur every 3 months (Visits 8, 11, 14, 17, 20, 23, 26, and 29/ETV). Patients will also have monthly treatment visits to the site primarily for dispensation and/or administration of study drug.

4.3. Exploratory Objectives

Table RHCG.4.3. Exploratory Objective and Endpoint

Objectives	Endpoints
Exploratory for the OLT and/or OLE Period	
CCI	

Objectives	Endpoints
CCI	

5. Study Design

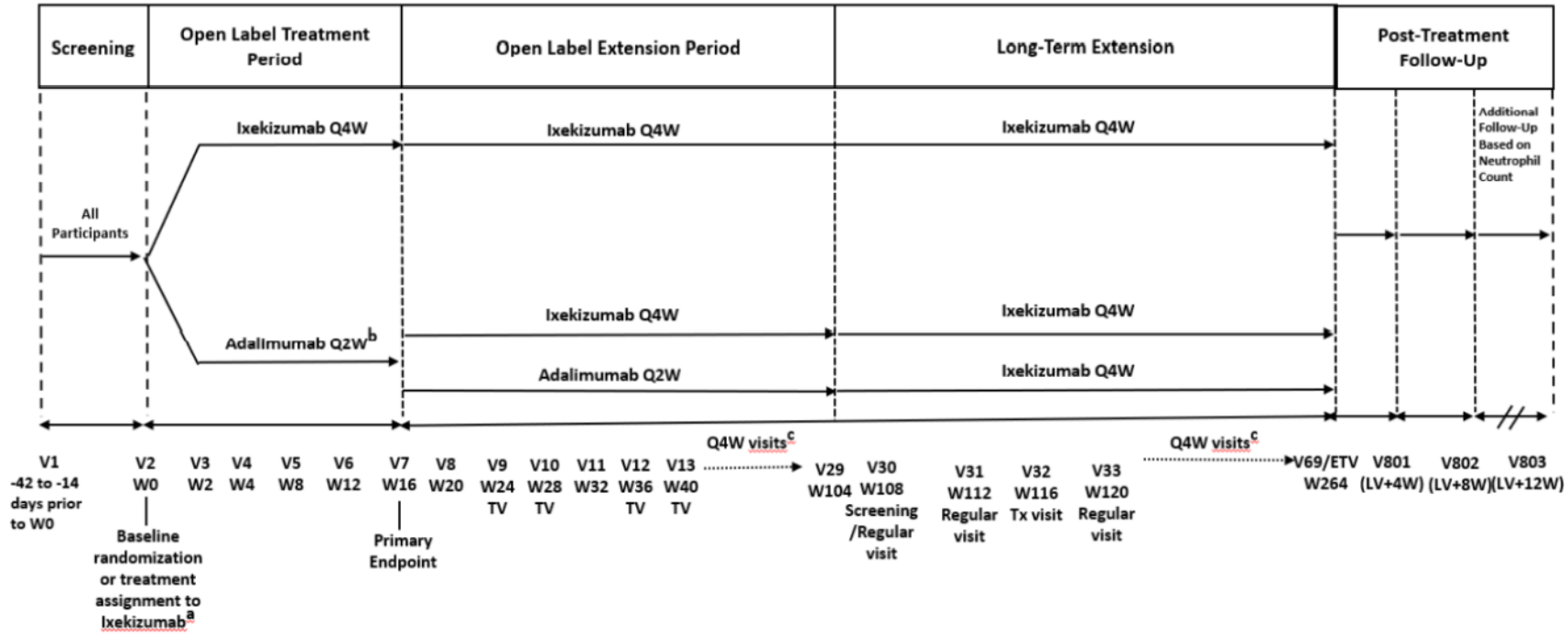
5.1. Summary of Study Design

Study I1F-MC-RHCG (RHCG) is a multicentre, randomized, open-label study of subcutaneous (SC) ixekizumab, with adalimumab as a reference arm in children from 2 to less than 18 years of age, who are biologic disease-modifying antirheumatic drug- (bDMARD-) naive or inadequate responder (bDMARD-IR) as per investigator's judgement, with JIA subtypes of ERA (including juvenile-onset ankylosing spondylitis [JoAS]) and juvenile psoriatic arthritis (JPsA).

The study consists of 5 periods:

- **Screening Period** (Visit 1) will assess subject eligibility and will occur approximately 7 to 42 days before the Open-Label Treatment (OLT) Period (baseline; Week 0; Visit 2).
- **Open-Label Treatment Period** (OLT) will occur from Week 0 (baseline; Visit 2) to Week 16 (Visit 7). CCI [redacted] Evaluation of the primary endpoint will occur at Week 16.
- **Open-Label Extension Period** (OLE) will occur from Week 16 (Visit 7) to Week 104 (Visit 29/ Early Termination Visit [ETV]). All patients who were receiving ixekizumab in the OLT period will continue to receive ixekizumab for approximately 88 weeks during the OLE Period. Patients receiving adalimumab during the OLT period who did NOT attain a JIA ACR30 response at Week 16 will be switched to ixekizumab in the OLE period. Patients receiving adalimumab during the OLT period who did attain a JIA ACR30 response at Week 16 will be given the option to switch or not to switch to ixekizumab at any visit during the OLE period. The decision to switch for adalimumab-treated patients who achieved a JIA ACR30 response at Week 16 will be left to the patient/patient's caregiver and investigator. After switching to ixekizumab, the patients will not have the option to resume adalimumab treatment during the remainder of the trial participation.
- **Long-Term Extension Period** (LTE): Participants who complete the OLT and OLE periods will be participating in the LTE period of this study which will occur from Week 104 (Visit 29) to Week 264 (Visit 69/ ETV). All participants entering the LTE portion of the study period will receive weight-based ixekizumab at Week 104. Participants who were previously assigned to adalimumab will be switched to ixekizumab as described in Section 7.1 Treatments Administered of the protocol. If a participant previously assigned to adalimumab does not want to switch to ixekizumab in the LTE period of the study, the patient should initiate the ETV process at Week 104.
- **Post-Treatment Follow-Up Period** (PTFU) is for safety monitoring after treatment discontinuation for any subject receiving at least 1 dose of study drug. Participants who have received at least 1 dose of study drug should enter the PTFU period for a minimum of 12 weeks after the last treatment period visit (Week 104) or ETV their last regularly scheduled visits (or the date of their ETV).

Figure RHCG.5.1 illustrates the study design for the main protocol.



Abbreviations: ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = inadequate response to biologic disease-modifying antirheumatic drug; ERA = enthesitis-related arthritis; ETV = early termination visit; JIA = juvenile idiopathic arthritis JPsA = Juvenile Psoriatic Arthritis; LV = last visit; OLE = open-label extension; PTFU = post-treatment follow-up period; OLT = open-label treatment; Q2W = every other week; Q4W = every 4 weeks; TV = treatment visit; Tx = treatment x; V = visit; W = week.

[a] Patients who are bDMARD-naive will be randomized to ixekizumab or adalimumab in a 1:1 ratio. At least 20 patients will be randomized to ixekizumab and 20 patients to adalimumab. Randomization will be stratified based on the category of JIA (ERA or JPsA). The remaining patients (approximately 60 patients) who are bDMARD-naive or bDMARD-IR will be assigned to ixekizumab.

[b] Patients receiving adalimumab during the OLT period who did NOT attain a JIA ACR30 response at Week 16 will be switched to ixekizumab in the OLE period. Patients receiving adalimumab during the OLT period who did attain a JIA ACR30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period.

[c] Regular visits will occur every 3 months, but patients will have monthly treatment visits to the site primarily for injection purposes. Participants who are treated with adalimumab through Week 104 may decide not to switch to ixekizumab at Week 104 and enter the PTFU period.

Figure RHCG.5.1. Illustration of study design for Study I1F-MC-RHCG.

5.2. Determination of Sample Size

The Bayesian methodology results in a posterior distribution which rigorously quantifies the uncertainty around the estimate of the JIA ACR30 response. The primary objective of this study is to detect a JIA ACR30 response rate of at least 50% for ixekizumab-treated patients at Week 16.

A sample size of at least 80 patients assigned to ixekizumab has been shown via simulation to have reasonable operating characteristics as follows:

- a study success rate greater than 80% if the true JIA ACR30 response is at 60%
- a false-positive rate of less than 1% if the true JIA ACR30 response is placebo-like at 35%

These rates are derived from the Bayesian decision criterion but are similar to a traditional power calculation.

Overall, approximately 100 patients will be assigned to therapy in this study: 40 will be randomized, 20 to ixekizumab and 20 to adalimumab. The remaining 60 will be assigned to ixekizumab.

The above sample size and power estimates are based on Fixed and Adaptive Clinical Trials Simulator version 6.0 (FACTS™).

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrolment will be randomized or assigned, as appropriate, to treatment at Visit 2. CCI [redacted] At least 20 patients will be randomized to ixekizumab and 20 patients to adalimumab. Randomization will be stratified based on the category of JIA (ERA or JPsA). The remaining patients (approximately 60 patients) who are bDMARD-naive or bDMARD-IR will be assigned to ixekizumab. In practice, this will be accomplished by randomizing the first 40 bDMARD-naive patients entering the study according to the ratio and stratification described above, with all the subsequent bDMARD-naive patients being assigned to ixekizumab. A listing of patient randomization for the Intent to Treat population by site will be provided.

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign cartons containing investigational product to each patient. Site personnel will confirm that they have located the correct cartons by entering a confirmation number found on the cartons into the IWRS before dispensing to patients.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter Lilly). The statistical analyses will be performed using SAS® Version 9.2 or higher. Not all displays described in this SAP will necessarily be included in the clinical study report (CSR). Any display described in this SAP and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

Bayesian analysis will be used as the primary analysis method for the primary endpoint, JIA ACR30 at Week 16. The posterior probability distribution of JIA ACR30 response rate at Week 16 will be summarized and the conclusion will be made based on the prespecified success criteria. If the study is not stopped for futility, the posterior probability of the Week 16 JIA ACR30 response rate exceeding 50% will be calculated, and the study objective will be successfully met (i.e., a positive study) if this posterior probability is at least 80%.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), minimum, median, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

Categorical data will be summarized in terms of the number of patients in the analysis population, the number of patients providing data at the relevant time point, frequency counts, and the percentages corresponding to the appropriate method. Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts. For condition/event that is gender-specific (as defined by the Medical Dictionary for Regulatory Activities [MedDRA]), the denominator and computation of the percentage will include only patients from the given gender. All confidence intervals (CIs) will be 2-sided with a 95% level of confidence, unless otherwise specified.

All efficacy and safety data collected will be summarized using descriptive statistics without any inferential statistics.

6.1.1. Populations for Analyses

For analysis purposes, populations are defined based on the different treatment period in Table RHCG.6.1. A disposition of the study analysis population and a listing of the analysis population will be provided as well.

Table RHCG.6.1. Analysis Populations

Population	Period	Description
Enrolled		All patients who sign informed consent.
ITT population	OLT	All patients, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the ITT Population during the OLT period. Patients will be analyzed according to the treatment to which they were assigned.
OLE period population	OLE	All patients who receive at least 1 dose of either treatment in OLE.
OLE period adalimumab switchers (switchers)	OLE	Patients initially randomized to adalimumab who switch to ixekizumab in the OLE period
OLT safety population	OLT	All patients who received at least 1 dose of either treatment product in OLT.
LTE safety population	LTE	All participants who received at least 1 dose of ixekizumab in the LTE period
PTFU period population	PTFU	Safety analyses for the Post-Treatment Follow-Up Period will be conducted on the Post-Treatment Follow-Up Period population, defined as all randomized patients who received at least 1 dose of study treatment at any time during the study period, and have entered the Post-Treatment Follow-Up Period. Patients will be analyzed according to the treatment in which they were assigned.

Abbreviations: ITT = Intend-To-Treat; OLE = Open-Label Extension; OLT = Open-Label Treatment; LTE = Long-Term Extension; PTFU = Post-Treatment Follow-Up.

6.1.2. General Statistical Considerations

For all treatment periods, change from baseline will be calculated as the postbaseline value minus the baseline value. Percent change from baseline is defined as: 100 times the change from baseline divided by baseline. Percent improvement from baseline is calculated as: the positive

percent change from baseline if a higher value postbaseline means improvement from baseline; and as the negative percent change from baseline if a lower value postbaseline means improvement from baseline. If the baseline value is missing for a particular variable, then the change from baseline and the percent improvement from baseline will not be calculated.

6.1.2.1. General Considerations for the OLT Period

The OLT period starts at the first injection of study treatment at Week 0 (Visit 2) and ends prior to the first injection of study treatment at Week 16 (Visit 7) or the ETV (between Weeks 0 and 16). Efficacy and health outcomes data collected in the OLT period will be summarized for intent-to-treat (ITT) population without inferential statistics.

Efficacy baseline will be defined as the last available value on or before the first injection at Week 0 (Visit 2) for efficacy and health outcomes. In most cases, this will be the measure recorded at Week 0 (Visit 2). For efficacy measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used.

For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection at Week 0 (Visit 2).

6.1.2.2. General Considerations for the OLE Period

Unless otherwise specified, the OLE period starts at the first injection of study treatment at Week 16 (Visit 7) and ends on the date of Week 104 (Visit 29) or the ETV (between Weeks 16 and 104).

6.1.2.2.1. OLE Period Population

Baseline for OLE Period Population will be defined as the last available value on or before the first injection of study treatment in the OLT Period at Week 0 (Visit 2) for efficacy, health outcomes. For patients without a date of first study drug injection at Week 0 (Visit 2), the last nonmissing assessment on or before randomization date will be used.

Unless otherwise specified, for the safety analyses during the OLE period, baseline is defined as the last available value on or before first injection of either ixekizumab or adalimumab in the OLE period. In most cases, this will be the measure recorded at Week 16 (Visit 7). For treatment-emergent adverse events (TEAEs), baseline are adverse events (AEs) which started prior to the study drug injection at Week 16 (Visit 7).

Additional Population Information

For patients who were initially randomized to adalimumab at Week 0 and were switched to ixekizumab by their investigators, only data up to the time of initiation of a switch to ixekizumab will be included in the OLE Period analyses using the OLE Period Population. These patients will be considered nonresponders to categorical assessment per the NRI method after the switch to ixekizumab. Data collected after switch to ixekizumab therapy has started will be summarized separately for the Switcher Population (Section 6.1.2.2.2).

6.1.2.2.2. OLE Period Switcher Population

For efficacy analyses on the Switcher Population, baseline is defined as the last nonmissing assessment recorded on or prior to the date of first study drug injection at Week 0 (Visit 2). For safety analyses, baseline is defined as the last nonmissing assessment prior to the first injection of a switch to ixekizumab. For TEAEs during a switch to ixekizumab, baseline is the event ongoing just prior to the first injection of a switch to ixekizumab.

For the Switcher Population, efficacy measures after initiation of a switch to ixekizumab will be summarized without inferential statistics.

6.1.2.3. General Considerations for the LTE Period

The LTE period starts at the first injection of ixekizumab at Week 104 (Visit 29) and ends after the injection of ixekizumab at Week 264 (Visit 69) or at ETV (between Weeks 104 and 264).

All safety data will be descriptively summarized using the LTE safety population. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to date/time of the first injection in the LTE period.

Efficacy and health outcomes data collected in the LTE period will be summarized for the ITT population who entered the LTE period without inferential statistics.

All safety data will be descriptively summarized using the LTE safety population, defined as ITT participants who receive at least 1 dose of ixekizumab in the LTE period.

6.1.2.4. General Considerations for the PTFU Period

For the safety analyses during the PTFU period, baseline is defined as the last nonmissing assessment on or prior to entering the PTFU period, that is, on or prior to Week 104 (Visit 29), or ETV.

Safety data will be summarized using descriptive statistics without inferential statistics by the study treatment the patient was receiving immediately prior to entering PTFU period.

6.2. Adjustments for Covariates

There are no adjustments for covariates.

6.3. Handling of Dropouts or Missing Data

6.3.1. Non-Responder Imputation for Clinical Response

The NRI method may be used to address missingness when the estimand of interest uses the composite strategy for handling intercurrent events.

Analysis of categorical efficacy and health outcome variables will be assessed using a NRI method. Patients will be considered non-responders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point of interest. All nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as non-responders for the

NRI analysis at Week 16. For the OLE Period Population, all non-responders at Week 104 (Visit 29), as well as patients who discontinue the originally assigned study treatment at any time prior to Week 104 for any reason, will be defined as non-responders for the NRI analysis at Week 104. For the Switcher population, all non-responders at Week 104 (Visit 29), as well as patients who discontinue ixekizumab after the switch at any time prior to Week 104 for any reason, will be defined as non-responders for the Week 104 analysis.

The NRI will be applied at any time point specified for analysis.

6.3.2. Last Observation Carried Forward

When last observation carried forward (LOCF) is applied, the last nonmissing postbaseline observation on or prior to the missed visit within the same period will be carried forward to subsequent time points for evaluation. Patients without at least 1 postbaseline observation will not be included for evaluation. This method will be used to handle missing data for individual components of a composite endpoint, such as JIA ACR or Disease Flare. Further details are described in Appendix 1 and Appendix 2.

6.3.3. Modified Baseline Observation Carried Forward

A complete guideline on statistical principles for clinical trials such as impact on trial design, conduct, and analysis, and documenting estimands and sensitivity analysis can be found in the *ICH E9 Statistical Principles for Clinical Trials* and the *addendum (R1)* (EMA 2020).

The mBOCF method is based on an estimand that handles the intercurrent event of discontinuing study drug due to an AE by defining the participant as not receiving any benefit from study drug after the event. That is the participant is defined as reverting back to baseline regardless of any continuing efficacy benefits they may still have received after the event. For other intercurrent events, the while on study intervention strategy is applied. That is, the endpoint is defined as the last observed value at or before the visit of interest before the participant discontinued study intervention.

For the ITT Population, OLE Period Population and LTE Safety Population if patients discontinue the study drug due to an AE, the baseline observation will be carried forward to the corresponding time point for evaluation; if they discontinue originally assigned study drug for any other reason, the last nonmissing observation before discontinuation from the originally assigned drug will be carried forward to the corresponding time point for evaluation. Randomized patients without at least 1 postbaseline observation will not be included for evaluation apart from patients discontinuing study treatment because of an AE. In the occurrences of intermittent missing observations, the last nonmissing observation will be carried forward.

For the Switcher Population, if patients discontinue ixekizumab due to an AE, baseline observation will be carried forward to subsequent time points; if they discontinue ixekizumab for any other reason, the last nonmissing observation while they are on ixekizumab will be carried forward. In the occurrences of intermittent missing observations, the last nonmissing observation will be carried forward.

An mBOCF analysis will be performed on continuous secondary efficacy, exploratory, and health outcomes variables.

6.3.4. Modified Nonresponder Imputation (mNRI)

If any patients missed a visit or discontinued study treatment due to the restriction of coronavirus disease 2019 (COVID-19) in the OLT period for the OLT period population, a multiple imputation (MI) method will be used to impute missing data for each component of JIA ACR30, and JIA ACR30 up to Week 16 will be derived using the MI-imputed components. In the MI analyses, missing data will be imputed to estimate what the observations would have been if the patient had not missed a visit or discontinued due to COVID-19. Specifically, MI is the partial imputation of nonmonotone missing data using Markov chain Monte Carlo method with the simple imputation model, followed by a sequential regression. All other missing JIA ACR30 up to Week 16 due to other reasons will be imputed with NRI.

6.4. Multiple Comparisons/Multiplicity

No multiplicity control measures will be used.

6.5. Patient Disposition

The number of patients along with, ITT, OLE, LTE Safety, OLE switcher, and PTFU populations will be summarized, and a listing of disposition will be summarized.

An overview of patient disposition will be summarized by each treatment period using the appropriate populations.

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 5.1):

- The number and percentage of patients completing Week 16 of the OLT Period on initially assigned treatment and the number and percentage of patients discontinuing on/prior to Week 16 of the OLT Period, by treatment group and primary reason for discontinuation (Analysis population: ITT Population).
- The number and percentage of Switchers completing the OLE Period or prematurely discontinuing from the OLE Period after Week 16, and primary reason for discontinuation (Analysis population: Switcher Population).
- The number and percentage of patients completing the OLE Period and the number and percentage of patients discontinuing from the OLE Period, by treatment group and primary reason for discontinuation, including classified as Switcher during OLE Period (Analysis population: OLE Period Population).
- The number and percentage of patients completing the LTE Period and the number and percentage of patients discontinuing from the LTE Period, by treatment group and primary reason for discontinuation (Analysis population: LTE Safety Population).

- The number and percentage of patients completing the PTFU Period and the number and percentage of patients discontinuing from the PTFU Period, by treatment group and primary reason for discontinuation (Analysis population: PTFU Period Population).

A by-patient listing will also be provided to include the following information:

- Patient disposition during each period, including the date of randomization at Visit 2, the date of first and last dose on initially assigned treatment during the OLT Period, date/reason of initiation of switch to ixekizumab if any, the date of completion or discontinuation of study treatment, the primary reason for discontinuation of study treatment if applicable and date of study discontinuation, and the time to discontinuation (Analysis population: ITT).

6.6. Patient Characteristics

6.6.1. Demographics and Baseline Characteristics

Demographic variables and baseline characteristics (including baseline clinical measures) will be summarized for ITT, OLE period and Switcher populations.

The continuous variables will be summarized using descriptive statistics, and the categorical variables will be summarized using frequency counts and percentages.

A listing of demographics and patient characteristics will be provided as well.

See Table RHCG.6.2 for the demographic variables to be presented.

