Statistical Analysis Plan: I1F-MC-RHCH

A Multicenter, Randomized, Double-Blind and Placebo-Controlled 16-Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Chinese Patients With Radiographic Axial Spondyloarthritis

NCT04285229

Approval Date: 28-Apr-2021

1. Statistical Analysis Plan:

I1F-MC-RHCH: A Multicenter, Randomized, Double-Blind and Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Chinese Patients with Radiographic Axial Spondyloarthritis

Ixekizumab (LY2439821)

Study I1F-MC-RHCH is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study to evaluate the efficacy and safety of ixekizumab (LY2439821) versus placebo at 16 weeks in Chinese patients with radiographic axial spondyloarthritis (r-axSpA) patients. Patients will be randomized to subcutaneous (SC) placebo, or ixekizumab. This study will also evaluate long-term efficacy and safety of ixekizumab during an Extended Treatment Period (36 weeks). All patients entering into the Extended Treatment Period from the placebo treatment group will receive ixekizumab 80 mg Q4W.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Approval Date: 28-Apr-2021 GMT

2. Table of Contents

Section **Page**

1. Statistical Analysis Plan: I1F-MC-RHCH: A Multicenter, Randomized, Double-Blind and Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Chinese Patients with Radiographic Axial Spondyloarthritis 1
2. Table of Contents 2
3. Revision History 8
4. Study Objectives 9
5. Study Design 11
   5.1. Summary of Study Design 11
   5.2. Method of Assignment to Treatment 11
   5.3. Determination of Sample Size 12
6. A Priori Statistical Methods 13
   6.1. General Considerations 13
      6.1.1. General Considerations for Analyses during the Blinded Treatment Dosing Period (Period 2) 13
      6.1.2. General Considerations for Analyses during the Extended Treatment Period (Period 3) 16
      6.1.3. General Considerations for Analyses during Combined Blinded Treatment Dosing Period and Extended Treatment Period (Combined Periods 2 and 3) 17
      6.1.4. General Considerations for Analyses during the Post-Treatment Follow-Up Period (Period 4) 18
      6.1.5. Analysis Populations 18
   6.2. Adjustments for Covariates 22
   6.3. Handling of Dropouts or Missing Data 22
      6.3.1. Nonresponder Imputation 22
      6.3.2. Modified Baseline Observation Carried Forward 22
      6.3.3. Multiple Imputation 22
   6.4. Multiple Comparisons/Multiplicity 22
   6.5. Patient Disposition 24
   6.6. Patient Characteristics 24
      6.6.1. Demographics and Baseline Characteristics 24
      6.6.2. Historical Illness and Preexisting Conditions 27
   6.7. Treatment Compliance 28
   6.8. Previous and Concomitant Therapy 29

6.8.1. Previous Therapy 29
6.8.2. Concomitant Therapy 29
6.9. Efficacy Analyses 29
6.9.1. Primary Outcome and Methodology 49
6.9.2. Major Secondary Efficacy Analyses 49
6.9.3. Additional Analyses of the Primary Outcome 50
6.9.4. Other Secondary Efficacy Analyses 50
6.9.4.1. Analyses on NSAID Intake 51
6.9.5. Sensitivity Analyses 52
6.9.5.1. Multiple Imputation 52
6.9.6. Additional Exploratory Analyses 52
6.9.7. Health Outcomes/Quality-of-Life Analyses 52
6.10. Pharmacokinetic/Pharmacodynamic Methods 59
6.11. Safety Analyses 59
6.11.1. Extent of Exposure 59
6.11.2. Adverse Events 60
6.11.2.1. Common Adverse Events 62
6.11.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events 62
6.11.3.1. Special Safety Topics including Adverse Events of Special Interest 62
6.11.3.2. Anterior Uveitis 74
6.11.4. Clinical Laboratory Evaluation 74
6.11.4.1. Leukocytes (WBC) and Platelets 75
6.11.4.2. Neutrophil Follow-Up 76
6.11.5. Vital Signs and Other Physical Findings 77
6.11.6. Quick Inventory of Depressive Symptomatology–Self Report 16 Items (QIDS-SR16) 78
6.11.7. Columbia-Suicide Severity Rating Scale (C-SSRS) 80
6.11.8. Immunogenicity 81
6.11.8.1. Definitions and Terms 81
6.11.8.1.1. Sample Category Definitions 81
6.11.8.1.2. Patient Category Definitions 81
6.11.8.1.3. Definitions for Clinical Interpretation of Assay Results 82
6.11.8.2. Immunogenicity Analyses 83
6.11.8.2.1. Analyses of Characteristics of ADA Immune Response 84
6.11.8.2.2. Analyses of ADA Effects on Efficacy 85

6.11.8.2.3. Analyses of Treatment-Emergent ADA on Specific Adverse Events 85
6.12. Subgroup Analyses 86
6.12.1. Efficacy Subgroup Analyses 86
6.13. Protocol Deviations 86
6.14. Interim Analyses 87
6.15. Clinical Trial Registry Analyses 87
7. Unblinding Plan 88
8. References 89
9. Appendices 93

Table of Contents

Table **Page**

Table RHCH.6.1. Major Analysis Purposes Intended for Each Analysis Population 20

Table RHCH.6.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population 21

Table RHCH.6.3. Description and Derivation of Primary and Secondary Efficacy Outcomes 30

Table RHCH.6.4. Description of Primary and Secondary Efficacy Analyses 38

Table RHCH.6.5. Description and Derivation of Health Outcomes and Quality-of-Life Measures 53

Table RHCH.6.6. Description of Health Outcomes and Quality-of-Life Analyses 56

Table RHCH.6.7. Definitions and Analyses of Special Safety Topics including Adverse Events of Special Interest 64

Table RHCH.6.8. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressures and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults 78

Table RHCH.6.9. Baseline Definition for Immunogenicity Analyses for Extended Treatment Period 82

Table RHCH.6.10. TE-ADA Status Dichotomous Variables for AE Analysis 83

Table of Contents

Figure **Page**

Figure RHCH.5. 1 Illustration of study design for Clinical Protocol I1F-MC-RHCH. 11

Figure RHCH.6. 1 Illustration of graphical multiple testing procedure with initial α allocation and weights. 23

Table of Contents

Appendix		Page
Appendix 1.	Algorithm for Determining ASAS Response	94
Appendix 2.	ASAS-NSAID Equivalent Score	96
Appendix 3.	Definition of DMARDs, Oral Corticosteroids, NSAIDs (including COX-2), and Opioids	97

3. Revision History

This is the first version.

4. Study Objectives

Objectives	Endpoints
Primary The primary objective is to compare ixekizumab regimen 80 mg every 4 weeks (Q4W) versus placebo in bDMARD-naïve patients with active r-axSpA at Week 16	• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response
Secondary **The major secondary objective is:** • To compare ixekizumab regimen 80 mg Q4W to placebo in overall study population at Week 16	• Proportion of patients achieving an ASAS40 response • Proportion of patients achieving an ASAS20 response • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Proportion of patients achieving ASDAS < 2.1 • Change from baseline in magnetic resonance imaging (MRI) of the spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score) • Change from baseline in Short Form 36 (SF-36) physical component score (PCS)
Other secondary objectives are: • To compare ixekizumab regimen 80 mg Q4