Table RHCG.6.2. Patient Characteristics

Variable	Continuous Measure Summary	Categorical / Interval Summary	Subgroup Analysis
Age [a]	Yes		
Age at JIA onset (years)[e]	Yes		
Sex	No	Male, Female	
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	
Country	No	Belgium, Denmark, France, Germany, Italy, Spain, Switzerland, Netherlands, UK	
Height (cm)	Yes	None	
Weight (kg)	Yes	None	
BMI[b]	No	Underweight (<18.5 kg/m^2), Normal (≥18.5 and <25 kg/m^2), Overweight (≥25 and <30 kg/m^2), Obese (≥30 and <40 kg/m^2), Extremely obese (≥40 kg/m^2)	
JIA Subtype	No	ERA, JPsA	Yes
Alcohol use	No	Never, Current, Former	
Caffeine/Xanthine consumption	No	Never, Current, Former	
Tobacco use	No	Never, Current, Former	
Prior biologic JIA therapy[c]	No	Never used, Ever used	Yes
Number of prior biologics for JIA[c]	No	0, 1, 2, >2	
Prior csDMARDs[j] therapy for JIA[d]	No	Never used, Ever used	Yes
Prior nonbiologic (Non-DMARD) therapy for JIA[d]	No	Never used, Ever used	Yes
Number of prior csDMARDs[j] for JIA[d]	No	0, 1, 2, >2	

Variable	Continuous Measure Summary	Categorical / Interval Summary	Subgroup Analysis
Number of non-biologic (Non-DMARD) therapies for JIA[d]	No	0, 1, 2, >2	
Number of active joints	Yes		
Number of joints with limited range of motion	Yes		
Physician's global assessment of disease activity (cm)	Yes		
Parent's global assessment of well-being (mm)	Yes		
Worst joint pain (NRS)	Yes		
CHAQ disability index	Yes		
Pain VAS (mm)	Yes		
hsCRP (mg/L)	No	>3 mg/L or ≤3 mg/L	
hsCRP (mg/L)	Yes		
ESR (mm/hour)	No	>20 mm/hour or ≤20 mm/hour	
ESR (mm/hour)	Yes		
Rheumatoid Factor Positive (RF+)	No	Yes or no	
HLA-B27 positive	No	Yes or no	
Juvenile Arthritis Disease Activity Score-27 (JADAS-27) score	Yes		
Juvenile Spondyloarthritis Disease Activity Index (JSpADA[f, g])	Yes		
European Quality of Life -5 Dimensions-Youth (EQ-5D-Y) score (VAS)	Yes		
Leeds Enthesitis Index (LEI) for patients with baseline enthesitis (LEI >0)	Yes		
Total Dactylitic Digit Count for patients with ≥1 Dactylitic Digit	Yes		

Variable	Continuous Measure Summary	Categorical / Interval Summary	Subgroup Analysis
Tender Dactylitic Digit Count for patients with ≥1 Tender Dactylitic Digit	Yes		
PASI total score[f] for patients who have baseline psoriatic lesion(s) involving Body Surface Area (BSA) ≥3%	Yes		
Percentage of BSA for patients who have baseline plaque psoriasis	Yes		
Percentage of BSA category for patients who have baseline plaque psoriasis	No	<3%, ≥3%	
Methotrexate (MTX) use at baseline	No	Yes or no	Yes
MTX dose among patients who take MTX concomitantly	Yes		
Sulfasalazine use at baseline	No	Yes or no	Yes
Sulfasalazine dose among patients who take Sulfasalazine concomitantly	Yes		
Previous biologic disease-modifying antirheumatic drugs (bDMARDs)	No	Never used or Ever used	
Previous conventional disease-modifying antirheumatic drugs (csDMARDs[j])	No	Never used, used 1 therapy, 2 therapies, ≥3 therapies	
Concomitant csDMARDs[j]	No	Yes or no	
Concomitant NSAIDs[d]	No	Yes or no	
Concomitant oral corticosteroids	No	Yes or no	
Children's Depression Inventory 2 SR(S) (CDI-2)	Yes		
Children's Depression Inventory 2 SR(S) (CDI-2)	No	<6, ≥6	
Columbia Suicide Severity Rating Scale (C-SSRS) since last assessed	No	Suicidal ideation, Suicidal behavior, Suicidal ideation or behavior	
Tanner Stage Scale	No	Female (Breasts): B1, B2, B3, B4, B5 Male (Genitals): G1, G2, G3, G4, G5 Both (Pubic Hair)	

Variable	Continuous Measure Summary	Categorical / Interval Summary	Subgroup Analysis
		PH1, PH2, PH3, PH4, PH5	
Time since JIA symptom onset[h] (years)	Yes		
Time since JIA diagnosis[i] (years)	Yes		
Duration of JIA diagnosis (years)[e] categories	No	0 to <2 years, 2 to <5 years, 5 to <10 years, ≥10 years	

Abbreviations: BMI = body mass index; CHAQ = Childhood Health Assessment Questionnaire; hsCRP = high-sensitivity C-Reactive Protein; ERA = enthesitis-related arthritis; ESR = erythrocyte sedimentation rate; HLA-B27 = human leukocyte antigen B27; JIA = juvenile idiopathic arthritis; JPsA = Juvenile Psoriatic Arthritis; NRS = Numeric Rating Scale; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; UK = United Kingdom; VAS = Visual Analogue Score.

a Age in years will be calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the electronic case report form (eCRF) to the informed consent date.

b BMI will be calculated as: $BMI\ (kg\ /\ m^2) = Weight\ (kg)\ /(Height\ (m)^2$.

c Biologic JIA therapies for example: anakinra, canankinumab, tocilizumab, sarilumab, rituximab, etanercept, adalimumab, infliximab, golimumab, abatacept, secukinumab.

d Other nonbiologics JIA therapies for example: NSAIDs (including COX-2 inhibitors), analgesics, systemic glucocorticoids.

e Age at diagnosis in years will be calculated as the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the date of JIA diagnosis.

f For JPsA patients who have this score available.

g For ERA patients who have this score available.

h Calculated as: (date of informed consent – date of JIA onset + 1) / 365.25
Patients who have a completely missing date of onset will have a missing value for the time since JIA onset, otherwise, "January" and "01" will be imputed for the missing month and day respectively in cases where either date components are missing.

i Calculated as: (date of informed consent – date of JIA diagnosis + 1) / 365.25
Patients who have a completely missing date of diagnosis will have a missing value for the time since JIA diagnosis, otherwise "January" and "01" will be imputed for the missing month and day respectively in cases where for these two date components are missing.

j csDMARDs include: methotrexate, sulfasalazine (the two most important), leflunomide, cyclosporine, and others rarely used.

6.6.2. Historical Illness and Pre-existing Conditions

Historical illnesses and preexisting conditions will be classified using the latest version of the MedDRA.

Historical illness/condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History electronic case report form (eCRF) page or on the Prespecified Medical History eCRF page with an end date prior to the date of informed consent.

A preexisting condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History eCRF page with a start date prior to the date of informed consent, and no end date (that is, the event is ongoing) or an end date on or after the date of informed consent. Adverse events occurring prior to the date of first study injection will also be reported. Note that, if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on Adverse Events eCRF page from the date of worsening onward.

The following summaries will be provided for the ITT Population:

- The number and percentage of patients with historical illnesses by treatment group and overall, by System Organ Class (SOC) and preferred term (PT).
- The number and percentage of patients with preexisting conditions and adverse events occurring prior to the first dose, by treatment group and overall, by SOC and PT.
- The number and percentage of patients with prespecified medical history (hypertension; diabetes mellitus, Type I; diabetes mellitus, Type II; dyslipidemia; psoriatic arthritis; inflammatory bowel disease [Crohn's disease and uncreative colitis]), by treatment group and overall.

Frequency counts and percentages of patients with selected preexisting conditions will be summarized for the ITT population, and also will be summarized by treatment group using the OLE and the OLE Switcher populations.

For a condition/event that is gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

By-patient listings of historical illnesses and preexisting conditions, respectively, for the ITT Populations will be provided.

6.7. Treatment Compliance

Study treatment dispensed will be listed (including the CT Lot number) for the Safety Population. Study treatment administration and compliance will be listed for the ITT Population.

Patients will record information in a Study Drug Administration Log (captured in the *Exposure* eCRF page), including the date, time, and anatomical location of administration of investigational product, syringe number, who administered the investigational product, and the reason if the investigational product was not fully administered.

Treatment compliance (%) for each patient will be calculated as:

$$100 \times \frac{\text{Total number of injections administered}}{\text{Total number of injections prescribed}}$$

Number of injections prescribed (that is, expected) can be found in Table RHCG.6.3.

Table RHCG.6.3. Number of Injections Prescribed (Assuming adalimumab responders)

To calculate the number of prescribed injections:

1. For patients who completed, please refer to Table RHCG.6.3
2. For adalimumab patients who switch to ixekizumab, refer to Table RHCG.2.2. Schedule of Activities – Open-Label Extension Period of the study protocol
3. For patients who discontinue during the OLT, OLE, and LTE Periods, the number of injections prescribed can be derived from the IWRS study drug dispense dataset.

If the response to the question "Was dose administered?" on the Exposure eCRF page is 'No' then treatment compliance will be 0% at respective visit.

A patient will be considered overall compliant for the OLT, the OLE, and the LTE Periods, if he/she is missing no more than 20% of the expected doses, does not miss 2 consecutive doses, and does not over-dose (that is, take more injections at the same time point than specified in the protocol) within the respective study period.

Treatment compliance with investigational product will be summarized for the following periods:

- OLT Period (ITT Population)
- Extension Period (OLE and OLE Switcher populations), and
- LTE Safety Population.

6.8. Previous and Concomitant Therapy

Medication/therapy will be classified into Anatomical Therapeutic Chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary.

Table RHCG.6.4. Previous and Concomitant JIA Therapies Grouping

Drug Class	Previous	Concomitant
csDMARDs	Yes	Yes
Oral corticosteroids	Yes	Yes
NSAIDs including cyclooxygenase-2 inhibitors	Yes	Yes
Analgesics	Yes	Yes
Biologics (bDMARDs)	Yes	No

Abbreviations: bDMARDs: biologic disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; JIA = juvenile idiopathic arthritis; NSAID = nonsteroidal anti-inflammatory drug.

A by-patient listing of previous and concomitant therapy, and a by-patient listing of previous JIA therapy for the ITT Population will be provided.

6.8.1. Previous Therapy

Previous therapy is defined as the therapy that starts and ends prior to the date of first dose of study treatment in the OLT Period. If a patient does not receive a treatment drug, the first dose date of the study will be replaced with the date of randomization. If therapy start and/or end dates

are missing or partial, the dates will be compared as far as possible with the date of first dose of study treatment in the OLT Period. If there is clear evidence to suggest that the therapy stopped prior to the first dose of study treatment in the OLT Period, the therapy will be assumed to be previous only.

A list of previous JIA therapies is found in Table RHCG.6.4.

The number and percentage of patients who received previous therapy for JIA, as recorded on the *Prior Therapy: Juvenile Idiopathic Arthritis (CM2001_LV1)* eCRF page will be summarized by treatment group, overall and preferred name. The number and percentage of patients with each reason for discontinuing previous therapy for JIA will also be presented by treatment group.

Previous therapy for JIA will be summarized for the ITT Population.

6.8.2. Concomitant Therapy

Concomitant therapy for treatment period is defined as the therapy that starts before, on, or after the first day of study treatment in treatment period and before the last visit date in the treatment period, and continues into the treatment period, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment in treatment period. If patient does not receive a treatment drug, the first day of the study treatment will be replaced with the date of randomization. Note, concomitant therapy will belong to a treatment period if the therapy starts and ends on the exact same day as the first day of study treatment of the treatment period.

A list of concomitant JIA therapies is found in Table RHCG.6.4.

If a partial or completely missing medication start date/time or end date/time is present, the following imputation rules will be utilized in the analysis:

- For the start date:
  - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
  - If either month or month and day are missing, then use January 1.
  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date.
  - If either month or month and day are missing, then use December 31.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date.
- For the end time:
  - Impute as 23:59
- If there is any doubt, the medication will be flagged as concomitant.

Concomitant will be summarized and analysed for the following populations:

- ITT Population (OLT Period)

- OLE Period Population and OLE Switcher Population (OLE Period), and
- LTE Period (LTE Safety Population).

6.9. Efficacy Analyses

6.9.1. Primary Outcome and Methodology

The analysis methods and analysis periods are described in Table RHCG.6.5 and Table RHCG.6.6.

The primary efficacy endpoint is the percentage of ixekizumab-treated patients meeting JIA ACR30 response criteria at Week 16. A JIA ACR30 response is defined as at least 30% improvement from baseline in at least 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by >30%.

The individual components that make up the JIA ACR30 core set variables are defined as follows:

- Number of active joints in 73 joints (active joint defined as a joint that is swollen, or in the absence of swelling, has loss of passive motion accompanied by either pain on motion or joint tenderness)
- Number of joints with limited range of motion in 69 joints
- Physician's Global Assessment of Disease Activity (21-circle Visual Analogue Scale [VAS])
- Parent's Global Assessment of Well-Being
- Physical function as assessed by the Childhood Health Assessment Questionnaire (CHAQ)
- Erythrocyte sedimentation rate (ESR)

A listing of the primary efficacy endpoint will be provided.

If the study is not stopped for futility, the posterior probability of the Week 16 JIA ACR30 response rate exceeding 50% will be calculated, and the study objective will be successfully met (i.e., a positive study) if this posterior probability is at least 80%.

The beta-binomial 2-stage Bayesian model will be used for the primary analysis. The beta shape parameters are:

- a: the degree of response
- b: the magnitude of non-response

The prior distribution of the JIA ACR30 response rate at Week 16, p, is:

$$p \sim beta(a, b)$$

where a and b are the prior parameters and have an intuitive interpretation of prior responders and non-responders, respectively. The prior will be pre-specified with parameters $a = b = 1/2$, which is largely accepted as a Jeffery prior.

Let $X_i|p$ be the JIA ACR30 response at Week 16 of the i^{th} patient treated with ixekizumab. X_i conditionally follows a Bernoulli distribution:

$$X_i|p \sim Bernoulli(p).$$

The number of JIA ACR30 responders at Week 16, K is binomial:

$$K|p \sim binomial(n, p)$$

where n is the sample size of the ixekizumab patients of the ITT population in the study.

Due to conjugacy in the beta-binomial model, the posterior distribution of p is:

$$p|k \sim beta(a + k, b + n - k)$$

The posterior mean, variance, and 95% credible interval will be summarized from this posterior distribution. The following will be provided:

- The posterior mean,
$$\mu_p = \frac{a + k}{a + b + n}$$
- The posterior standard deviation,
$$\sigma_p = \sqrt{\frac{(a + k)(b + n - k)}{(a + b + n)^2(a + b + n + 1)}}$$
- 95% credible interval, which will include the 2.5th and 97.5th percentiles of the posterior distribution

The beta posterior probability of the response rate exceeding 0.5 is given by:

$$P(p > 0.5|k) = \int_{0.5}^{1} \frac{1}{B(a + k, b + n - k)} p^{a+k-1}(1 - p)^{b+n-k-1} dp$$
$$= \int_{0.5}^{1} \frac{1}{B\left(\frac{1}{2} + k, \frac{1}{2} + n - k\right)} p^{k-1/2}(1 - p)^{n-k-1/2} dp$$

where:

$$B(\alpha, \beta) = \int_{0}^{1} t^{\alpha-1}(1 - t)^{\beta-1} dt$$

$$\alpha > 0, \beta > 0$$

is the beta function.

The following example and SAS® code illustrate how the posterior probability is obtained.

```
%macro bayesian_algo (p_0=,a=,b=,k=,n=);
      data bayesian;
            p=&k/&n;
            a_post=&a+&k;
```

```
            b_post=&b+&n-&k;
            k=&k;
            n=&n;
            h_0=&k/&n;
            h_1=1-&k/&n;
            x1=probbeta(h_0,a_post,b_post);
            x2=1-probbeta(h_1,a_post,b_post);
            postProb=1-probbeta(&p_0,a_post,b_post);
      run;
%mend bayesian_algo;

%bayesian_algo(p_0=0.5,a=0.5,b=0.5,k=35,n=80);
```

Table RHCG.6.5. Description and Derivation of Primary Efficacy Endpoint

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
JIA ACR30 Responder Index	Juvenile Idiopathic Arthritis American College of Rheumatology, JIA ACR, is comprised of 6 variables: active joint count, limitation of motion joint count, physician global assessment, patient/parent global assessment, Childhood Health Assessment Questionnaire (CHAQ), and acute-phase reactant level (ESR). A JIA ACR30 response is defined as at least 30% improvement from baseline in at least 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by more than 30% (Giannini et al. 1997).	Proportion of patients with Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) 30 at Week 16, nonresponder imputation (NRI)	See Section 6.9.1 and Appendix 1	See Appendix 1

Abbreviations: ACR = American College of Rheumatology; ESR = erythrocyte sedimentation rate; JIA = Juvenile Idiopathic Arthritis; NRI = nonresponder imputation.

Table RHCG.6.6. Description of Analysis Period and Analysis Method of Primary Efficacy Endpoint

Measure	Variable	Population	Analysis Timepoint	Analysis Method
JIA ACR30 Responder Index	Proportion of patients with JIA ACR30	ITT	Week 16	Bayesian statistics

Abbreviations: ACR = American College of Rheumatology; JIA = Juvenile Idiopathic Arthritis.

6.9.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be based on each treatment period with the respective population at each visit. A listing of each secondary efficacy analysis may be provided. The analysis methods and analysis periods are described in Table RHCG.6.7 and Table RHCG.6.8.

Table RHCG.6.7. Description and Derivation of Secondary Efficacy Endpoints

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
JIA ACR Responder Index	Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR), is comprised of 6 variables: active joint count, limitation of motion joint count, physician global assessment, patient/parent global assessment, Childhood Health Assessment Questionnaire (CHAQ), and acute-phase reactant level (ESR). JIA ACR*x* response is defined as at least *x*% improvement from baseline in at least 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by more than *x*%. *x* is a number from 0 to 100.	Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) 30/50/70/90/100	See Section 6.9.1 and Appendix 1	See Appendix 1
Active joint count	Number of active joints (defined as a joint that is swollen or in the absence of swelling has loss of passive motion accompanied by either pain on motion or joint tenderness) in 73 joints.	Change from baseline of active joint count	Calculation: Change from baseline: observed active joint count at visit minus baseline active joint count	Missing if baseline or post-baseline value is missing.
Limited range of motion joint count	Number of joints with limited range of motion in 69 joints	Change from baseline of limited of motion joint count	Calculation: Change from baseline: observed limited range of motion joint count at visit minus baseline limited range of motion joint count	Missing if baseline or post-baseline value is missing.
Physician's global assessment of disease activity (VAS)	The Physician's Global Assessment of Disease Activity is used to assess the patient's current disease activity, as it relates to their signs and symptoms. The instrument uses a 21 circle VAS ranging from 0 to 10 (using 0.5 increments) where 0 = "no activity" and 10 = "maximum activity" (Filocamo et al. 2010).	Change from baseline of physician's global assessment of disease activity	Calculation: Change from baseline: observed score at visit minus baseline score	Missing if baseline or post-baseline value is missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
Parent's global assessment of overall well-being measured by CHAQ (0-100 mm VAS)	The parent is generally asked to make a global assessment of the child's overall well-being on a 100 mm VAS, with anchors of '0 = very good' and '100 = very poor', which is located at the bottom of the CHAQ	Change from baseline of parent's global assessment of overall well-being	The detail of physical function calculation is documented in Appendix 3 Calculation: Change from baseline: observed score at visit minus baseline score	Missing if baseline or post-baseline value is missing.
Physical function as measured by CHAQ (0-3)	The CHAQ assesses health status and physical function over the past week in children with juvenile arthritis over the past week, which the parent or legal guardian completes, regardless of the age of the patient. Physical function is measured by CHAQ from disability index. The Disability Index contains 30 items grouped into the following 8 domains (not including assistive devices/aids questions): physical function, dressing, and grooming (4 items), arising (2 items), eating (3 items), walking (2 items), hygiene (5 items), reach (4 items), grip (5 items), and activities (5 items). Each item is scored from 0 to 3 (0 = no difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do or not applicable) (Singh et al. 1994). The total score is the average of domain score, which is range from 0 to 3. At least 6 domains are required in calculation.	CHAQ – Physical Function Score Change from baseline of physical function	The detail of physical function calculation is documented in Appendix 3 Change from baseline: observed score at visit minus baseline score	Missing if baseline or post-baseline value is missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
ESR (mm/hr)	An erythrocyte sedimentation rate (ESR) is a type of blood test that measures how quickly erythrocytes (red blood cells) settle at the bottom of a test tube that contains a blood sample. Normally, red blood cells settle relatively slowly. A faster-than-normal rate may indicate inflammation in the body.	Change from baseline of ESR	Calculation: Change from baseline: observed lab value at visit minus baseline lab value	Missing if baseline or post-baseline value is missing.
Disease flare	Disease flare is defined as a worsening of ≥30% in at least 3 of the 6 JIA ACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria from the patient's condition at randomization baseline. More information on Disease Flare can be found in Appendix 2.	Disease Flare	The detail of disease flare calculation is documented in Appendix 2.	See Appendix 2 for more details.
PASI	Psoriasis Area and Severity Index (PASI): For patients with plaque psoriasis, combines assessments of the extent of body-surface	PASI total score Change from baseline	The composite PASI score is calculated by multiplying the sum of the individual-severity scores for each area	If any individual score is missing, the PASI score will not be

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration thickness (T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into 4 anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement; up to 6 for 90% to 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90% 6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of BSA.	in PASI total score % Improvement in PASI total score	by the weighted area-of-involvement score for that respective area, and then summing the 4 resulting quantities as follows: $PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l$ Where, R_h, R_u, R_t, R_l = redness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; A_h, A_u, A_t, A_l = numerical value translation of % area of psoriatic involvement score for the head, upper limb, trunk, and lower limb, respectively PASI scores are treated as a continuous score, with 0.1 increments within these values.	calculated, hence missing. Change from baseline in PASI is missing if baseline or observed value are missing % Improvement in PASI total score is missing if baseline or observed value are missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
			PASI scores are treated as a continuous score, with 0.1 increments within these values. Change from baseline in PASI total score calculated as: observed PASI – baseline PASI % Improvement in PASI total score calculated as: $100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$	
LEI	For patients with enthesitis, an assessment that consists of 18 entheseal points is performed by site personnel. The Leeds Enthesitis Index (LEI) has been developed specifically for use in PsA and measures enthesitis at 6 sites (lateral epicondyle [left and right], medial femoral condyle [left and right], and Achilles tendon insertion [left and right]) (Healy and Helliwell 2008).	LEI score Change from baseline in LEI	Each site is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score (range: 0 to 6). Change from baseline in LEI calculated as: observed LEI – baseline LEI	If one or more sites are missing, then set to missing. Change from baseline in LEI Missing if baseline or observed value are missing.
PK	Characterize ixekizumab pharmacokinetics (PK) in children with JIA subtypes of ERA (including JoAS) and JPsA.	Trough concentrations of ixekizumab in patients with JIA subtypes of ERA (including JoAS) and JPsA	The detail of PK calculation is documented in 6.11.	See Section 6.11
Anti-ixekizumab antibodies	See Section 6.12.12	Percentage of patients with anti-ixekizumab antibodies	The detail of Anti-ixekizumab antibodies calculation is documented in Section 6.12.12.	See Section 6.12.12

Abbreviations: BSA = body surface area; JIA = Juvenile Idiopathic Arthritis; ERA = Enthesitis-related Arthritis; JoAS = Juvenile-onset Ankylosing Spondylitis; JPsA = Juvenile Psoriatic Arthritis; VAS = Visual Analog Scale.

Table RHCG.6.8. Description of Analysis Period and Analysis Method of Secondary Efficacy Endpoint

Measure	Variable	Population	Analysis Timepoint	Analysis Method
JIA ACR response	JIA ACR30/50/70/90/ 100 response rates	ITT	Week 2 to Week 16	Summary Statistics NRI for missing post-baseline values mNRI for missing post-baseline values (JIA ACR30)
	JIA ACR30	ITT	Week 16	Bayesian Analysis mNRI for missing post-baseline values
		OLE	Week 16 to Week 104	Summary Statistics NRI for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary Statistics NRI for missing post-baseline values
Active joint count	Change from baseline of active joint count	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
Limited of range motion joint count	Change from baseline of limited range of motion joint count	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
Physician's global assessment of disease activity	Change from baseline of physician's global assessment of disease activity	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values

Measure	Variable	Population	Analysis Timepoint	Analysis Method
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
Physical function as measured by CHAQ	Change from baseline of physical function	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
Parent's global assessment of overall well-being as measured by CHAQ	Change from baseline of parent's global assessment of overall well-being	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
ESR (mm/hr)	Change from baseline of ESR	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
Disease flare	Disease flare	ITT	Week 2 to Week 16	Summary statistics NRI for missing post-baseline values.

Measure	Variable	Population	Analysis Timepoint	Analysis Method
		OLE	Week 16 to Week 104	Summary statistics NRI for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics NRI for missing post-baseline values
PASI	PASI total score Change from baseline in PASI total score % Improvement in PASI total score	ITT – JPsA patients with baseline psoriatic lesion(s) involving BSA ≥3%	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE – JPsA patients with baseline psoriatic lesion(s) involving BSA ≥3%	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher – JPsA patients with baseline psoriatic lesion(s) involving BSA ≥3%	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
LEI	Change from baseline in LEI	ITT with baseline LEI > 0	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE with baseline LEI > 0	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher with baseline LEI > 0	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values

Measure	Variable	Population	Analysis Timepoint	Analysis Method
PK	Trough concentrations of ixekizumab in patients with JIA subtypes of ERA (including JoAS) and JPsA	ITT	Week 0 to Week 16	See Section 6.11
Anti-ixekizumab antibodies	Percentage of patients with anti-ixekizumab antibodies	Safety Population	Week 0 to Week 16	See Section 6.12.12
		OLE Population	Week 16 to Week 104	See Section 6.12.12

Abbreviations: ACR = American College of Rheumatology; BSA = Body Surface Area; CHAQ = Childhood Health Assessment Questionnaire; ERA = Enthesitis-related Arthritis; ESR = Erythrocyte Sedimentation Rate; ITT = intent-to-treat; IXE = ixekizumab; JIA = juvenile idiopathic arthritis; JoAS = Juvenile-onset Ankylosing Spondylitis; JPsA = Juvenile Psoriatic Arthritis; LEI = Leeds Enthesitis Index; mBOCF = Modified Baseline Observation Carried Forward; NRI = Nonresponder Imputation; OLE = open-label extension; PASI = Psoriasis Area and Severity Index; PK = Pharmacokinetics; VAS = Visual Analog Scale.

6.9.3. Other Secondary Efficacy Analyses

Other secondary efficacy analyses will be based on each treatment period with the respective population at each visit. A listing of each other secondary efficacy analysis may be provided. The analysis methods and analysis periods are described in Table RHCG.6.9 and Table RHCG.6.10.

Table RHCG.6.9. Description and Derivation of Other Secondary Efficacy Endpoints

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
JIA ACR Responder Index	Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) is comprised of 6 variables: active joint count, limitation of motion joint count, physician global assessment, patient/parent global assessment, Childhood Health Assessment Questionnaire (CHAQ), and acute-phase reactant level (either ESR). JIA ACR*x* response is defined as at least *x*% improvement from baseline in at least 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by more than *x*%. *x* is a number from 0 to 100.	Time to First Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) 30/50/70/90/100 Response	(Date of first JIA ACR*x* response in defined treatment period – date of first injection + 1) / 7. If the date of first dosing is missing, the date of randomization is used.	Censoring at time of last available visit using Survival analysis (Kaplan-Meier)
hsCRP (mg/L)	The hsCRP test is a highly sensitive quantification of C-Reactive protein (CRP), an acute-phase protein that increases during inflammation.	Change from baseline of hsCRP	Calculation: Change from baseline: observed lab value at visit minus baseline lab value	Missing if baseline or post-baseline value is missing.
PASI	Psoriasis Area and Severity Index (PASI): For patients with plaque psoriasis, combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration thickness (T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index	PASI 75	A clinically meaningful response; at least a 75% improvement in PASI score from baseline.	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	(R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into 4 anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement; up to 6 for 90% to 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90% 6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of BSA.			
		PASI 90	Higher level of clearance; at least a 90% improvement in PASI score from baseline.	Missing if baseline or observed value is missing
		PASI 100	Complete resolution of plaque psoriasis; a 100% improvement in PASI score from baseline.	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
LEI	For patients with enthesitis, an assessment that consists of 18 entheseal points is performed by site personnel. The Leeds Enthesitis Index (LEI) has been developed specifically for use in PsA and measures enthesitis at 6 sites (lateral epicondyle [left and right], medial femoral condyle [left and right], and Achilles tendon insertion [left and right]) (Healy and Helliwell 2008).	LEI resolution	Post baseline LEI = 0	If one or more sites are missing, then set to missing. Missing if baseline or observed value are missing
BSA	Percentage of Body Surface Area (BSA): The investigator will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (Van Voorhees et al. 2016).	Percentage of BSA Change from baseline in BSA	Range from 0% to 100%. Change from baseline in BSA calculated as: observed BSA – baseline BSA	Missing if observed value is missing Change from baseline in BSA Missing if baseline or observed value is missing
Pain being measured by CHAQ (0-100 mm VAS)	The patient is asked to make a pain assessment due to illness. The question uses a 0 to 100 mm VAS where 0 = "no pain" and 100 = "very severe pain"	Change from baseline in Pain VAS	Calculation: Change from baseline: observed score at visit minus baseline score	Missing if post-baseline value missing. Missing if baseline or post-baseline value is missing.

Abbreviations: hsCRP = high-sensitivity C-reactive protein; ESR = erythrocyte sedimentation rate; PsA = psoriatic arthritis; VAS = Visual Analog Scale.

Table RHCG.6.10. Description of Analysis Period and Analysis Method of Other Secondary Efficacy Endpoint

Measure	Variable	Population	Analysis Timepoint	Analysis Method
JIA ACR response	Time to First Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) 30/50/70/90/100 Response	ITT	Week 0 to Week 16	For time to event, Kaplan-Meier
hsCRP (mg/L)	Change from baseline of hsCRP	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
PASI	PASI 75/90/100	ITT – JPsA patients with baseline psoriatic lesion(s) involving BSA ≥3%	Week 2 to Week 16	Summary statistics NRI for missing post-baseline values.
		OLE – JPsA patients with baseline psoriatic lesion(s) involving BSA ≥3%	Week 16 to Week 104	Summary statistics NRI for missing post-baseline values
		OLE Switcher – JPsA patients with baseline psoriatic lesion(s) involving BSA ≥3%	Week 16 (or Switch to IXE) to Week 104	Summary statistics NRI for missing post-baseline values
LEI	Proportion of patients with complete resolution in enthesitis (LEI score = 0)	ITT with baseline LEI > 0	Week 2 to Week 16	Summary statistics NRI for missing post-baseline values.
		OLE with baseline LEI > 0	Week 16 to Week 104	Summary statistics NRI for missing post-baseline values
		OLE Switcher with baseline LEI > 0	Week 16 (or Switch to IXE) to Week 104	Summary statistics NRI for missing post-baseline values

Measure	Variable	Population	Analysis Timepoint	Analysis Method
BSA	Percentage of BSA Change from baseline in BSA	ITT population with baseline plaque psoriasis	Week 2 to Week 16	Summary statistics mBOCF will be applied for post baseline missing values
		OLE population with baseline plaque psoriasis	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher population with baseline plaque psoriasis	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values
Pain being measured by CHAQ (0-100 mm VAS)	Change from baseline in Pain VAS	ITT	Week 2 to Week 16	Summary statistics mBOCF for missing post-baseline values
		OLE	Week 16 to Week 104	Summary statistics mBOCF for missing post-baseline values
		OLE Switcher	Week 16 (or Switch to IXE) to Week 104	Summary statistics mBOCF for missing post-baseline values

Abbreviations: BSA = body surface area; CHAQ = Childhood Health Assessment Questionnaire; hsCRP = high-sensitivity C-reactive protein; ITT = intent-to-treat; IXE = ixekizumab; JIA ACR = Juvenile Idiopathic Arthritis American College of Rheumatology; JPsA = juvenile psoriatic arthritis; LEI = Leeds Enthesitis Index; mBOCF = Modified Baseline Observation Carried Forward; NRI = Nonresponder Imputation; OLE = open-label extension; PASI = Psoriasis Area and Severity Index; VAS = Visual Analogue Scale.

6.9.4. Exploratory Analyses

Exploratory efficacy analyses will be based on each treatment period with the respective population at each visit. A listing of each exploratory efficacy analysis may be provided. The analysis methods and analysis periods are described in Table RHCG.6.11 and Table RHCG.6.12.

Table RHCG.6.11. Description and Derivation of Exploratory Efficacy Endpoints


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Table RHCG.6.12. Description of Analysis Period and Analysis Method of Exploratory Efficacy


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6.9.5. Sensitivity Analyses

Juvenile idiopathic arthritis ACR30 up to Week 16 will be analyzed based on the ITT Population using the mNRI method, as described in Section 6.3.4. Bayesian analysis will be performed for JIA ACR30 at Week 16.

Sensitivity analyses will be performed as deemed appropriate.

6.10. Health Outcomes/Quality-of-Life Analyses

Health Outcomes analyses will be based on each treatment period with the respective population at each visit. A listing of each health outcome analysis may be provided. See Table RHCG.6.7 and Table RHCG.6.11 for analysis of CHAQ and EQ-5D-Y, respectively. For description of analysis period and analysis methods of CHAQ and EQ-5D-Y, see Table RHCG.6.8 and Table RHCG.6.12, respectively.

6.11. Pharmacokinetic/Pharmacodynamic Analyses

Observed ixekizumab serum trough concentrations will be summarized by time point across the study. Data may also be summarized by weight category, disease, and age as deemed appropriate.

In addition, the clearance of ixekizumab in this patient population may be determined using population PK methods. If this analysis is conducted, then the data from this study may be combined with data from prior studies to aid in model development.

The exposure-response relationship will be investigated between steady-state trough concentrations of ixekizumab and JIA ACR 30 response at Week 16 using graphical methods and, if appropriate, modeling methods. Evaluation of additional time points or endpoints may also be considered.

If applicable, the potential impact of immunogenicity on ixekizumab exposure may be evaluated by graphical assessments, as appropriate, to compare drug exposure between antidrug antibody- (ADA-) negative and treatment-emergent- (TE-) ADA-positive patients at corresponding visits.

Additional analyses may be performed upon receipt of the data. More details of the pharmacokinetic/pharmacodynamic (PK/PD) analyses can be found in a separate PK/PD analysis plan.

6.12. Safety Analyses

The planned safety analyses are consistent with compound-level standards, which are based on various sources, including company standards, internal and external subject matter experts, and cross-industry. Descriptions of the safety analyses are provided in this statistical analysis plan (SAP).

Safety will be assessed by summarizing and analyzing adverse events (AEs), laboratory analytes, including neutrophil counts and immunogenicity, vital signs, Children's Depression Inventory 2

(CDI-2) and Columbia Suicide Severity Rating Scale (C-SSRS). The duration of dosing exposure will also be summarized.

For the OLT Period, the safety data will be summarized and analyzed for the Safety Population for each treatment arm.

For the OLE Period, the select safety data will be summarized and analyzed for the OLE period before the switch, and OLE period after the switch with the corresponding analysis populations. The mean change of the continuous safety measures will be summarized by visits.

For patients who switched to ixekizumab on or after Week 16, categorical safety data after switch of treatment will be summarized with incidence rates by initially assigned treatment group for the Switcher Population (that is, TEAEs, serious adverse events [SAEs], AEs as reason for study treatment discontinuation, treatment-emergent clinical laboratory assessments, treatment-emergent vitals).

For the LTE Period, the safety data will be summarized and analyzed for the LTE Safety Population. For the PTFU Period, the select safety data will be summarized and analyzed for the PTFU Period Population. Summaries of safety data collected during the Post-Treatment Follow-up Period will be presented separately by treatment, according to last treatment received before entering PTFU period. Unless otherwise specified, the Post-Treatment Follow-up Period baseline is defined as the last nonmissing assessment on or prior to the Week 104 (Visit 29) or ETV. The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized by visits.

The detail of each population is defined in Section 6.1.1.

Safety topics that will be addressed include the following: AEs, SAE, clinical laboratory evaluations, vital signs and physical characteristics, safety in special groups and circumstances, including adverse events of special interest (AESI) (see Section 6.12.11).

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 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, regardless of treatment period).

6.12.1. Extent of Exposure

Duration of exposure to study treatment (defined as time since first injection of study treatment in days) will be summarized by treatment group during the OLT Period and the OLE Period.

The duration of exposure during the **OLT Period for the Safety Population** will be calculated as:

(Date of last study visit in OLT Period – Date of first injection of study treatment + 1)

The duration of exposure on initially assigned treatment for the **OLE Period Population** will be calculated as:

Date of last visit on initially assigned treatment – Date of first dose in OLE Period +1

The duration of exposure during the **OLE Period** for the OLE Switcher Population will be calculated as:

(Date of last study visit in OLE Period – The first date of switch to ixekizumab + 1)

The duration of exposure during the **LTE Period** for LTE Safety population will be calculated as:

(Date of last study visit in LTE Period – Date of first injection of study treatment + 1)

Descriptive statistics will be provided for patient days of exposure and the frequency of patients falling into the following different exposure ranges (that is, only the exposure ranges that fall within the treatment period will be presented) will be summarized:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, ≥365 days.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, ≥365 days.

Overall exposure for each treatment group within the OLT Period and the OLE Period for respective populations will also be summarized in total patient years. This will be calculated as follows:

Exposure in patient years = Sum of duration of exposure with the defined treatment period (for all patients in treatment group) / 365.25.

A listing of study drug exposure will also be provided.

6.12.2. Adverse Events

6.12.2.1. Analysis of Adverse Events

Adverse events are classified based on MedDRA. A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline severity (in some cases baseline period is a single time point). Events with a missing severity during the treatment period will be considered treatment emergent. The treatment period will be included as post-baseline for the analysis. If an event is pre-existing during the baseline period but it has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the post-baseline level of severity. Adverse events with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date in the treatment period (i.e., a

patient has no pre-existing conditions with that LLT), or if the severity is greater than the pre-treatment severity for that LLT.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Week 104 (Visit 29) or the ETV. The MedDRA LLT will be used when classifying FEAEs as follow-up emergent. For AEs that are ongoing at the date of Week 104 (Visit 29) or ETV, the maximum severity recorded for each LLT on the date of Week 104 (Visit 29) or ETV will be used as the follow-up baseline severity for that lowest level term.

An overview table will be provided and will include the frequency and percentage of patients who experienced a TEAE, TEAE by maximum severity, a treatment-emergent AESI, SAE, died, or discontinued from the study due to an AE (including death) will be summarized by treatment group for each treatment period. A listing will be provided as well.

The number and percentage of patients, and the number of events (where applicable) will be presented, by treatment group for each treatment period, separately. When the SOC is presented, events will be ordered by decreasing frequency in the ixekizumab dose group, within SOC. When the SOC is not presented, the events will be ordered by decreasing frequency in the overall group followed in the order of ixekizumab Q4W then adalimumab Q2W. For incidence counts, each patient will be counted only once within each Preferred Term and within each SOC. Percentages will be based on the number of patients in a particular treatment group. For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

The following summary tables will be provided for the OLT Period (Safety Population), OLE Period (OLE Period Population and OLE Switcher Population), and LTE Period (LTE Safety Population):

- An overview summary of AEs
- TEAEs, by SOC and Preferred Term
- TEAEs, by Preferred Term
- TEAEs by maximum severity, by SOC and Preferred Term

The following summary tables will be provided for the PTFU Period (PTFU Population):

- FEAEs, by Preferred Term

By-patient listing of all TEAEs will be provided.

If a partial or completely missing AE start date/time or end date/time is present the following imputation rules will be utilized in the analysis:

- For the start date:
    - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
    - If either month or month and day are missing, then use January 1.
    - If only day is missing, impute the first day of the month.

- For the start time:
  - Impute as 23:59
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date in the follow-up period.
  - If either month or month and day are missing, then use December 31.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date in the follow-up period.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the event will be flagged as treatment-emergent or follow-up emergent according to the corresponding study period. If a follow-up emergent event was already counted as treatment-emergent during the prior treatment period, it will not be counted as a follow-up emergent event.

6.12.3. Deaths, Other Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

6.12.3.1. Deaths

A listing of deaths will be provided. All deaths will be included, regardless of the Investigator's or the Sponsor's judgment about causality, including (1) any deaths occurring during participation in the study in the database for which data are being presented, (2) any deaths occurring after a patient leaves (i.e., discontinued from the study or completes the study) the study in the database for which data are being presented if the death is (a) the result of a process initiated during the study, regardless of when it actually occurs, or (b) occurs during the PTFU Period after discontinuation of study drug.

6.12.3.2. Serious Adverse Event Analyses

The number and percentage of patients who experienced an SAE will be summarized by treatment for the OLT Period (Safety Population), OLE Period (OLE Period Population and OLE Switcher Population), and LTE Period (LTE Safety Population) using MedDRA Preferred Term nested within SOC. Events will be ordered by decreasing frequency in the overall group followed in the order of ixekizumab Q4W (when applicable) then adalimumab Q2W (when applicable) group within SOC.

A follow-up emergent SAE is defined as a new SAE which occurs after the last visit during the treatment period, or an existing event worsens beyond the greatest severity reported during the PTFU Period. The baseline severity for SAEs occurring during the PTFU Period will be the maximum severity from the preceding visit before entering the PTFU Period. The number and percentage of patients who experienced a follow-up emergent SAE in the PTFU Period (PTFU Period Population) will be summarized using MedDRA Preferred Term nested within SOC. Events will be ordered by decreasing frequency in the overall group followed in the order of ixekizumab Q4W then adalimumab Q2W group within SOC.

By-patient listing of all SAEs (including death) will be provided.

6.12.3.3. Adverse Events Leading to Study Treatment Discontinuation

The number and percentage of patients who discontinued from the study treatment due to an AE, including patients who died, will be summarized by treatment for the OLT Period (Safety Population), OLE Period (OLE Period Population and OLE Switcher Population), and LTE Period (LTE Safety Population) using MedDRA Preferred Term nested within SOC. Events will be ordered by decreasing frequency in the overall group followed in the order of ixekizumab Q4W then adalimumab Q2W group within SOC.

Additionally, the number and percentage of patients who discontinued the study due to an AE, including patients who died, will be summarized by treatment for the PTFU Period (PTFU Period Population).

By-patient listing of AEs leading to discontinuation of study treatment will be provided.

6.12.4. Clinical Laboratory Evaluation

Laboratory evaluations will be summarized and analyzed for the following periods:

- OLT Period (Safety Population)
- OLE Period (OLE Period Population and OLE Switcher Population)
- LTE Period (LTE Safety Population), and
- Post-Treatment Follow-up Period (PTFU Period Population).

Laboratory evaluation results will be provided in a by-patient listing. Additionally, a listing of abnormal laboratory results for parameters of special interest (including laboratory analyte measurements and qualitative measures) will be provided.

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol. However, unplanned/unscheduled measurements of planned analytes will be included/ excluded as specified in the relevant sections. Examples of unplanned/unscheduled measurements include those that the clinical investigator orders as a repeat test or "retest" of a laboratory test if he/she has received an abnormal value, and those the investigator orders for a "follow-up visit" due to clinical concerns.

Change from baseline to last observation for laboratory tests will be summarized for patients who have both baseline and at least one post-baseline result for each treatment period. Baseline will be the last nonmissing observation in the baseline period. The last nonmissing observation in each treatment period will be analyzed. Original-scale data will be analyzed. Unscheduled visits and repeat measurements will be excluded. Box plots for observed and change values will be rendered in Spotfire. Analyses will be provided in both standard (SI) and conventional (CN) units (when different).

The number and percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time will be summarized by treatment for each treatment period. Scheduled visits, unscheduled visits, and repeat measurements will be included.

- Categorical laboratory tests:
  - A treatment-emergent **abnormal** result is defined as a change from normal at all baseline visits to abnormal at any time during the treatment period.
- Numerical laboratory tests:
  - A treatment-emergent **high** result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the treatment period.
  - A treatment-emergent **low** result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the treatment period.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), neutrophils, leukocytes, platelets, and lymphocytes will not be included in this treatment-emergent abnormal, high, or low laboratory results analysis. A separate analysis to address the risk of liver injury is described in Table RHCG.6.16 in which Covance reference ranges will be used.

For lower limit of normal (LLN)s of neutrophils, lymphocytes, platelets, and leukocytes, there are inconsistencies encountered for cytopenias across the large clinical trial population, Covance, and commonly accepted standard- (Wu 2006; Greer et al. 2008) based reference limits. For at least one type of cytopenia with either the large clinical trial population-based reference limits or Covance reference limits, there are certain age and gender subcategories for which the LLN is below the lower limit of the Grade 1 category as defined above, thus preventing a shift from normal to Grade 1. In order to use a set of LLNs that allow for such shifts, the LLN for the hematology parameters above will be defined by setting the LLN values using equal increments above the lower limit for Grade 1 as are defined for the incremental ranges used for Grades 2-4. This allows for equal separation of categories. Additionally, these limits are generally consistent with various commonly accepted reference limits. The only exception to this approach will be for platelets, for which the LLN will be defined as $150x10^9$/L. This value is consistent with the LLNs of multiple other references ranges for platelets. Patients with neutropenia or thrombocytopenia with any grades will be categorized into 4 categories related to recovery: Recovered, Recovered with Reoccurrence, Not Recovered, and Last Visit Only. The number and percentages of patients with neutropenia and thrombocytopenia will be analyzed by grade and by recovery category.

Summaries for elevations in hepatic laboratory tests from maximum baseline category to abnormal maximum post-baseline category as well as shifts from maximum baseline to maximum post-baseline category for hepatic laboratory tests will be provided.

6.12.4.1. Leukocytes (White Blood Count [WBC]) and Platelets

Change from baseline to last observation for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils will be summarized for patients who have both baseline and at least one post-baseline result for each treatment period. Unless otherwise specified, neutrophils will be summarized for segmented and absolute neutrophils. Baseline will be the last nonmissing observation in the baseline period. The last nonmissing observation in

each treatment period will be analyzed. Original-scale data will be analyzed. Unscheduled visits and repeat measurements will be excluded. Analyses will be provided in both SI and conventional units (when different).

Neutrophils will include both segmented neutrophils and absolute neutrophils (derived by adding segmented neutrophils and band neutrophil). The segmented neutrophils and absolute neutrophils will be summarized using the same categories.

Shift table will be produced showing the number and percentage of patients shifting from baseline to a minimum postbaseline result in each relevant category by treatment groups in the OLT, OLE, and LTE Periods:

The following LLNs will be defined for the analyses:

- Leukocytes: LLN=4.0 $\times 10^9$/L
- Neutrophils: LLN=2.0$\times 10^9$/L
- Lymphocytes: LLN=1.1$\times 10^9$/L
- Platelets: LLN=150$\times 10^9$/L

Such shift tables will be produced using the following categories:

- Neutrophils: $\geq$1 $\times$ LLN (Normal), < LLN to $\geq$1.5 $\times$ 10^9/L (Grade 1), <1.5 $\times$ 10^9/L to $\geq$1.0 $\times$ 10^9/L (Grade 2), <1.0 $\times$ 10^9/L to $\geq$0.5 $\times$ 10^9/L (Grade 3), and <0.5 $\times$ 10^9/L (Grade 4).
- Leukocytes; $\geq$1 $\times$ LLN (Normal), < LLN to $\geq$3.0 $\times$ 10^9/L (Grade 1), <3.0 $\times$ 10^9/L to $\geq$2.0 $\times$ 10^9/L (Grade 2), <2.0 $\times$ 10^9/L to $\geq$1.0 $\times$ 10^9/L (Grade 3), and <1.0 $\times$ 10^9/L (Grade 4).
- Platelets: >1 $\times$ LLN (Normal), < LLN to $\geq$75.0 $\times$ 10^9/L (Grade 1), <75.0 $\times$ 10^9/L to $\geq$50.0 $\times$ 10^9/L (Grade 2), <50.0 $\times$ 10^9/L to $\geq$25.0 $\times$ 10^9/L (Grade 3), and <25.0 $\times$ 10^9/L (Grade 4).
- Lymphocytes: $\geq$1 $\times$ LLN (Normal), < LLN to $\geq$0.8 $\times$ 10^9/L (Grade 1), <0.8 $\times$ 10^9/L to $\geq$0.5 $\times$ 10^9/L (Grade 2), <0.5 $\times$ 10^9/L to $\geq$0.2 $\times$ 10^9/L (Grade 3), and <0.2 $\times$ 10^9/L (Grade 4).

In addition, for the above parameters (neutrophils, leukocytes, platelets, and lymphocytes), the number and percentage of patients with minimum post-baseline results will be presented overall and by treatment within the following group using the categories as defined above:

- Decreased: post-baseline category < baseline category
- Increased: post-baseline category > baseline category
- Same: post-baseline category = baseline category

6.12.4.2. Neutrophil Follow-up

The following analyses will be conducted on the Neutrophil Follow-up Population defined as patients who have an absolute neutrophil count <1500 cells/µL (SI units: <1.5 $\times$ 10^9/L) at the last scheduled visit or early termination visit prior to entering the follow-up period and less than the

patient's baseline neutrophil count (that is, prior to first injection at Week 0). These patients are monitored during the follow-up period until neutrophil recovery.

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/µL (SI units: ≥1.5 × 10^9/L) or greater than or equal to a patient's minimum neutrophil count for baseline (defined as the minimum assessment recorded on or prior to the date of first study drug injection at Week 0 [Visit 2]).

If a patient's neutrophil count has not recovered, within 12 weeks after entering the follow-up period (Visit 802), the patient will return for Visit 803 (12 weeks after Visit 802). Additional visits may be required for appropriate patient management depending upon the degree of neutropenia. If at Visit 802, a patient has met the criteria for neutrophil recovery, the patient's participation in the study will be considered complete, unless the investigator deems additional follow-up may be necessary.

The number and percentage of patients achieving neutrophil clinical recovery will be presented by dosing regimen and week interval for Neutrophil Follow-Up Population for PTFU Period. The number and percentage of patients with an absolute neutrophil cell count that is at least 25%, 50%, 75%, or 100% of the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

6.12.5. Vital Signs and Other Physical Findings

Vital Signs evaluations will be summarized and analyzed for the following periods:

- OLT Period (Safety Population)
- OLE Period (OLE Period Population and OLE Switcher Population), and
- LTE Period (LTE Safety Population).

A listing of vital signs and other physical characteristics will be provided.

The planned summaries for vital signs (systolic blood pressure [BP], diastolic BP, pulse, weight, body mass index [BMI], temperature) are provided in Table RHCG.6.13 and are described more fully in compound-level safety standards and in the vitals-related Pharmaceutical Users Software Exchange (PhUSE) white papers (Analyses and Displays Associated with Measures of Central Tendency – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents [PhUSE 2013] and Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Summary Documents [PhUSE 2015]).

Table RHCG.6.13. Summary Tables/Figures Related to Vital Signs

Analysis
Box plot for observed (spotfire)
Box plot for change from baseline (spotfire)
Tables with percentages of patients who shift from normal/high to low (i.e., treatment-emergent low) and percentages of patients who shift from normal/low to high (i.e., treatment-emergent high). The limits are defined in the compound-level safety standards and are based on literature.

For vital signs and physical characteristics, original-scale data will be analyzed. Mean changes from baseline and as incidence of abnormal values will be summarized.

The number and percentage of patients with treatment-emergent high blood pressure and pulse at any time for the populations mentioned in this section will be summarized. For treatment-emergent high blood pressure:

- A treatment-emergent prehypertension is defined as a change from a value less than the low limit of prehypertension at all baseline visits to a value that is within the limits of prehypertension at any time postbaseline during the treatment period.
- A treatment-emergent stage 1 hypertension is defined as a change from a value less than the low limit of stage 1 hypertension at all baseline visits to a value that is within the limits of stage 1 hypertension at any time postbaseline during the treatment period.
- A treatment-emergent stage 2 hypertension is defined as a change from a value less than the low limit of stage 2 hypertension at all baseline visits to a value that is greater than or equal to the limits of stage 2 hypertension at any time postbaseline during the treatment period.

For treatment-emergent high or low value in pulse rate:

- A treatment-emergent high value is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline during the treatment period.
- Treatment-emergent low value is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline during the treatment period.

Table RHCG.6.14 provides the blood pressure levels for children by age and gender and Table RHCG.6.15 provides the criteria for abnormal treatment-emergent pulse rate in children and adolescents by age and gender.

Table RHCG.6.14. Blood Pressure Levels for Children by Age and Gender (Median Height)

		Boy		Girl	
Age (Year)	Hypertension Stage	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)
6	Prehypertension	≥110 and <114	≥70 and <74	≥108 and <111	≥70 and <74
	Stage 1	≥114 and <126	≥74 and <87	≥111 and <124	≥74 and <86
	Stage 2	≥126	≥87	≥124	≥86
7	Prehypertension	≥111 and <115	≥72 and <76	≥109 and <113	≥71 and <75
	Stage 1	≥115 and <127	≥76 and <89	≥113 and <125	≥75 and <87
	Stage 2	≥127	≥89	≥125	≥87
8	Prehypertension	≥112 and <116	≥73 and <78	≥111 and <115	≥72 and <76
	Stage 1	≥116 and <128	≥78 and <91	≥115 and <127	≥76 and <88
	Stage 2	≥128	≥91	≥127	≥88
9	Prehypertension	≥114 and <118	≥75 and <79	≥113 and <117	≥73 and <77
	Stage 1	≥118 and <130	≥79 and <92	≥117 and <129	≥77 and <89
	Stage 2	≥130	≥92	≥129	≥89
10	Prehypertension	≥115 and <119	≥75 and <80	≥115 and <119	≥74 and <78
	Stage 1	≥119 and <132	≥80 and <93	≥119 and <131	≥78 and <91
	Stage 2	≥132	≥93	≥131	≥91
11	Prehypertension	≥117 and <121	≥76 and <80	≥117 and <121	≥75 and <79
	Stage 1	≥121 and <134	≥80 and <93	≥121 and <133	≥79 and <92
	Stage 2	≥134	≥93	≥133	≥92
12	Prehypertension	≥120 and <123	≥76 and <81	≥119 and <123	≥76 and <80
	Stage 1	≥123 and <136	≥81 and <94	≥123 and <135	≥80 and <93
	Stage 2	≥136	≥94	≥135	≥93
13	Prehypertension	≥120 and <126	≥77 and <81	≥120 and <124	≥77 and <81
	Stage 1	≥126 and <138	≥81 and <94	≥124 and <137	≥81 and <94
	Stage 2	≥138	≥94	≥137	≥94
14	Prehypertension	≥120 and <128	≥78 and <82	≥120 and <126	≥78 and <82
	Stage 1	≥128 and <141	≥82 and <95	≥126 and <138	≥82 and <95
	Stage 2	≥141	≥95	≥138	≥95
15	Prehypertension	≥120 and <131	≥79 and <83	≥120 and <127	≥79 and <83
	Stage 1	≥131 and <143	≥83 and <96	≥127 and <139	≥83 and <96
	Stage 2	≥143	≥96	≥139	≥96
16	Prehypertension	≥120 and <134	≥80 and <84	≥120 and <128	≥80 and <84
	Stage 1	≥134 and <146	≥84 and <97	≥128 and <140	≥84 and <96
	Stage 2	≥146	≥97	≥140	≥96
17	Prehypertension	≥120 and <136	≥80 and <87	≥120 and <129	≥80 and <84
	Stage 1	≥136 and <148	≥87 and <99	≥129 and <141	≥84 and <96

		Boy		Girl	
Age (Year)	Hypertension Stage	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)
	Stage 2	≥148	≥99	≥141	≥96

Abbreviations: BP = blood pressure; mmHg = millimeters of mercury. Source: [NIH 2005] The Fourth report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Revised May 2005

Table RHCG.6.15. Categorical Criteria for Abnormal Treatment-Emergent Pulse Rate in Children and Adolescents Requiring Evaluation and Potential Intervention by a Health Care Professional Pressure Levels for Children by Age and Gender (Median Height)

Parameter	Age (year)	Low	High
Pulse (bpm)[a]	6 - 9	<60	>150
	10 - 11	<60	>140
	12 - 14	<50	>120
	15 - 17	<50	>100

Abbreviations: bpm = beats per minute. Source: See the Selected Reference Limits for Pulse/Heart Rate, Arterial Blood Pressure [Including Orthostasis], and Electrocardiogram Numerical Parameters for Use in Analyses of Phase 2-4 Clinical Trials guidance, located on the CV SAC Collaboration site.

[a] Baseline abnormal values are defined by the value presented.

6.12.6. Growth Monitoring

Weight, height, and BMI data will be merged to the Centers for Disease Control and Prevention (CDC) standard growth data (released in 2000) by age and gender in order to compare patients' growth with the standard. Z-score and standardized percentile of weight, height, and BMI at each visit will be calculated and compared to the 2000 CDC growth charts (CDC 2023).

The z-score and percentile calculations are based on algorithms and data provided by the National Center for Health Statistics. The details are provided in the CDC website (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm [CDC 2019]).

- The following summaries will be provided in each treatment period with the corresponding safety population: baseline, mean change of actual measure, z-score and standardized percentile of weight, height, and BMI will be summarized.
- Patients' mean weight, height, and BMI standardized percentile will be plotted versus investigational product exposure time.

Height and weight will be measured at baseline and postbaseline for the assessment of physical growth according to the Schedule of Activities in the protocol. Occipital frontal circumference will be collected in patients up to 3 years of age. Height, weight and occipital frontal circumference changes in pediatric patients (both at an individual and group level) will be reviewed by the data monitoring committee (DMC).

6.12.7. Children's Depression Inventory – 2

The CDI-2 is a comprehensive multi-rater assessment of depressive symptoms in youth aged 7 to 17 years. When results from the CDI-2 are combined with other sources of verified information, the CDI-2 can aid in the early identification of depressive symptoms, the diagnosis of depression and related disorders, as well as the monitoring of treatment effectiveness (Kovacs 2010).

The CDI-2 quantifies depressive symptomatology using reports from children/adolescents (full-length and short), teachers, and parents (or alternative caregivers). It can be administered and scored using paper-and-pencil format with Multi-Health System's (MHS) QuikScore™ forms, or online through the MHS Online Assessment Center.

The CDI-2: Self-Report Short version (CDI-2:SR[S]) is an efficient screening measure that contains 12 items and takes about half the time as the full-length to administer (5–10 minutes).

Scoring the CDI-2:SR(S): Each of the 12 items is scored from 0-2.

A change from baseline summary analysis will be presented for the Safety Population, the OLE Period Population, and the LTE Safety Population. A shift table will be produced showing the number and percentage of patients shifting from baseline score to a maximum postbaseline score in categories of <6 and ≥ 6 for the Safety Population, the OLE Period Population, and the LTE Safety Population.

6.12.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an assessment tool that evaluates suicidal ideation and behavior. Information on the C-SSRS scale can be found through the following link: http://cssrs.columbia.edu/wp-content/uploads/C-SSRS_Pediatric-SLC_11.14.16.pdf (RFMH 2008).

Specifically, the following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

- **Suicidal ideation:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- **Suicidal behavior:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
- **Suicidal ideation or behavior:** A "yes" answer at any time during treatment to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The Self-Harm Supplement Form is a 1-question form that is completed, at any visit, including baseline visit, that asks for the number of suicidal behaviors, possible suicidal behaviors, or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-up Form) which collects supplemental information on the self-injurious behavior is to be completed.

Given that few or no suicidal ideation or behaviors are anticipated, C-SSRS will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient's answers are all "no" for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point, then all his/her ideation and behavior will be displayed, even if not positive. Note that missing data should not been imputed.

The Self-Harm data will be listed by patient and visit if number of events on Self-Harm Supplement Form is not zero in the eCRF Self Harm Questionnaire Supplement.

6.12.9. Tanner Stage Scale

The Tanner Stage Scales are a series of line drawings that are designed to aid the investigator in appropriately assessing the sexual maturity of the subject. Data gathered will be assessed to determine that no pubertal disruption has occurred during the study. Although the line drawings were originally intended for child self-assessment, evidence suggests that pubertal assessment by the child or the parents/legal guardian is not a reliable measure of exact pubertal staging, and should be augmented by a physical examination (Rasmussen et al. 2015). The drawings will be used by the dermatologist investigator as an aid.

For each of the staging assessments (breasts in females, genitals in males, and groin/pubic for both, the Tanner Stage Score ranges from 1 to 5.

Shift table will be produced showing the number and percentage of patients shifting from the stage score at baseline to the highest postbaseline stage score by gender for each scale item for the Safety Population, OLE Period Population, and the LTE Safety Population.

A by-patient listing of Tanner stage data will be provided.

6.12.10. Uveitis

At each study visit, the investigator will ask the patient/caregiver whether they developed uveitis since the last visit and evaluate the patient for any symptoms of acute anterior uveitis since the last visit as specified in the protocol Schedule of Activities. If the patient has no prior

ophthalmologist-diagnosed uveitis and develops eye pain or discomfort, eye redness, blurring of vision, or any other symptoms suggestive of acute anterior uveitis, the patient must be evaluated by an ophthalmologist. It is expected that all children with JIA will be on screening and regular evaluation with ophthalmologists based on local/regional/national guidelines.

Uveitis data will be captured using uveitis CRF. Percent of patients reporting uveitis will be summarized at each scheduled visit for patients with or without prior uveitis, separately. The analysis periods and populations are specified in Table RHCG.6.12. No imputation will be used. A by-patient listing of uveitis data will be provided as well.

6.12.11. Special Safety Topics

Safety information on special topics including AESI will be presented by treatment group and by study period. Table RHCG.6.16 provides the definitions/derivations and analyses methods (including analyses, summaries and by-patient listings) of special safety topics including AESIs.

Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA PT listing. Preferred terms within an SMQ will be classified as broad and narrow. In the Lilly-defined MedDRA PT listings, Lilly has provided the broad and narrow classification. The Lilly-defined broad terms are for a more sensitive search of potential events of interest and the Lilly-defined narrow terms are for a more specific search. Therefore, the summaries will include the classifications of broad term (same as pooling narrow and broad terms together) and narrow term. In the event that the listing of terms or analysis changes for a special safety topic, it will be documented in the program safety analysis plan (PSAP) which will supersede this document; it will not warrant an amendment to the individual study SAP.

Table RHCG.6.16. Definitions and Analyses of Special Safety Topics

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Hepatic	Hepatic AE analysis will include events that are potentially drug-related hepatic disorders by using the MedDRA PTs contained in any of the following SMQs: • Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009) • Broad and narrow terms in the Hepatitis, non-infectious (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015)	**OLT Period (Safety Population):** TEAE by PT within SMQ or sub-SMQ **OLE Period (OLE Period Population):** TEAE by PT within SMQ or sub-SMQ **LTE Period (LTE Safety Population):** TEAE by PT within SMQ or sub-SMQ **Listing (Safety Population):** TEAE
	The number and percentages of patients with the following elevations in hepatic laboratory tests at any time will be summarized between treatment groups: • The number and percentages of patients with an ALT or AST measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing lab ULN during the treatment period will be summarized for all patients with a post-baseline value. o The analysis of 3 × ULN will contain four subsets: patients whose non-missing maximum baseline value is ≤1 × ULN, patients whose maximum baseline is >1 × ULN but <3 × ULN, patients whose maximum baseline value is ≥3 × ULN, and patients whose baseline values are missing. o The analysis of 5 × ULN will contain five subsets: patients whose non-missing maximum baseline value is ≤ to 1 × ULN, patients whose maximum baseline is >1 × ULN but <3 × ULN, patients whose maximum baseline is ≥3 × ULN but <5 × ULN, patients whose maximum baseline value is ≥5 × ULN, and patients whose baseline values are missing. o The analysis of 10 × ULN will contain six subsets: patients whose non-missing maximum baseline value is ≤1 × ULN, patients whose maximum baseline is >1 × ULN but <3 × ULN, patients whose maximum baseline is ≥3 × ULN but <5 × ULN, patients whose maximum baseline is ≥5 × ULN but <10 × ULN, patients whose maximum baseline value is ≥10 × ULN, and patients whose baseline values are missing.	**Listing (Safety Population):** Elevations in hepatic laboratory tests

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	○ The analysis of 20 × ULN will contain seven subsets: patients whose non-missing maximum baseline value is ≤1 × ULN, patients whose maximum baseline is >1 × ULN but <3 × ULN, patients whose maximum baseline is ≥3 × ULN but <5 × ULN, patients whose maximum baseline is ≥5 × ULN but <10 × ULN, patients whose maximum baseline is ≥10 × ULN but <20 × ULN, patients whose maximum baseline value is ≥20 × ULN, and patients whose baseline values are missing. • The number and percentages of patients with a total bilirubin measurement ≥1.5×, and ≥2 × the Performing lab ULN during the treatment period will be summarized for all patients with a post-baseline value. ○ The analysis of 1.5 × ULN will contain four subsets: patients whose non-missing maximum baseline value is ≤1 × ULN, patients whose maximum baseline is >1 × ULN but <1.5 × ULN, patients whose maximum baseline value is ≥1.5 × ULN, and patients whose baseline values are missing. ○ The analysis of 2 × ULN will contain five subsets: patients whose non-missing maximum baseline value is ≤1 × ULN, patients whose maximum baseline is >1 × ULN but <1.5 × ULN, patients whose maximum baseline is ≥1.5 × ULN but <2 × ULN, patients whose maximum baseline value is ≥2 × ULN, and patients whose baseline values are missing. • The number and percentages of patients with an ALP measurement >1.5× the Performing lab ULN during the treatment period will be summarized for all patients with a post-baseline value, and divided into four subsets: patients whose non-missing maximum baseline value is ≤1 × ULN, patients whose maximum baseline is >1 × ULN but ≤1.5 × ULN, patients whose maximum baseline value is >1.5 × ULN, and patients whose baseline values are missing. • The number and percentages of patients meeting the following elevated hepatic criteria: maximum ALT ≥3 × ULN and maximum Total Bilirubin ≥2 × ULN during the treatment period will be summarized.	
	Shift tables (or scatterplots) will be produced showing the number and percentage of patients with a maximum post-baseline result in each of the categories below, by treatment group and baseline result. Note that for these tables, a single maximum baseline time point will be used. Maximum baseline will be the maximum non-missing observation in the baseline period. The maximum post-baseline value will be the maximum non-missing value from within each	**Listing (Safety Population):** Shift in hepatic laboratory tests

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	treatment period. Scheduled visits, unscheduled visits, and repeat measurements will be included. Such shift tables will be produced for the following parameters and categories: • ALT; ≤1 × ULN, >1 to <3 × ULN, ≥3 to <5 × ULN, ≥5 to <10 × ULN, ≥10 to <20 × ULN, and ≥20 × ULN. • AST; ≤1 × ULN, >1 to <3 × ULN, ≥3 to <5 × ULN, ≥5 to <10 × ULN, ≥10× to <20 × ULN and ≥20 × ULN. • Total bilirubin; ≤1 × ULN, >1 to <1.5 × ULN, ≥1.5 to <2.0 × ULN, ≥2.0 × ULN. • ALP; ≤1 × ULN, >1 to ≤1.5 × ULN, >1.5 × ULN. In addition, the number and percentage of patients with maximum post-baseline results will be presented overall and by treatment group for each treatment period within the following classes: • Decreased; post-baseline category < baseline category. • Increased; post-baseline category > baseline category. • Same; post-baseline category = baseline category.	
	Elevated hepatic criteria: maximum ALT ≥3 × ULN, maximum total bilirubin ≥2 × ULN. Listing of patients who meet any of the following criteria: • Elevated hepatic criteria: defined as maximum ALT ≥3 × ULN, maximum total bilirubin ≥2 × ULN • An ALT or AST ≥3 × ULN • An ALP ≥1.5 × ULN • A total bilirubin ≥2 × ULN The listing will include: patient demographics, concomitant medications, ALT/AST/ALP/total bilirubin/GGT by visit, treatment start and stop dates, and reason for treatment discontinuation	**Listing (Safety Population):** Elevations in hepatic criteria
	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot: To further evaluate potential hepatotoxicity, an eDISH plot will be created. Each patient with at least 1 post-baseline ALT and total bilirubin contributes 1 point to the plot. The maximum ALT measurement and the maximum total bilirubin measurement after the first injection will be included. Patients will be classified into 2 groups: never on ixekizumab or ever on ixekizumab. The measurements do not need to be taken at the same blood draw. There will only be 1 eDISH plot for each indication, regardless of treatment periods.	**Figure (Safety Population):** eDISH plot (display in Spotfire) **Figure (OLE Period Population):** eDISH plot (display in Spotfire) **Figure (LTE Safety Population):** eDISH plot (display in Spotfire)
Cytopenias	Cytopenias will be defined using the PTs from the following 2 sub SMQs of the Haematopoietic cytopenias SMQ (20000027) as defined in MedDRA Version: • Broad and narrow terms in the Haematopoietic leukopenia (20000030)	**OLT Period (Safety Population)**: TEAE by PT within sub-SMQ

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031) The number and percentage of patients with TEAEs will be summarized by treatment group using MedDRA PT nested within SMQ. Two summaries will be created: (1) pooling narrow and broad terms together, and (2) narrow terms only. Events will be ordered by decreasing frequency in ixekizumab group (or combined ixekizumab group in the event of multiple cohorts/doses) nested within SMQ.	**OLE Period (OLE Period Population)**: TEAE by PT within sub-SMQ **LTE Period (LTE Safety Population):** TEAE by PT within SMQ or sub-SMQ **Listing (Safety Population):** TEAE
Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections, and infections resulting in anti-infective medication administration (i.e., antibacterial, antiviral, antifungals, antiparasitic treatment.) as defined in Appendix 5. The relationship between TEAEs-infections and other clinical, laboratory, and hematology parameters will be examined using Spotfire tool.	**OLT Period (Safety Population)**: TEAE by PT SAE by PT DCAE by PT **OLE Period (OLE Period Population)**: TEAE by PT SAE by PT DCAE by PT **LTE Period (LTE Safety Population):** TEAE by PT SAE by PT DCAE by PT **Listing (Safety Population):** TEAE
	The opportunistic infections (OI) are defined in Appendix 6. This list contain PTs as contained within Categories (narrow or broad) from the infections and infestations SOC and from the investigations SOC which can assist in identifying potential OIs. The narrow terms are considered opportunistic infections unless medical review determines that the reported term is not consistent with the patient's clinical history/presentation/course. Medical review of broad terms is needed for final determination of patients meeting the program definition of OIs. The number and percentage of patients with TEAEs that represent potential OIs will be summarized by treatment group using MedDRA PT nested within categories. Events will be ordered by decreasing frequency in the ixekizumab group (or combined ixekizumab group in the event of	**OLT Period (Safety Population)**: TEAE of OIs by PT **OLE Period (OLE Period Population)**: TEAE of OIs by PT **LTE Period (LTE Safety Population):** TEAE of OIs by PT

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	multiple cohorts/doses) nested within categories. The relationship between TEAEs-infections and other clinical, laboratory, and hematology parameters will be examined using Spotfire tool.	**Listing (Safety Population):** TEAE of OIs
	The duration of each common TEAE PT of Infections and narrow terms for Opportunistic infections will be evaluated by treatment group using Spotfire. Duration is defined as follows: *Duration of treatment-emergent AE-Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7.* Patients who do not have the PT will not be included in the analysis. If the TEAE has not ended by the date of completion from the study, or date of early discontinuation, it will be censored as of that date. If a patient has multiple episodes of the same TEAE, the episode with the greatest severity will be used for the duration of event calculation. If a patient has multiple episodes of the same TEAE with the same severity, the episode with the longest duration will be used for the duration of event calculation.	**OLT Period (Safety Population)**: Duration of Common TEAE – Infections (additional display in Spotfire) **OLE Period (OLE Period Population)**: Duration of Common TEAE – Infections (additional display in Spotfire) **LTE Period (LTE Safety Population):** Duration of Common TEAE – Infections (additional display in Spotfire)
Allergic Reactions/Hypersensitivities	Allergic reactions/hypersensitivity events will be categorized as either anaphylaxis or non-anaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. Medical reviews are needed for final determination of patients with allergic reactions/hypersensitivities. **Allergic/Hypersensitivity Events, Anaphylaxis.** Anaphylaxis has been broadly defined as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson et al. 2006). Identification of cases of potential anaphylaxis from the clinical trial data involves two screening criteria, one designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021), and the second to identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 1 for anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ: • Anaphylactic reaction • Anaphylactic shock • Anaphylactoid reaction • Anaphylactoid shock • Kounis Syndrome	**OLT Period (Safety Population):** TEAE by PT within Category SAE by PT within Category AE leading to discontinuation of study drug within Category **OLE Period (OLE Period Population):** TEAE by PT within Category, SAE by PT within Category AE leading to discontinuation of study drug within Category **LTE Period (LTE Safety Population):** TEAE by PT within Category SAE by PT within Category AE leading to discontinuation of study drug within Category

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• Type 1 hypersensitivity Criterion 2 for anaphylaxis requires having TEAEs from 2 or more of 4 categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident; based on recording of events on eCRFs. All qualifying events must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: • Category A: Involvement of the skin-mucosal tissue • Category B: Respiratory compromise • Category C: Reduced blood pressure or associated symptoms • Category D: Persistent gastrointestinal symptoms The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in Appendix 7. Summaries of Criterion 2 anaphylactic TEAEs will be provided by the specific combination of categories as follows: • AB: events based on meeting Category A and Category B (but no other category); • AC: events based on meeting Category A and Category C (but no other category); • AD: events based on meeting Category A and Category D (but no other category); • BC: events based on meeting Category B and Category C (but no other category); • BD: events based on meeting Category B and Category D (but no other category); • CD: events based on meeting Category C and Category D (but no other category); • ABC: events based on meeting Category A, Category B and Category C (but no other category); • ABD: events based on meeting Category A, Category B and Category D (but no other category); • ACD: events based on meeting Category A, Category C and Category D (but no other category); • BCD: events based on meeting Category B, Category C and Category D (but no other category); • ABCD: events based on meeting each of the 4 Criterion 2 categories. Summaries of treatment-emergent anaphylactic AEs will be provided for patients meeting each of the 2 criteria and for patients who meet either criteria overall. Separate summaries will be provided for TEAEs by maximum severity, SAEs, and AEs resulting in study drug discontinuation. Severity of treatment-emergent Criterion 2 anaphylactic AEs will be based on the maximum severity of the specific events met by the patient. Maximum severity of an (overall) treatment-emergent anaphylactic AE will be based on the maximum severity within Criterion 1 and/or Criterion 2.	**Listing (Safety Population):** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	Allergic Reactions/Hypersensitivity Events, Non-Anaphylaxis: TEAEs of allergic reaction/hypersensitivity categorized as non-anaphylaxis events are defined by the narrow terms within Hypersensitivity SMQ (20000214) excluding the PTs noted in Appendix 8 and excluding the anaphylactic events as defined above.	
Injection Site Reactions	Injection site reactions will be defined using the PTs from the MedDRA High Level Term Injection Site Reactions as defined by MedDRA excluding the following 10 PTs (the excluded PTs were determined by the most current MedDRA Version): 1) Embolia cutis medicamentosa 2) Injection site joint discomfort 3) Injection site joint effusion 4) Injection site joint redness 5) Injection site joint infection 6) Injection site joint inflammation 7) Injection site joint movement impairment 8) Injection site joint pain 9) Injection site joint swelling 10) Injection site joint warmth The *Injection Site Reaction* eCRF page captures the injection site reactions identified by the investigator. Redness (Scored 0-4) [0] Subject's normal skin color, no increased redness [1] Noticeable, but very mild redness [2] Clearly red [3] Bright red [4] Dark with some scar formation Swelling (Scored 0-4 after running a finger over injected area) [0] No bump [1] Barely noticeable [2] Clear bump but very thin [3] Clear bump 1 mm thick	**OLT Period (Safety Population)**: TEAE by PT within HLT, SAE by PT within HLT (additional display in Spotfire), AE leading to treatment discontinuation by PT within HLT (additional display in Spotfire) **OLE Period (OLE Period Population):** TEAE by PT within HLT, SAE by PT within HLT (additional display in Spotfire), AE leading to treatment discontinuation by PT within HLT (additional display in Spotfire) **LTE Period (LTE Safety Population):** TEAE by PT within HLT, SAE by PT within HLT (additional display in Spotfire), AE leading to treatment discontinuation by PT within HLT (additional display in Spotfire) **Listing (Safety Population):** TEAE (additional display in Spotfire)

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	[4] Clear bump 2 mm thick or more Pain (including burning) (Scored 0-3) [0] None [1] Mild [2] Moderate [3] Severe	**OLT Period (Safety Population)**: TEAE by maximum severity TEAE by maximum redness category TEAE by maximum swelling category TEAE by maximum pain category **OLE Period (OLE Period Population):** TEAE by maximum severity TEAE by maximum redness category TEAE by maximum swelling category TEAE by maximum pain category **LTE Period (LTE Safety Population):** TEAE by maximum severity TEAE by maximum redness category TEAE by maximum swelling category TEAE by maximum pain category
Malignancies	Malignancies will be defined using PTs from the Malignant or unspecified tumors SMQ as defined in MedDRA (SMQ: 20000091, which includes the sub-SMQs: • 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours] • 20000195 [Tumours of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy] The number and percentage of patients with TEAEs will be summarized by treatment group using MedDRA PT nested within the following categories: • Non-Melanoma Skin Cancer (NMSC) o Basal Cell Carcinoma, ▪ PTs include: Basal cell carcinoma, Basosquamous carcinoma, and Basosquamous carcinoma of skin	**OLT Period (Safety Population):** TEAE by PT within Category **OLE Period (OLE Period Population):** TEAE by PT within Category **LTE Period (LTE Safety Population):** TEAE by maximum severity TEAE by maximum redness category TEAE by maximum swelling category TEAE by maximum pain category

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	○ Squamous Cell Carcinoma: ▪ PT: Squamous cell carcinoma of skin, Bowen's disease, Lip squamous cell carcinoma, Skin squamous cell carcinoma metastatic, and Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	**Listing (Safety Population):** TEAE
Depression and Suicide/self-injury	Depression and suicide/self-injury will be defined using the PTs from the Depression and Suicide/self-injury SMQ as defined in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excl suicide and self-injury)]).	**OLT Period (Safety Population):** TEAE by PT within SMQ and sub-SMQ **OLE Period (OLE Period Population):** TEAE by PT within SMQ and sub-SMQ **LTE Period (LTE Safety Population):** TEAE by PT within SMQ or sub-SMQ **Listing (Safety Population):** TEAE
Inflammatory Bowel Disease	Inflammatory Bowel Disease (IBD) will be externally adjudicated by the Central Events Committee (CEC). The CEC will adjudicate investigator-reported events selected for adjudication and render an assessment as to whether the event represents a confirmed event (meeting the event definition with all necessary documentation). If an adjudicated result is "definitive" or "probable" event then the event is considered positively adjudicated. All events positively adjudicated will be used for the analysis of IBD. The categories and subcategories of reported events used for the adjudication will can be found below. Inflammatory Bowel Disease (IBD) will be identified using the following subcategory and MedDRA PTs: The narrow terms are considered IBD. Medical reviews of broad terms are needed for final determination of patients with IBD. IBD (Narrow terms) • Inflammatory Bowel Disease: Inflammatory bowel disease • Crohn's Disease: Crohn's disease • Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative Non-Specific Terms: The PTs in this category are listed in Appendix 9.	**OLT Period (Safety Population):** IBD (included in AE overview) **OLE Period (OLE Period Population):** IBD confirmed by adjudication (included in AE overview) **LTE Period (LTE Safety Population):** IBD (included in AE overview) **Listing (Safety Population):** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Interstitial Lung Disease	Interstitial Lung Disease will be defined using the PTs: • Narrow terms in the Interstitial lung disease SMQ (20000042); • The following 6 PTs from the Eosinophilic Pneumonia SMQ (20000157) will also be included in the analyses: 1) Angiolymphoid hyperplasia with eosinophilia (Narrow), 2) Eosinophilic bronchitis (Narrow), 3) Hypereosinophilic syndrome (Narrow), 4) Loeffler's syndrome (Narrow), 5) Pulmonary eosinophilia (Narrow), 6) Pulmonary vasculitis (Narrow).	**OLT Period (Safety Population):** TEAE by PT within Category **OLE Period (OLE Period Population):** TEAE by PT within Category **LTE Period (LTE Safety Population):** TEAE by PT within Category **Listing (Safety Population):** TEAE

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DCAE = discontinuation due to adverse event; eCRF = electronic case report form; HLT = high-level term; LTE = long-term extension; MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension; OLT = open-label treatment; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = System Organ Class; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

6.12.12. Immunogenicity

6.12.12.1. Definitions and Terms

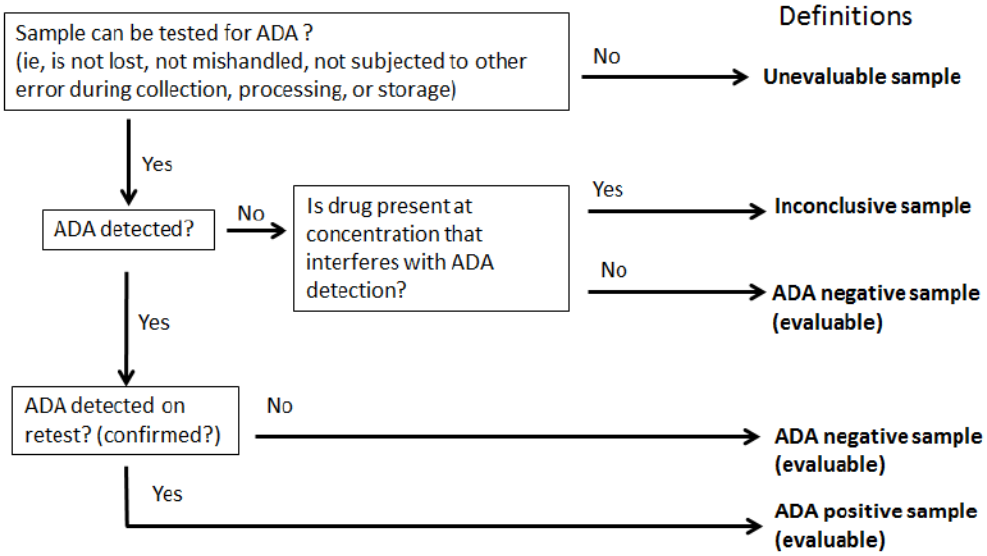
The following sample- and patient-related definitions and parameters will be used to describe the immunogenicity data.

6.12.12.1.1. Sample Category Definitions

Samples are classified into the following categories:

- **Unevaluable sample:** Sample could not be tested for ADA due to sample loss, mishandling, or errors in collection, processing, storage, and so on.
- **Anti-drug antibody- (ADA-) Positive sample:** The presences of ADA is detected and confirmed. The samples are reported as positive. If the sample is positive, a titer value is reported.
- **Neutralizing anti-drug antibody- (NAb-) Positive sample:** NAb are reported as detected.
- **Anti-drug antibody (ADA-) Negative sample:** The presence of ADA is not detected and the assay drug tolerance level is not exceeded.
- **NAb-Negative sample:** The presence of NAb is not detected and the assay drug tolerance level is not exceeded.
- **NAb-Inconclusive:** A patient without a NAb positive sample and with at least 1 sample for which drug levels may interfere with the NAb assay.

Figure RHCG.6.1 illustrates the relationship of some of the above terms.



Abbreviation: ADA = anti-drug antibody.

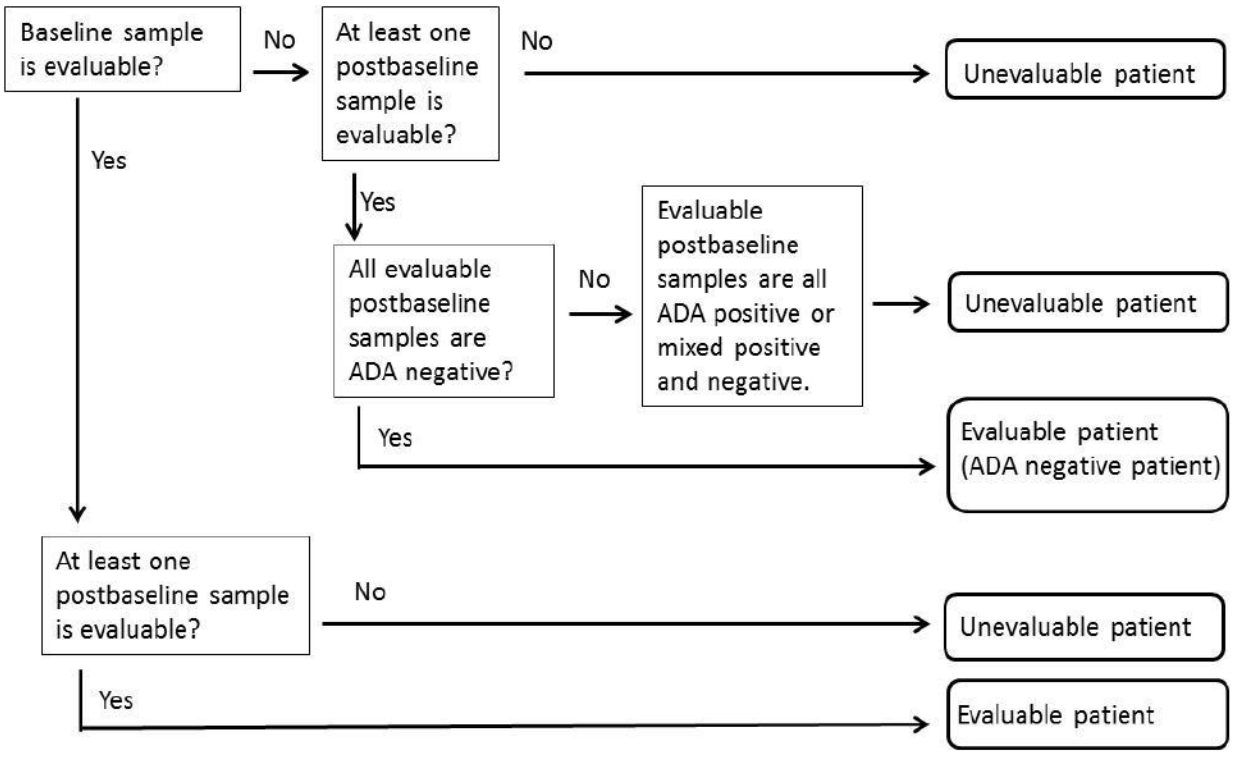
Figure RHCG.6.1. Sample definitions.

6.12.12.1.2. Patient Category Definitions

The following categories are applied to patients, based on the classification of their samples:

- **Unevaluable patient:** a) a patient with no evaluable baseline sample and/or no evaluable postbaseline samples; b) a patient with an evaluable baseline sample, but no evaluable postbaseline sample; c) a patient with no evaluable baseline sample, but whose evaluable postbaseline values are all ADA-positive or a mix of positive and negative. Note: If all postbaseline samples are negative, the patient is considered "evaluable" and will be classified as ADA-negative.
- **Evaluable patient:** a) Patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); b) patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative.

Figure RHCG.6.2 illustrates the relationship of the above terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHCG.6.2. Patient categories (evaluable/unevaluable) based on sample status at baseline and postbaseline.

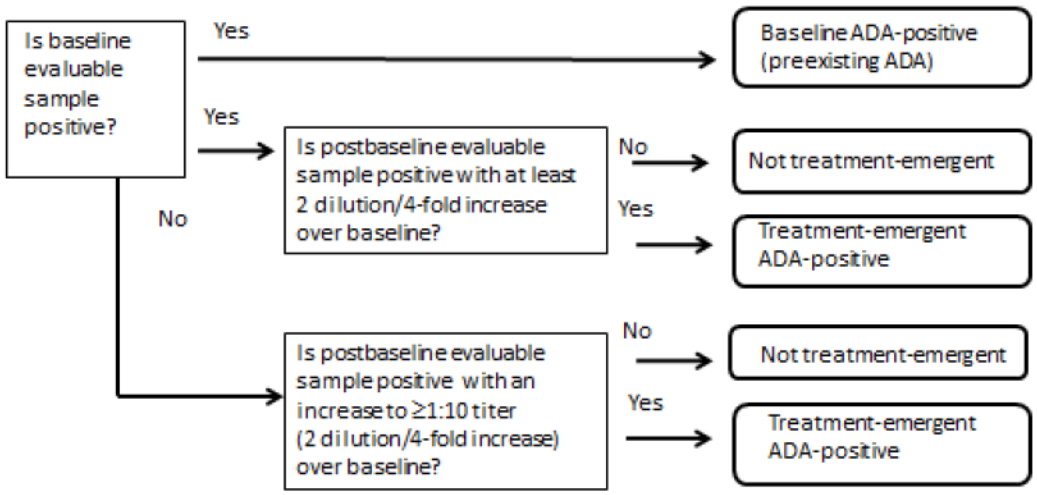
6.12.12.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment of ixekizumab. For patients originally randomized to ixekizumab in the OLT period and for patients receiving adalimumab continuously throughout the OLT and OLE periods (i.e., never received

ixekizumab treatment), baseline is Week 0. For patients who first receive ixekizumab during the OLE period, baseline is the last nonmissing observation on, or prior to, the date of the first injection of ixekizumab.

- **Baseline ADA-positive (preexisting antibody):** ADA detected in a sample collected at baseline.
- **Baseline ADA-negative:** ADA is not detected in a sample collected at baseline.
- **Treatment-emergent- (TE-) ADA positive:** a) a patient with a ≥4-fold increase over a positive baseline antibody titer; or b) for a negative baseline titer, a patient with an increase from the baseline to a level of ≥1:10.
- **TE-ADA inconclusive:** A patient without a TE-ADA positive sample and with at least 1 sample for which drug levels may interfere with the ADA assay.
- **TE-ADA negative:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.

Figure RHCG.6.3 illustrates the relationship of some of these terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHCG.6.3. Relationship of terms for clinical interpretation of assay results for evaluable patients.

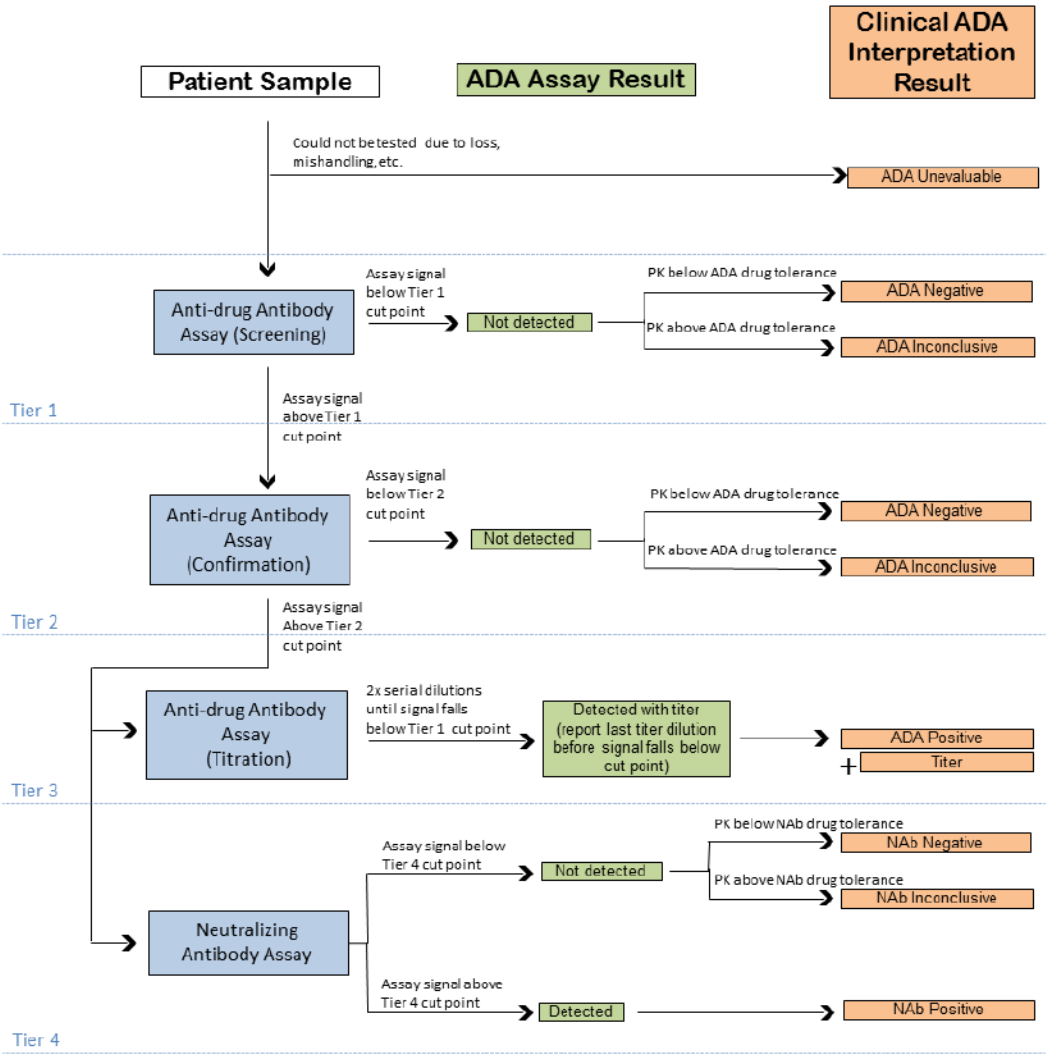
- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment and follow-up periods. This excludes unevaluable patients.

All ADA positive samples will be evaluated for NAb. Definitions for NAb patient status will be defined as follows:

- **NAb-positive:** A patient where a NAb positive result is detected for ≥1 TE-ADA positive samples.
- **NAb-inconclusive:** A patient without a NAb positive sample and with at least 1 sample for which drug levels may interfere with the NAb assay.

- **NAb-negative:** A patient who is evaluable for NAb and is not either NAb positive or NAb inconclusive.

A flow chart that reflects the connection between the analytical test results and the clinical interpretation based on the definitions is shown in Figure RHCG.6.4.



Abbreviation: ADA = anti-drug antibody.

Figure RHCG.6.4. Flow chart of ADA assessment with clinical interpretation of the various result possibilities.

6.12.12.2. Immunogenicity Analyses

Immunogenicity evaluable patients will be identified as TE-ADA positive, TE-ADA negative, or TE-ADA inconclusive, according to the definitions provided in Section 6.12.12.1.2 and further grouped into TE-ADA status groups and time-varying TE-ADA status groups:

TE-ADA Status Groups:

- TE-ADA status (positive, negative, or inconclusive)

- NAb status (positive, negative, or inconclusive) for TE-ADA positive patients
- TE-ADA titer groups for TE-ADA positive patients:
  - Low Titer: TE-ADA titer value (LOCF) <1:160
  - Moderate Titer: TE-ADA titer value (LOCF) ≥1:160 and <1:1280
  - High Titer: TE-ADA titer value (LOCF) ≥1:1280

Time-Varying TE-ADA Status Groups:

Individual ADA samples will be ascribed into 3 different dichotomous variables as explained in Table RHCG.6.17. Each variable has possible values of a "greater-TE-ADA status" or a "lesser-TE-ADA status," in the sense that the level of TE-ADA detected in the greater-TE-ADA category is higher than in the lesser-TE-ADA category.

Table RHCG.6.17. TE-ADA Status Dichotomous Variables for AE Analysis

TE-ADA Status Dichotomous Variable	Greater-TE-ADA Status	Lesser-TE-ADA Status
TE-ADA positive	TE-ADA positive	not TE-ADA positive
TE-ADA moderate-to-high	TE-ADA positive with moderate titer or high titer	not TE-ADA positive, or TE-ADA positive with low titer
TE-ADA high status	TE-ADA positive with high titer	not TE-ADA positive, or TE-ADA positive with low or moderate titer

Abbreviations: AE = adverse event; TE-ADA = treatment-emergent antidrug antibodies.

Note: For purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive." A TE-ADA low is defined as a TE-ADA positive with a titer value <1:160; a TE-ADA moderate is defined as a TE-ADA positive with a titer value ≥1:160 and <1:1280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1280.

For each TE-ADA status dichotomous variable, a time-varying TE-ADA status will be computed. At time *t*, the TE-ADA status is taken to be the highest of the TE-ADA values bracketing time *t*. More formally, the TE-ADA status at time *t* is given by the greater of: (a) the TE-ADA status at the most-recent postbaseline measurement prior to *t*; and (b) the TE-ADA status at the first TE-ADA postbaseline measurement at or after time *t*. In this computation, "greater" is given by the greater-TE-ADA status of Table RHCG.6.17. If there is no value satisfying criterion (a), then the value (b) is used. Similarly, if there is no value (b), then the value (a) is use.

For each TE-ADA status dichotomous variable, patients will be categorized according to whether they were: (1) always in lesser-TE-ADA status postbaseline; or (2) at some point postbaseline, were in greater-TE-ADA status.

6.12.12.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of ADA effects will be conducted on all evaluable patients within the defined Safety Population, OLE Period Population, and LTE Safety Population.

The overall frequency and percentage (incidence) of patients will be summarized for the TE-ADA status groups and the time-varying TE-ADA status groups. Scheduled visits, unscheduled visits, and repeat measurements will be included.

In addition, the overall frequency and percentage (incidence) of patients will be summarized for the patients who are baseline ADA positive by TE-ADA status groups. For those patients who are TE-ADA positive, a summary of titer values and the proportion of patients who are NAb positive will also be provided.

The time to the development of TE-ADAs (TE-ADA positive, low titer, moderate titer, high titer, and NAb positive) will be calculated as follows:

Time to development of TE-ADAs/NAb (in weeks) = (Date of development of TE-ADAs/NAb – Date of first injection of study treatment + 1) / 7.

If a patient has not developed TE-ADAs/NAbs, he/she will be censored at the date of the last immunogenicity assessment. If a patient does not have any postbaseline assessments for immunogenicity, he/she will be censored at the date of randomization.

For each TE-ADA status dichotomous variable (as defined in Table RHCG.6.17), summaries will be provided of the total postbaseline time in the greater-TE-ADA status for patients who were at some point postbaseline in the greater-TE-ADA status group. Postbaseline time in greater-TE-ADA status for each patient will be aggregated.

A by-patient listing to include treatment, visit date, visit, ADA result, TE-ADA result, NAb result, ADA titer value, ixekizumab concentration, and ADA and NAb inconclusive results will also be provided, for patients with any one sample of ADA (or NAb) positive or inconclusive.

6.12.12.2.2. Analyses of Treatment-Emergent ADA Effects on Efficacy

Efficacy analyses for the OLT (Safety Population) and OLE (OLE Period Populations) Periods will be conducted on all evaluable patients.

Assessment of JIA ACR 30 at Weeks 16 and 104 with NRI will be summarized by the TE-ADA and TE-ADA positive status groups, as described in Section 6.12.12.2.1 for the Safety and OLE Period Populations, respectively.

6.12.12.2.3. Analyses of Treatment-Emergent ADA on Specific Adverse Events

The analyses of TE-ADA effects on safety will be conducted on all immunogenicity evaluable patients for the OLT (Safety Population), OLE (OLE Period Population), and LTE (LTE Safety Population) Periods when patients are on ixekizumab, including switch to ixekizumab.

Adverse events of special interest of allergic reaction/hypersensitivity (anaphylaxis and non-anaphylaxis) and of injection-site reactions will be included in an assessment of AE to TE-ADA over time. Timing of an AE will be taken to be the reported AE start date.

For each TE-ADA status dichotomous variable (as defined in Table RHCG.6.17), patients will be categorized according to whether they were (i) always in lesser-TE-ADA status postbaseline or (ii) at some point postbaseline, were in greater-TE-ADA status. For each AESI, within the time-varying TE-ADA status groups, a summary will be provided of the number of patients who had no event, events only while in lesser-TE-ADA status for group (i), or – for group (ii) – at least 1 event while in greater-TE-ADA status.

Additionally, summaries will be provided of the total number of AESI events (with unique start dates) by time-varying TE-ADA status groups at the event date. The summaries will aggregate time respectively in greater-TE-ADA status and in lesser-TE-ADA status, along with the event rates (rates per 100 patient-years) relative to those aggregate times.

By-patient listings will be provided for patients with TE-ADA who experience a treatment-emergent allergic reaction/hypersensitivity reaction or an injection site reaction. A listing of immunogenicity results will also be provided.

6.13. Subgroup Analyses

The descriptive statistical analysis will be conducted for the following subsets of patients at each post-baseline visit for the OLT (ITT Population), and the OLE (OLE and Switcher Populations) Periods. Subgroups from Table RHCG.6.2 will be analyzed for JIA ACR30/50/70/90/100.

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

6.14. Protocol Violations

Protocol deviations will be tracked by the clinical team, and their importance will be assessed by key team members during protocol deviation review meetings.

Potential examples of deviations include patients who receive excluded concomitant therapy, significant noncompliance 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 the Trial Issue Management Plan (TIMP) for the stat-identified important protocol deviations (IPDs).

The number and percentage of patients having IPD(s) will be summarized in the OLT and OLE Periods (by treatment) within category and subcategory of deviation using the ITT, OLE, and Switcher populations, respectively. Individual patient listings of IPDs will be provided.

6.15. Interim Analyses and Data Monitoring

An interim analysis will be conducted under the auspices of a DMC according to the specifications set forth in the protocol.

An interim analysis will be performed to determine if the study should be stopped for futility when 40 evaluable ixekizumab-treated patients have completed the OLT period, i.e. completed Week 16 (Visit 7) or "early terminated between Weeks 0 and 16" or "discontinued between Weeks 0 and 16." If the Week 16 JIA ACR30 response rate (subject to NRI imputation as appropriate) is less than 40% at interim, futility will be declared, and the study will be terminated, after the applicable required regulatory agreements are obtained.

An interim analysis may be performed at the time (that is, a cut-off date) the last patient completes the OLT period.

A DMC will oversee the conduct of Study RHCG. The DMC will consist of members external to Lilly with the exception of the LRL Senior Management Designee. This DMC will follow the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. The DMC will review and evaluate planned interim analyses.

Data that the DMC will review include, but is not limited to, study discontinuation data, summary of reasons for missing JIA ACR30 data at Week 16, AEs including SAEs, PK data, clinical laboratory data, vital signs data, and growth. The DMC may recommend continuation of the study as designed, temporary suspension of enrollment, or discontinuation of a particular dose regimen or discontinuation of the entire study. The DMC may request to review efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study. Details of the DMC and interim safety analyses will be documented in a DMC charter and DMC analysis plan.

6.15.1. Interim Analysis Plan

Analyses for the DMC will include listings and/or summaries of the following information:

- patient disposition, demographics, and baseline characteristics
- exposure
- adverse events, to include the following:
    - treatment-emergent adverse events
    - serious adverse events, including deaths
    - selected special safety topics
- clinical laboratory results
- vital signs
- growth parameters (for example, height, weight, assessment of bone age)

All listings will include patient ID. Summaries will include TEAEs, SAEs, special topics AEs, and treatment-emergent high and low laboratory and vital signs in terms of counts, percentages and incidence rates, where applicable. For continuous analyses, box plots of laboratory analytes will be provided by time point.

The DMC will request efficacy data to confirm a reasonable benefit/risk profile for ongoing patients in the studies. Further details are given in the DMC charter.

In order to mitigate the effects of potentially slow enrollment, and in order to avoid unnecessary exposure of pediatric patients to treatment, Study RHCG will conduct automated continual learning (ACL) if the study continues beyond the futility interim at 40 evaluable ixekizumab-treated patients. After the interim, the sponsor will conduct periodic ACL snapshots of the raw data to determine if it will still be possible to meet the efficacy critical success factor (CSF) at the study's conclusion. By construction, Study RHCG will meet the efficacy CSF if and only if there are fewer than 37 ixekizumab nonresponders at the end of the study (subject to NRI imputation as appropriate). If an ACL snapshot records fewer than 37 ixekizumab nonresponders, then it is still possible to meet the CSF, and the study will continue. However, if the number of ixekizumab nonresponders in an ACL snapshot is at least 37, then there will be 43 or fewer ixekizumab

responders at the end of the study, which is not enough responders to meet the CSF success in the final analysis. For this reason, if an ACL snapshot reports at least 37 nonresponders, then the sponsor will conduct an additional futility interim.

6.16. Annual Report Analyses

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

6.17. 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.

- 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 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 patients/subjects 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.

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8. Appendices

Appendix 1. Algorithm for Determining JIA ACR*x* Response

Details presented in this appendix will use "*x*" as a generic symbol, and the appropriate number (either 30, 50, 70, 90, or 100) is to be filled in when implementing in dataset programming code.

Juvenile idiopathic arthritis (JIA) American College of Rheumatology (ACR) *x* response is defined as at least *x*% improvement from baseline in at least 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by more than *30*% from baseline.

- active joint count
- limited range of motion joint count
- physician global assessment of disease activity
- parent's global assessment of well-being
- physical function as measured by Childhood Health Assessment Questionnaire (CHAQ), and
- erythrocyte sedimentation rate (ESR).

% change from baseline at a visit is calculated as:

(value at visit – baseline value) * 100 / baseline value

Change at a visit is calculated as:

value at visit – baseline value

The following abbreviations will be used throughout this appendix to refer to the items needed in the algorithm definitions:

Parameter	**Abbreviation for the Parameter**
% change from baseline in active joint count	*AJ73*
% change from baseline in limited range of motion joint count	*LOM69*
% change from baseline in parent's global assessment of well-being	*PGAWB*
% change from baseline in physician's global assessment of disease activity	*PHYGA*
% change from baseline in physical function as measured by Childhood Health Assessment Questionnaire (CHAQ)	*CHAQ*
% change from baseline in erythrocyte sedimentation rate (ESR)	*ESR*
Value of erythrocyte sedimentation rate	*esr*

Note:

- An *esr* value is within normal range if it is ≤20.
- If the *esr* is elevated (*esr* >20) due to JIA, then *esr* is used for calculation.
- If the *esr* is elevated due to a reason other than JIA, then *esr* is not used for calculation.
- If both baseline and postbaseline value of *esr* is within normal range (≤20), then the percent change of *esr* is set at 0 (no change).

JIA ACR30 Response Calculation

Two-step calculation; first step calculates worsening, and second step calculates improvement.

Step 1: Worsening (the increase in the score is worsening):
Check >30% worsening. Specifically check if percent change from baseline is more than 30%, i.e.,

If (*parameter* > 30%) = 1, *else* 0

Count how many variables have more than 30% worsening; if the worsening count is 2 or more, conclude that the patient is a nonresponder. If the worsening count is 1 or less, proceed to Step 2.

Step 2: Improvement (count):
Check ≥30% improvement. Specifically, check if percent change from baseline is less than or equal to -30%, i.e.,

If (*parameter* ≤ -30%) = 1, *else* 0

Count how many variables have at least 30% improvement; if the count is 3 or more, conclude that the patient is a responder; if count is 2 or less, conclude that the patient is a nonresponder.

Note:
Scenario 1: If no variable is missing, proceed as described in Step 1 and/or Step 2, whichever applies.

Scenario 2: If there are variables missing at post-baseline, apply last observation carried forward (LOCF) first at component level, then back to Scenario 1 (LOCF cannot be applied across study periods, and the patient needs to have at least 1 post-baseline visit to apply LOCF. The baseline value cannot be carried forward).

> Note for ESR : If the *esr* at a particular visit is missing, then the last observation is carried forward for the visit. However, for the LOCF visit, if the elevation is attributable to a medical condition other than the study condition as well, then the *esr* value at the current visit is treated as missing.

Scenario 3: If there are variables missing at baseline, use nonmissing components as the core sets, then back to Scenario 1. Unless specified otherwise, if there are variables with baseline value = 0, all postbaseline percent improvement is not calculatable; hence, consider these variables as missing and use nonmissing components as core sets, then back to Scenario 1.

Note: for Scenario 3:

- If 1 component is missing, the remaining 5 components will be used as core set. If 3 out of 5 components are improving and no more than 1 out of 5 is worsening, the patient will be considered as a responder.
- If 2 components are missing, the remaining 4 components will be used as core set. If 3 out of 4 components are improving and no more than 1 out of 4 is worsening, the patient will be considered as a responder.
- If 3 components are missing, the remaining 3 components will be used as core set. If all 3 components are improving, the patient will be considered as a responder.
- If more than 3 components are missing, there will not be sufficient information; thus, the patient will be considered as a nonresponder.

Appendix 2. Algorithm for Calculating Disease Flare

Disease Flare is a worsening of ≥30% from baseline in at least 3 of the 6 juvenile idiopathic arthritis (JIA) American College of Rheumatology (ACR) core set criteria and an improvement of ≥30% in no more than 1 of the criteria.

- active joint count,
- limited range of motion joint count,
- physician global assessment of disease activity,
- parent's global assessment of well-being,
- physical function as measured by Childhood Health Assessment Questionnaire (CHAQ), and
- erythrocyte sedimentation rate (ESR).

% change from baseline at a visit is calculated as:

(value at visit – baseline value) * 100 / baseline value

Change at a visit is calculated as:

value at visit – baseline value

The following abbreviations will be used throughout this appendix to refer to the items needed in the algorithm definitions:

Parameter	**Abbreviation for the Parameter**
% change from baseline in active joint count	*AJ73*
% change from baseline in limited range of motion joint count	*LOM69*
% change from baseline in parent's global assessment of well-being	*PGAWB*
% change from baseline in physician's global assessment of disease activity	*PHYGA*
% change from baseline in physical function as measured by Childhood Health Assessment Questionnaire (CHAQ)	*CHAQ*
% change from baseline in erythrocyte sedimentation rate (ESR)	*ESR*
Change in active joint count	*aj73*
Change in limited range of motion joint count	*lom69*
Change in parent's global assessment of well-being	*pgawb*
Change in physician's global assessment of disease activity	*phyga*
Value of erythrocyte sedimentation rate	*esr*

Note:

- An *esr* value is within normal range if it is at most 20.
- If the ***esr*** is elevated (*esr* >20) due to JIA, then ***esr*** is used for calculation.
- If the ***esr*** is elevated due to a reason other than JIA, then ***esr*** is not used for calculation.
- If both baseline and postbaseline value of *esr* is within normal range (≤20), then the percent change of *esr* is set at 0 (no change).
- If either the number of joints with active arthritis or the number of joints with limitation of motion are used in the calculation of flare for a study visit, then a minimum worsening of at least 2 active joints or 2 joints with limitation of motion must be present.
- If either the Physician's Global Assessment of Disease Activity or the Parent's Global Assessment of Well-Being are used in the calculation of flare for a study visit, then a minimum worsening of at least 20 mm in 0 to 100 mm visual analogue scale (VAS) or 2 scores in the VAS of 21 circles from 0 to 10 must be present.

Flare Calculation

Calculation of flare (two-step calculation; the first step calculates improvement, and the second step calculates worsening).

Step 1: Improvement:

Check ≥30% improvement. Specifically, check if percent change from baseline is less than or equal to -30%, i.e.,

$$if\ (parameter \leq -30\%) = 1, else\ 0$$

Count how many variables have not less than 30% improvement, if the improvement count is 2 or more, conclude that the patient is a non-flare patient. If the improvement count is 1 or less, proceed to Step 2.

Step 2: Worsening

Check >30% worsening. Specifically check if percent change from baseline is more than 30%, i.e.,

$$Criteria\ 1: if\ (parameter \geq 30\%) = 1, else\ 0$$

For variable: active joint count, limit of motion joint count, and Physician's Global Assessment of Disease Activity, also evaluate

$$Criteria\ 2: if\ (variable\ at\ visit - variable\ at\ randomization \geq 2) = 1, else\ 0$$

Note: if any of active joint count, limit of motion joint count, or physician assessment of disease activity has baseline value = 0, only Criteria 2 is required to determine the worsening, otherwise both Criteria 1 and 2 are required.

For variable: Parent's Global Assessment of Well-Being, also evaluate

$$Criteria\ 3: if\ (variable\ at\ visit - variable\ at\ randomization \geq 20mm) = 1, else\ 0$$

Note: if Parent's Assessment of Patient Well-Being is with baseline value = 0, only Criteria 3 is required to determine the worsening, otherwise both Criteria 1 and 3 are required.

If baseline value of ESR is 0 and post-baseline value is nonmissing and out of normal range (i.e. ESR >20 mm/hr), consider it as worsening.

Count how many variables are worsening. If the worsening count is 3 or more, conclude as a flare patient, otherwise conclude as a non-flare patient.

Note:

Scenario 1: If no variable is missing, proceed as described in Step 1 and/or Step 2 whichever applies.

Scenario 2: If there are variables missing at postbaseline, apply LOCF first at component level, then back to Scenario 1 (LOCF cannot be applied across study periods and the patient needs to have at least 1 postbaseline visit to apply LOCF. The baseline value cannot be carried forward).

> Note for ESR: If the *esr* at a particular visit is missing, then the last observation is carried forward for the visit. However, for the LOCF visit, if the elevation is attributable to a medical condition other than the study condition as well, then the *esr* value at the current visit is treated as missing.

Scenario 3: If there are variables missing at baseline, use nonmissing components as the core sets and back to Scenario 1. Unless otherwise specified, if there are variables with baseline value = 0, all postbaseline percent improvement is not calculatable, hence consider these variables as missing and use nonmissing components as core sets and back to Scenario 1.

Note: for Scenario 3:

- If 1 component is missing, the rest of 5 components will be used as core set. If 3 out of 5 components are worsening and no more than 1 out of 5 is improving, the patient will be considered as a flare patient.
- If 2 components are missing, the rest of 4 components will be used as core set. If 3 out of 4 components are worsening and no more than 1 out of 4 is improving, the patient will be considered as a flare patient.
- If 3 components are missing, the rest of 3 components will be used as core set. If all 3 components are worsening, the patient will be considered as a flare patient.
- If more than 3 components are missing, there will not be sufficient information, thus the patient will be considered as a non-flare patient.

Appendix 3. Algorithm for Calculating the CHAQ

The Childhood Health Assessment Questionnaire (HAQ) has been adapted from the Stanford Health Assessment Questionnaire. The Stanford HAQ assesses four outcome dimensions: disability, discomfort and pain, drug side effects, and dollar costs. Disability is measured in the categories of dressing, arising, eating, walking, hygiene, grip, and activities. Discomfort is determined by the presence of pain and its severity. The HAQ is either parent- or self-administered. Parents are reliable proxy-reporters for their child's functional status, describe below is the parent-administered format. Parents are given the questionnaire and asked to complete it without additional instructions.

Disability Index – Daily Function

General Description:

This section is designed to assess the patient's functional ability over the past week. It is composed of eight domains, each of which has at least two component questions. Parents are also asked to indicate the use of any aids or devices or if the child needs help from another person for any of these activities.

The eight domains are: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. For each of these domains, parents are asked to record the amount of difficulty their child may have. Parents are requested to note only those difficulties that are caused by arthritis.

The time frame is over the past week. By repeating the questionnaire at specific time periods we can look at the patterns of function.

Scoring and Coding:

Possible responses for the component questions are:

Without any difficulty = 0
With some difficulty = 1
With much difficulty = 2
Unable to do = 3.

The patient must have a score for at least 6 of the 8 domains. If there are less than six domains completed, a CHAQ cannot be computed. The highest score for any component question determines the score for that category. If a component question is left blank, then the score for that category is determined by the remaining completed question(s). If all component questions are blank, then the category is left blank.

If either devices and/or help from another person is checked for a category, the score = 2. This may determine the score unless the score on any other component question = 3. For example, the response to "Dress yourself..." is with Some difficulty (score = 1). The parent has checked the use of a device for dressing, thereby increasing the score to 2. The response to "Shampoo your

hair" is Unable to do (score = 3). Therefore, the score for the Dressing category is 3. The index is calculated by adding the scores for each of the domains and dividing by the number of domains answered. This gives a score in the 0 to 3.0 range.

Devices associated with each category:

CHAQ Category	Companion aids or devices item
Dressing and Grooming	Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)
Arising	Built up or special chair
Eating	Built up or special utensils
Walking	Cane, walker, crutches, wheelchair
Hygiene	Raised toilet seat, bathtub seat, bathtub bar, long-handled appliances in bathroom
Reach	Long handled appliances for reach
Grip	Jar opener (for jars previously opened)

Devices written in the "Other" sections are considered only if they would be used for any of the stated domains.

Discomfort – Index or VAS

General Description:

This question is designed to obtain information about the presence or absence of arthritis-related pain and its severity. The time frame is in the past week. The Discomfort Index of the CHAQ includes (Ruperto et al. 2001):

- Parent's Global Assessment of Well-being
  - This is a component of the JIA ACR 30 core response set
  - The instrument uses a 0 to 100 mm VAS where 0 = "very well" and 100 = "very poor"
- Pain assessment due to illness
  - The question uses a 0 to 100 mm VAS where 0 = "no pain" and 100 = "very severe pain"

Appendix 4. Algorithm for Calculating Total and Tender Dactylitic Digit

Dactylitic digits are evaluated and recorded as either non-evaluable, or if evaluable, then if tenderness is present or absent. In total, 20 dactylitic joints are assessed.

The total and tender dactylitic digit scores will be calculated by summing all dactylitic joints, and those checked to have tenderness present, respectively. If at least half but not all the dactylitic joints are evaluable, then the observed prorated joint count will be calculated instead. The prorated scores for tenderness count will be adjusted based upon the number of evaluable dactylitic joints: the counted score will be multiplied by 20 then divided by the number of dactylitic joints evaluated (excluding non-evaluable dactylitic joints and any dactylitic joints with a missing response). For example: if only 15 of the 20 dactylitic joints are assessed to be evaluable at a visit, and 12 of those 15 are tender, the prorated joint count is (12/15)*20=36.27 (not 12). The prorated joint count will be rounded up to the next integer and be used in calculating the percent change from baseline in tenderness count. If less than half of the dactylitic joints are evaluable, the tender dactylitic joint count is missing.

The Total Dactylitic Digit score is the sum of dactylitic joints.

The Tender Dactylitic Digit score is the sum of tender dactylitic joints.

Change from baseline: observed total dactylitic digit at visit minus baseline Total Dactylitic Digit

Change from baseline: observed tender dactylitic digit at visit minus baseline Tender dactylitic digit

% Improvement in Total Dactylitic Digit score calculated as:

$$\%\ \text{improvement from baseline} = 100 \times \frac{(\text{Baseline Total Dactylitic Digit score} - \text{Observed Total Dactylitic Digit score})}{\text{Baseline Total Dactylitic Digit score}}$$

% Improvement in Tender Dactylitic Digit score calculated as:

$$\%\ \text{improvement from baseline} = 100 \times \frac{(\text{Baseline Tender Dactylitic Digit score} - \text{Observed Tender Dactylitic Digit score})}{\text{Baseline Tender Dactylitic Digit score}}$$

Appendix 5. Anti-infective Medications and Anatomical Therapeutic Chemical (ATC) Code List and Programming Guide

This appendix provides the code list of ATC of anti-infective medications and the programming guidance.

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
A01AB	4	ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREA
A02BD	4	COMBINATIONS FOR ERADICATION OF HELICOBACTER PYLOR
A07A	3	INTESTINAL ANTIINFECTIVES
A07AA	4	ANTIBIOTICS
A07AB	4	SULFONAMIDES
A07AC	4	IMIDAZOLE DERIVATIVES
A07AX	4	OTHER INTESTINAL ANTIINFECTIVES
B05CA	4	ANTIINFECTIVES
C05AB	4	ANTIBIOTICS
D01	2	ANTIFUNGALS FOR DERMATOLOGICAL USE
D01A	3	ANTIFUNGALS FOR TOPICAL USE
D01AA	4	ANTIBIOTICS
D01AC	4	IMIDAZOLE AND TRIAZOLE DERIVATIVES
D01AE	4	OTHER ANTIFUNGALS FOR TOPICAL USE
D01B	3	ANTIFUNGALS FOR SYSTEMIC USE
D01BA	4	ANTIFUNGALS FOR SYSTEMIC USE
D06	2	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGIC
D06A	3	ANTIBIOTICS FOR TOPICAL USE
D06AA	4	TETRACYCLINE AND DERIVATIVES
D06AX	4	OTHER ANTIBIOTICS FOR TOPICAL USE
D06B	3	CHEMOTHERAPEUTICS FOR TOPICAL USE
D06BA	4	SULFONAMIDES
D06BB	4	ANTIVIRALS
D06BX	4	OTHER CHEMOTHERAPEUTICS
D06C	3	ANTIBIOTICS AND CHEMOTHERAPEUTICS, COMBINATIONS
D07C	3	CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS
D07CA	4	CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS
D07CB	4	CORTICOSTEROIDS, MODERATELY POTENT, COMBINATIONS WITH ANTIBIOTICS
D07CC	4	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS
D07CD	4	CORTICOSTEROIDS, VERY POTENT, COMBINATIONS WITH ANTIBIOTICS
D09AA	4	MEDICATED DRESSINGS WITH ANTIINFECTIVES
D10AF	4	ANTIINFECTIVES FOR TREATMENT OF ACNE
G01AA	4	ANTIBIOTICS
G01AC	4	QUINOLINE DERIVATIVES
G01AE	4	SULFONAMIDES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
G01AF	4	IMIDAZOLE DERIVATIVES
G01AG	4	TRIAZOLE DERIVATIVES
G01AX	4	OTHER ANTIINFECTIVES AND ANTISEPTICS
G01BA	4	ANTIBIOTICS AND CORTICOSTEROIDS
G01BC	4	QUINOLINE DERIVATIVES AND CORTICOSTEROIDS
G01BE	4	SULFONAMIDES AND CORTICOSTEROIDS
G01BF	4	IMIDAZOLE DERIVATIVES AND CORTICOSTEROIDS
G04AB	4	QUINOLONE DERIVATIVES (EXCL. J01M)
G04AC	4	NITROFURAN DERIVATIVES
G04AG	4	OTHER URINARY ANTISEPTICS AND ANTIINFECT
G04AH	4	SULFONAMIDES IN COMBINATION WITH OTHER DRUGS
G04AK	4	URINARY ANTISEPT&ANTIINF, COMB EXCL SULFONAMIDES
J01	2	ANTIBACTERIALS FOR SYSTEMIC USE
J01A	3	TETRACYCLINES
J01AA	4	TETRACYCLINES
J01B	3	AMPHENICOLS
J01BA	4	AMPHENICOLS
J01C	3	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01CA	4	PENICILLINS WITH EXTENDED SPECTRUM
J01CE	4	BETA-LACTAMASE SENSITIVE PENICILLINS
J01CF	4	BETA-LACTAMASE RESISTANT PENICILLINS
J01CG	4	BETA-LACTAMASE INHIBITORS
J01CR	4	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE
J01D	3	OTHER BETA-LACTAM ANTIBACTERIALS
J01DA	4	CEPHALOSPORINS AND RELATED SUBSTANCES
J01DB	4	FIRST-GENERATION CEPHALOSPORINS
J01DC	4	SECOND-GENERATION CEPHALOSPORINS
J01DD	4	THIRD-GENERATION CEPHALOSPORINS
J01DE	4	FOURTH-GENERATION CEPHALOSPORINS
J01DF	4	MONOBACTAMS
J01DH	4	CARBAPENEMS
J01DI	4	OTHER CEPHALOSPORINS
J01E	3	SULFONAMIDES AND TRIMETHOPRIM
J01EA	4	TRIMETHOPRIM AND DERIVATIVES
J01EB	4	SHORT-ACTING SULFONAMIDES
J01EC	4	INTERMEDIATE-ACTING SULFONAMIDES
J01ED	4	LONG-ACTING SULFONAMIDES
J01EE	4	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INC
J01F	3	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01FA	4	MACROLIDES
J01FF	4	LINCOSAMIDES
J01FG	4	STREPTOGRAMINS
J01G	3	AMINOGLYCOSIDE ANTIBACTERIALS
J01GA	4	STREPTOMYCINS
J01GB	4	OTHER AMINOGLYCOSIDES
J01M	3	QUINOLONE ANTIBACTERIALS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
J01MA	4	FLUOROQUINOLONES
J01MB	4	OTHER QUINOLONES
J01R	3	COMBINATIONS OF ANTIBACTERIALS
J01RA	4	COMBINATIONS OF ANTIBACTERIALS
J01WA	4	HERBAL ANTIBACTERIALS FOR SYSTEMIC USE
J01WB	4	HERBAL URINARY ANTISEPTICS AND ANTIINFECTIVES
J01X	3	OTHER ANTIBACTERIALS
J01XA	4	GLYCOPEPTIDE ANTIBACTERIALS
J01XB	4	POLYMYXINS
J01XC	4	STEROID ANTIBACTERIALS
J01XD	4	IMIDAZOLE DERIVATIVES
J01XE	4	NITROFURAN DERIVATIVES
J01XX	4	OTHER ANTIBACTERIALS
J02	2	ANTIMYCOTICS FOR SYSTEMIC USE
J02A	3	ANTIMYCOTICS FOR SYSTEMIC USE
J02AA	4	ANTIBIOTICS
J02AB	4	IMIDAZOLE DERIVATIVES
J02AC	4	TRIAZOLE DERIVATIVES
J02AX	4	OTHER ANTIMYCOTICS FOR SYSTEMIC USE
J04AA	4	AMINOSALICYLIC ACID AND DERIVATIVES
J04AB	4	ANTIBIOTICS
J04AC	4	HYDRAZIDES
J04AK	4	OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS
J04AM	4	COMBINATIONS OF DRUGS FOR TREATMENT OF TUBERCULOSI
J04B	3	DRUGS FOR TREATMENT OF LEPRA
J04BA	4	DRUGS FOR TREATMENT OF LEPRA
J05	2	ANTIVIRALS FOR SYSTEMIC USE
J05A	3	DIRECT ACTING ANTIVIRALS
J05AA	4	THIOSEMICARBAZONES
J05AB	4	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRI
J05AC	4	CYCLIC AMINES
J05AD	4	PHOSPHONIC ACID DERIVATIVES
J05AE	4	PROTEASE INHIBITORS
J05AF	4	NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE IN
J05AG	4	NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
J05AH	4	NEURAMINIDASE INHIBITORS
J05AR	4	ANTIVIRALS FOR TREATMENT OF HIV INFECTIONS, COMBIN
J05AX	4	OTHER ANTIVIRALS
P01A	3	AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISE
P01AA	4	HYDROXYQUINOLINE DERIVATIVES
P01AB	4	NITROIMIDAZOLE DERIVATIVES
P01AC	4	DICHLOROACETAMIDE DERIVATIVES
P01AR	4	ARSENIC COMPOUNDS
P01AX	4	OTHER AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOA
P01BA	4	AMINOQUINOLINES
P01BC	4	METHANOLQUINOLINES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
P01BD	4	DIAMINOPYRIMIDINES
P01BE	4	ARTEMISININ AND DERIVATIVES, PLAIN
P01BF	4	ARTEMISININ AND DERIVATIVES, COMBINATIONS
P01BX	4	OTHER ANTIMALARIALS
P01C	3	AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS
P01CA	4	NITROIMIDAZOLE DERIVATIVES
P01CB	4	ANTIMONY COMPOUNDS
P01CC	4	NITROFURAN DERIVATIVES
P01CD	4	ARSENIC COMPOUNDS
P01CX	4	OTHER AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMI
P02	2	ANTHELMINTICS
P02B	3	ANTITREMATODALS
P02BA	4	QUINOLINE DERIVATIVES AND RELATED SUBSTANCES
P02BB	4	ORGANOPHOSPHOROUS COMPOUNDS
P02BX	4	OTHER ANTITREMATODAL AGENTS
P02C	3	ANTINEMATODAL AGENTS
P02CA	4	BENZIMIDAZOLE DERIVATIVES
P02CB	4	PIPERAZINE AND DERIVATIVES
P02CC	4	TETRAHYDROPYRIMIDINE DERIVATIVES
P02CE	4	IMIDAZOTHIAZOLE DERIVATIVES
P02CF	4	AVERMECTINES
P02CX	4	OTHER ANTINEMATODALS
P02D	3	ANTICESTODALS
P02DA	4	SALICYLIC ACID DERIVATIVES
P02DW	4	HERBAL ANTICESTODALS
P02DX	4	OTHER ANTICESTODALS
P02WA	4	HERBAL ANTHELMINTICS
P03A	3	ECTOPARASITICIDES, INCL. SCABICIDES
P03AA	4	SULFUR CONTAINING PRODUCTS
P03AB	4	CHLORINE CONTAINING PRODUCTS
P03AC	4	PYRETHRINES, INCL. SYNTHETIC COMPOUNDS
P03AX	4	OTHER ECTOPARASITICIDES, INCL. SCABICIDES
P03BA	4	PYRETHRINES
R02AB	4	ANTIBIOTICS
S01A	3	ANTIINFECTIVES
S01AA	4	ANTIBIOTICS
S01AB	4	SULFONAMIDES
S01AD	4	ANTIVIRALS
S01AE	4	FLUOROQUINOLONES
S01AX	4	OTHER ANTIINFECTIVES
S01C	3	ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMB
S01CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S01CB	4	CORTICOSTEROIDS/ANTIINFECTIVES/MYDRIATICS IN COMBI
S01CC	4	ANTIINFLAMMATORY AGENTS, NON-STEROIDS AND ANTIINFECTIVES
S02A	3	ANTIINFECTIVES
S02AA	4	ANTIINFECTIVES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
S02C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S02CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03A	3	ANTIINFECTIVES
S03AA	4	ANTIINFECTIVES
S03C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION

Abbreviation: ATC = World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) Anatomical Therapeutic Chemical (ATC) classification system.

For the above list, the higher level of ATC includes all the lower levels under that level; for example, level 2 term includes all the level 3 terms under it, level 3 term includes all the level 4 terms under it. Therefore, for programming simplicity, the table below provides all the required ATC codes by highest level.

ATC Level 2	ATC Level 3	ATC Level 4
		A01AB
		A02BD
	A07A	
		B05CA
		C05AB
D01		
D06		
	D07C	
		D09AA
		D10AF
		G01AA
		G01AC
		G01AE
		G01AF
		G01AG
		G01AX
		G01BA
		G01BC
		G01BE
		G01BF
		G04AB
		G04AC
		G04AG
		G04AH
		G04AK
J01		
J02		
		J04AA
		J04AB
		J04AC
		J04AK

ATC Level 2	ATC Level 3	ATC Level 4
		J04AM
	J04B	
J05		
	P01A	
		P01BA
		P01BC
		P01BD
		P01BE
		P01BF
		P01BX
	P01C	
P02		
	P03A	
		P03BA
		R02AB
	S01A	
	S01C	
	S02A	
	S02C	
	S03A	
	S03C	

Abbreviation: ATC = World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) Anatomical Therapeutic Chemical (ATC) classification system.

Appendix 6. Lilly-Defined MedDRA Preferred Terms for Opportunistic Infections (OI)

Please see the latest version of the Preferred Terms for Opportunistic Infections (OI) (MedDRA Version 23.0).

Opportunistic Infection	**Preferred Term (MedDRA Version 23.0)**	**Lilly Defined Classification**
Pneumocystis jirovecii (II)	*Pneumocystis jirovecii* pneumonia *Pneumocystis jirovecii* infection	Narrow
	Pneumocystis test positive Blood beta-D-glucan Blood beta-D-glucan abnormal Blood beta-D-glucan increased Gomori methenamine silver stain Lung diffusion test	Broad
Human polyomavirus infection including BK virus disease including PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	Human polyomavirus infection Polyomavirus-associated nephropathy BK virus infection Progressive multifocal leukoencephalopathy JC virus infection JC virus granule cell neuronopathy	Narrow
	Anti-JC virus antibody index JC polyomavirus test Polyomavirus test Polyomavirus test positive	Broad
Cytomegalovirus disease (V)	Cytomegalovirus chorioretinitis Cytomegalovirus colitis Cytomegalovirus duodenitis Cytomegalovirus enteritis Cytomegalovirus enterocolitis Cytomegalovirus gastritis Cytomegalovirus gastroenteritis Cytomegalovirus gastrointestinal infection Cytomegalovirus gastrointestinal ulcer Cytomegalovirus hepatitis Cytomegalovirus infection Cytomegalovirus mononucleosis Cytomegalovirus mucocutaneous ulcer Cytomegalovirus myelomeningoradiculitis Cytomegalovirus myocarditis Cytomegalovirus nephritis Cytomegalovirus oesophagitis Cytomegalovirus pancreatitis Cytomegalovirus pericarditis Cytomegalovirus syndrome Cytomegalovirus urinary tract infection	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Cytomegalovirus viraemia Disseminated cytomegaloviral infection Encephalitis cytomegalovirus Pneumonia cytomegaloviral	
	Cytomegalovirus test Cytomegalovirus test positive	Broad
Post-transplant lymphoproliferative disorder (EBV) (V)	Epstein-Barr virus associated lymphoma Epstein-Barr virus associated lymphoproliferative disorder Epstein Barr virus positive mucocutaneous ulcer Post-transplant lymphoproliferative disorder	Narrow
	Epstein-Barr viraemia Epstein-Barr virus infection Lymphoproliferative disorder Lymphoproliferative disorder in remission Oral hairy leukoplakia	Broad
Bartonellosis (disseminated disease only) (V)	Bacillary angiomatosis Peliosis hepatis Splenic peliosis Systemic bartonellosis Trench fever	Narrow
	Bartonella test *Bartonella* test positive Bartonellosis Cat scratch disease	Broad
Blastomycosis (IV)	Blastomycosis Epididymitis blastomyces Osteomyelitis blastomyces Pneumonia blastomyces	Narrow
	N/A	Broad
Toxoplasmosis (myocarditis, pneumonitis, or characteristic retinochoroiditis only) (IV)	Cerebral toxoplasmosis Eye infection toxoplasmal Hepatitis toxoplasmal Meningitis toxoplasmal Myocarditis toxoplasmal Pneumonia toxoplasmal	Narrow
	Toxoplasma serology *Toxoplasma* serology positive Toxoplasmosis	Broad
Coccidioidomycosis (II)	*Coccidioides* encephalitis Coccidioidomycosis Cutaneous coccidioidomycosis Meningitis coccidioides	Narrow
	N/A	Broad
Histoplasmosis (II)	Acute pulmonary histoplasmosis Chronic pulmonary histoplasmosis Endocarditis histoplasma	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Histoplasmosis Histoplasmosis cutaneous Histoplasmosis disseminated Meningitis histoplasma Pericarditis histoplasma Retinitis histoplasma	
	Presumed ocular histoplasmosis syndrome	Broad
Aspergillosis (invasive disease only) (II)	Aspergillosis oral Cerebral aspergillosis Meningitis aspergillus Oro-pharyngeal aspergillosis	Narrow
	Aspergillus infection *Aspergillus* test *Aspergillus* test positive Bronchopulmonary aspergillosis Sinusitis aspergillus	Broad
Candidiasis (invasive disease or oral not limited to the tongue) (II)	*Candida* endophthalmitis *Candida* osteomyelitis *Candida* pneumonia *Candida* retinitis *Candida* sepsis Cerebral candidiasis Endocarditis candida Fungal oesophagitis Gastrointestinal candidiasis Hepatic candidiasis Hepatosplenic candidiasis Meningitis candida Oesophageal candidiasis Oropharyngeal candidiasis Peritoneal candidiasis Splenic candidiasis Systemic candida	Narrow
	Bladder candidiasis *Candida* infection *Candida* test *Candida* test positive Mucocutaneous candidiasis Oral candidiasis Oral fungal infection Respiratory moniliasis	Broad
Cryptococcosis (II)	Cryptococcal cutaneous infection Cryptococcal fungaemia Cryptococcosis Disseminated cryptococcosis Gastroenteritis cryptococcal Meningitis cryptococcal Neurocryptococcosis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Osseous cryptococcosis Pneumonia cryptococcal	
	Cryptococcus test *Cryptococcus* test positive	Broad
Other invasive fungi: Mucormycosis (zygomycosis [*Rhizopus*, *Mucor*, and *Lichtheimia*]), *Scedosporum/Pseudallescheria boydii*, *Fusarium* (II)	Allescheriosis *Fusarium* infection Mucormycosis *Scedosporium* infection Phaeohyphomycosis Phaeohyphomycotic brain abscess *Pseudallescheria* infection *Pseudallescheria* sepsis	Narrow
	See "Non-specific terms" below	Broad
Legionellosis (II)	*Legionella* infection Pneumonia legionella Pontiac fever	Narrow
	Legionella test *Legionella* test positive	Broad
Listeria monocytogenes (invasive disease only) (II)	*Listeria* encephalitis *Listeria* sepsis Meningitis listeria	Narrow
	Listeraemia Listeriosis *Listeria* test *Listeria* test positive	Broad
Tuberculosis (I)	Adrenal gland tuberculosis Bone tuberculosis Choroid tubercles Conjunctivitis tuberculous Cutaneous tuberculosis Disseminated Bacillus Calmette-Guerin infection Disseminated tuberculosis Ear tuberculosis Epididymitis tuberculous Extrapulmonary tuberculosis Immune reconstitution inflammatory syndrome associated tuberculosis Intestinal tuberculosis Joint tuberculosis Lymph node tuberculosis Male genital tract tuberculosis Meningitis tuberculous Oesophageal tuberculosis Oral tuberculosis Pericarditis tuberculous Peritoneal tuberculosis Prostatitis tuberculous	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Pulmonary tuberculoma Pulmonary tuberculosis Renal tuberculosis Salpingitis tuberculous Silico tuberculosis Spleen tuberculosis Thyroid tuberculosis Tuberculid Tuberculoma of central nervous system Tuberculosis Tuberculosis bladder Tuberculosis gastrointestinal Tuberculosis liver Tuberculosis of central nervous system Tuberculosis of eye Tuberculosis of genitourinary system Tuberculosis of intrathoracic lymph nodes Tuberculosis of peripheral lymph nodes Tuberculosis ureter Tuberculous abscess central nervous system Tuberculous endometritis Tuberculous laryngitis Tuberculous pleurisy Tuberculous tenosynovitis	
	Interferon gamma release assay Interferon gamma release assay positive *Mycobacterium tuberculosis* complex test *Mycobacterium tuberculosis* complex test positive Tuberculin test Tuberculin test false negative Tuberculin test positive	Broad
Nocardiosis (II)	Cutaneous nocardiosis *Nocardia* sepsis Nocardiosis Pulmonary nocardiosis	Narrow
	Nocardia test positive	Broad
Nontuberculous mycobacterium disease (II)	Atypical mycobacterial infection Atypical mycobacterial lower respiratory tract infection Atypical mycobacterial lymphadenitis Atypical mycobacterial pneumonia Atypical mycobacterium pericarditis Borderline leprosy Bovine tuberculosis Indeterminate leprosy Leprosy Lepromatous leprosy	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Mycobacterial infection Mycobacterial peritonitis *Mycobacterium abscessus* infection *Mycobacterium avium* complex immune restoration disease *Mycobacterium avium* complex infection *Mycobacterium chelonae* infection *Mycobacterium fortuitum* infection *Mycobacterium kansasii* infection *Mycobacterium marinum* infection *Mycobacterium ulcerans* infection Superinfection mycobacterial Tuberculoid leprosy Type 1 lepra reaction Type 2 lepra reaction	
	Atypical mycobacterium test positive Mycobacterial disease carrier *Mycobacterium leprae* test positive *Mycobacterium* test *Mycobacterium* test positive	Broad
Salmonellosis (invasive disease only) (II)	Aortitis salmonella Arthritis salmonella Meningitis salmonella Osteomyelitis salmonella Paratyphoid fever Pneumonia salmonella *Salmonella* sepsis *Salmonella* bacteraemia Typhoid fever	Narrow
	Salmonella test positive Salmonellosis	Broad
HBV reactivation (IV)	Hepatitis B reactivation	Narrow
	Asymptomatic viral hepatitis Chronic hepatitis B HBV-DNA polymerase increased Hepatitis B Hepatitis B antigen Hepatitis B antigen positive Hepatitis B core antigen Hepatitis B core antigen positive Hepatitis B DNA assay Hepatitis B DNA assay positive Hepatitis B DNA increased Hepatitis B e antigen Hepatitis B e antigen positive Hepatitis B surface antigen Hepatitis B surface antigen positive Hepatitis B virus test	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Hepatitis B virus test positive Hepatitis infectious Hepatitis post transfusion Hepatitis viral Withdrawal hepatitis	
Herpes simplex (invasive disease only) (IV)	Colitis herpes Gastritis herpes Herpes oesophagitis Herpes sepsis Herpes simplex colitis Herpes simplex encephalitis Herpes simplex gastritis Herpes simplex hepatitis Herpes simplex meningitis Herpes simplex meningoencephalitis Herpes simplex meningomyelitis Herpes simplex necrotising retinopathy Herpes simplex oesophagitis Herpes simplex pneumonia Herpes simplex sepsis Herpes simplex viraemia Herpes simplex visceral Meningitis herpes Meningoencephalitis herpetic Meningomyelitis herpes Pneumonia herpes viral	Narrow
	Eczema herpeticum Herpes ophthalmic Herpes simplex Herpes simplex DNA test positive Herpes virus infection Herpes virus test abnormal Herpes simplex virus test positive Ophthalmic herpes simplex	Broad
Herpes zoster (any form) (II)	Disseminated varicella zoster vaccine virus infection Encephalitis post varicella Genital herpes zoster Herpes zoster Herpes zoster cutaneous disseminated Herpes zoster disseminated Herpes zoster infection neurological Herpes zoster meningitis Herpes zoster meningoencephalitis Herpes zoster meningomyelitis Herpes zoster meningoradiculitis Herpes zoster necrotising retinopathy Herpes zoster oticus	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Herpes zoster pharyngitis Necrotising herpetic retinopathy Ophthalmic herpes zoster Varicella keratitis	
	Varicella zoster virus infection Varicella virus test Varicella virus test positive	Broad
Stronglyoides (hyperinfection syndrome and disseminated forms only) (IV)	Strongyloidiasis	Narrow
	N/A	Broad
Paracoccidioides infections (V)	*Paracoccidioides* infection Pulmonary paracoccidioidomycosis	Narrow
	N/A	Broad
Penicillium marneffei (V)	*Penicillium* infection	Narrow
	Penicillium test positive	Broad
Sporothrix schenckii (V)	Cutaneous sporotrichosis Pulmonary sporotrichosis Sporotrichosis	Narrow
	N/A	Broad
Cryptosporidium species (chronic disease only) (IV)	Biliary tract infection cryptosporidial	Narrow
	Cryptosporidiosis infection Gastroenteritis cryptosporidial	Broad
Microsporidiosis (IV)	Microsporidia infection	Narrow
	N/A	Broad
Leishmaniasis (Visceral only) (IV)	Visceral leishmaniasis	Narrow
	Leishmaniasis	Broad
Trypanosoma cruzi infection (Chagas' Disease) (progression of chronic and disseminated disease only) (V)	Chagas' cardiomyopathy Meningitis trypanosomal	Narrow
	American trypanosomiasis Trypanosomiasis *Trypanosoma* serology positive	Broad
Campylobacteriosis (invasive disease only) (V)	*Campylobacter* sepsis	Narrow
	Campylobacter infection *Campylobacter* test positive	Broad
Shigellosis (invasive disease only) (V)	*Shigella* sepsis	Narrow
	Shigella infection *Shigella* test positive	Broad
Vibriosis (invasive disease due to *V. vulnificus*) (V)	N/A	Narrow
	Vibrio test positive *Vibrio vulnificus* infection	Broad
HCV progression (V)	N/A	Narrow
	Chronic hepatitis C Hepatitis C Hepatitis C RNA Hepatitis C RNA increased Hepatitis C RNA fluctuation Hepatitis C RNA positive Hepatitis C virus test	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 23.0)	Lilly Defined Classification
	Hepatitis C virus test positive	
Non-specific terms	N/A	Narrow
	Abscess fungal Alternaria infection Arthritis fungal Biliary tract infection fungal Central nervous system fungal infection Cerebral fungal infection Encephalitis fungal Erythema induratum Eye infection fungal Fungaemia Fungal abscess central nervous system Fungal endocarditis Fungal labyrinthitis Fungal oesophagitis Fungal peritonitis Fungal pharyngitis Fungal retinitis Fungal sepsis Hepatic infection fungal Meningitis fungal Mycotic endophthalmitis Myocarditis mycotic Oropharyngitis fungal Osteomyelitis fungal Otitis media fungal Pancreatitis fungal Parasitic lung infection Parasitic pneumonia Pericarditis fungal Phaehyphomycosis Pneumonia fungal Pulmonary mycosis Pulmonary trichosporonosis Sinusitis fungal Splenic infection fungal Systemic mycosis	Broad

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable; PVAN = polyomavirus-associated nephropathy.

Appendix 7. MedDRA Preferred Terms for each Category Associated with Criterion 2 for Anaphylactic Allergic Reactions/Hypersensitivity Events

Please see the latest version of the Preferred Terms for each Category Associated with Criterion 2 for Anaphylactic Allergic Reactions/Hypersensitivity Events (MedDRA Version 23.0).

Preferred Terms (MedDRA Version 23.0)	
Category A: Involvement of the Skin/Mucosal Tissue	
Administration site hypersensitivity	Localised oedema
Administration site rash	Mouth swelling
Administration site dermatitis	Nasal obstruction
Administration site eczema	Nodular rash
Administration site pruritus	Ocular hyperaemia
Administration site urticaria	Oedema
Administration site vasculitis	Oedema mouth
Allergic oedema	Oedema mucosal
Allergic otitis externa	Orbital oedema
Angioedema	Palatal oedema
Circumoral oedema	Palatal swelling
Circumoral swelling	Perineal rash
Drug eruption	Periorbital oedema
Erythema	Periorbital swelling
Eye allergy	Pruritus
Eye oedema	Pruritus allergic
Eye pruritus	Rash
Eye swelling	Rash erythematous
Eyelid oedema	Rash pruritic
Eyelid pruritus	Rash vesicular
Face oedema	Skin oedema
Flushing	Skin swelling
Gingival oedema	Swelling
Gingival swelling	Swelling of eyelid
Idiopathic urticaria	Swelling face
Injection site dermatitis	Swollen tongue
Injection site eczema	Tongue oedema
Injection site hypersensitivity	Urticaria
Injection site rash	Urticaria papular
Injection site urticaria	Urticarial dermatitis
Injection site vasculitis	Urticarial vasculitis
Lip oedema	
Lip swelling	
Category B: Respiratory Compromise	
Acute respiratory failure	Laryngotracheal oedema
Allergic cough	Oropharyngeal spasm
Allergic pharyngitis	Oropharyngeal swelling

Preferred Terms (MedDRA Version 23.0)	
Asthma	Pharyngeal oedema
Asthmatic crisis	Respiratory arrest
Bronchial hyperreactivity	Respiratory distress
Bronchial oedema	Respiratory failure
Bronchospasm	Respiratory tract oedema
Cardio-respiratory distress	Reversible airways obstruction
Chest discomfort	Sensation of foreign body
Choking	Sneezing
Choking sensation	Spasmodic dysphonia
Cough	Status asthmaticus
Cyanosis	Stridor
Dyspnoea	Tachypnea
Epiglottic oedema	Tachypnoea
Hyperventilation	Throat tightness
Hypoxia	Tracheal obstruction
Laryngeal dyspnoea	Tracheal oedema
Laryngeal obstruction	Upper airway obstruction
Laryngeal oedema	Wheezing
Laryngitis allergic	
Laryngospasm	
Category C: Reduced Blood Pressure or Associated Symptoms	
Blood pressure decreased	Hypoperfusion
Blood pressure diastolic decreased	Hypotension
Blood pressure systolic decreased	Hypotensive crisis
Blood pressure ambulatory decreased	Hypovolaemic shock
Cardiac arrest	Incontinence
Cardiac failure	Mean arterial pressure decreased
Cardiopulmonary failure	Peripheral circulatory failure
Cardio-respiratory arrest	Presyncope
Cardiovascular insufficiency	Shock
Circulatory collapse	Shock symptom
Diastolic hypotension	Syncope
Distributive shock	Urinary Incontinence
Dizziness	
Category D: Persistent Gastrointestinal Symptoms	
Abdominal discomfort	Gastrointestinal pain
Abdominal pain	Intestinal angioedema
Abdominal pain lower	Nausea
Abdominal pain upper	Retching
Diarrhoea	Visceral pain
Epigastric discomfort	Vomiting
Gastrointestinal oedema	

Appendix 8. Allergic Reactions/Hypersensitivities MedDRA Preferred Term Excluded from Non-Anaphylaxis

The following Preferred Terms (based on review of MedDRA Version 23.0) from the Hypersensitivity SMQ (20000214) will be excluded from the non-anaphylaxis analysis:

Administration site dermatitis	Injection site rash
Administration site eczema	Injection site recall reaction
Administration site rash	Injection site urticaria
Administration site recall reaction	Injection site vasculitis
Administration related reaction	Instillation site hypersensitivity
Administration site hypersensitivity	Instillation site rash
Administration site urticaria	Instillation site urticaria
Allergic otitis externa	Iodine allergy
Allergic otitis media	Mast cell degranulation present
Allergic sinusitis	Medical device site dermatitis
Allergic transfusion reaction	Medical device site eczema
Allergy alert test positive	Medical device site hypersensitivity
Allergy test positive	Medical device site rash
Allergy to surgical sutures	Medical device site recall reaction
Allergy to vaccine	Medical device site urticaria
Anaphylactic transfusion reaction	Nodular rash
Antiallergic therapy	Pathergy reaction
Application site dermatitis	Procedural shock
Application site eczema	Radioallergosorbent test positive
Application site hypersensitivity	Reaction to azo-dyes
Application site rash	Reaction to colouring
Application site recall reaction	Reaction to food additive
Application site urticaria	Reaction to preservatives
Application site vasculitis	Rhinitis allergic
Arthritis allergic	Shock
Aspirin-exacerbated respiratory disease	Shock symptom
Asthma-chronic obstructive pulmonary disease	Skin test positive
overlap syndrome	Solvent sensitivity
Blepharitis allergic	Stoma site hypersensitivity
Blood immunoglobulin E abnormal	Stoma site rash
Blood immunoglobulin E increased	Urticaria contact
Bromoderma	Urticarial vasculitis
Catheter site dermatitis	Vaccination site dermatitis
Catheter site eczema	Vaccination site exfoliation
Catheter site hypersensitivity	Vaccination site eczema
Catheter site rash	Vaccination site hypersensitivity
Catheter site urticaria	Vaccination site rash
Catheter site vasculitis	Vaccination site recall reaction
Chronic eosinophilic rhinosinusitis	Vaccination site urticaria

Chronic hyperplastic eosinophilic sinusitis	Vaccination site vasculitis
Circulatory collapse	Vaccination site vesicles
Conjunctivitis allergic	Vaginal ulceration
Contact stomatitis	Vessel puncture site rash
Complement factor decreased	Vessel puncture site vesicles
Complement factor C1 decreased	Vulvovaginal rash
Complement factor C2 decreased	Vulval eczema
Complement factor C3 decreased	Vulval ulceration
Complement factor C4 decreased	Vulvovaginal ulceration
Contrast media allergy	Vulvovaginitis allergic
Contrast media reaction	Acute respiratory failure
Dennie-Morgan fold	Allergy to chemicals
Dermatitis acneiform	Allergy to fermented products
Dermatitis contact	Anti-insulin antibody increased
Dermatitis herpetiformis	Anti-insulin antibody positive
Dermatitis infected	Anti-insulin receptor antibody increased
Device allergy	Anti-insulin receptor antibody positive
Dialysis membrane reaction	Haemolytic transfusion reaction
Distributive shock	Fixed eruption
Drug provocation test	
Eczema infantile	
Eczema vaccinatum	
Giant papillary conjunctivitis	
Hand dermatitis	
Heparin-induced thrombocytopenia	
Hereditary angioedema	
Implant site dermatitis	
Implant site hypersensitivity	
Implant site rash	
Implant site urticaria	
Incision site dermatitis	
Incision site rash	
Infusion related hypersensitivity reaction	
Infusion related reaction	
Infusion site dermatitis	
Infusion site eczema	
Infusion site hypersensitivity	
Infusion site rash	
Infusion site recall reaction	
Infusion site urticaria	
Infusion site vasculitis	
Injection related reaction	
Injection site dermatitis	
Injection site eczema	
Injection site hypersensitivity	

Appendix 9. Lilly-Defined MedDRA Preferred Terms for Inflammatory Bowel Disease (IBD)

Please see the latest version of Lilly-Defined MedDRA Preferred Terms for Inflammatory Bowel Disease (IBD) (MedDRA Version 23.0).

Condition	Preferred Term (MedDRA version 23.0)	Lilly-Defined Classification
Inflammatory bowel disease	Inflammatory bowel disease	Narrow
Crohn's disease	Crohn's disease	Narrow
Ulcerative colitis	Acute haemorrhagic ulcerative colitis	Narrow
	Colitis ulcerative	Narrow
	Proctitis ulcerative	Narrow
Non-specific terms	Abscess intestinal	Broad
	Anal abscess	Broad
	Anal fistula	Broad
	Anal fistula repair	Broad
	Anal fistula excision	Broad
	Anal fistula infection	Broad
	Anovulvar fistula	Broad
	Colitis	Broad
	Colon fistula repair	Broad
	Colonic fistula	Broad
	Diverticular fistula	Broad
	Duodenal fistula	Broad
	Enterocolitis haemorrhagic	Broad
	Enterocolonic fistula	Broad
	Enterocutaneous fistula	Broad
	Enterovesical fistula	Broad
	Gastrointestinal fistula	Broad
	Gastrointestinal fistula repair	Broad
	Fistula of small intestine	Broad
	Intestinal fistula	Broad
	Intestinal fistula infection	Broad
	Intestinal fistula repair	Broad
	Jejunal fistula	Broad
	Large intestinal ulcer perforation	Broad
	Rectal fistula repair	Broad
	Faecal calprotectin abnormal	Broad
	Faecal calprotectin increased	Broad
	Proctitis haemorrhagic	Broad
	Pseudopolyposis	Broad
	Rectoprostatic fistula	Broad
	Rectourethral fistula	Broad

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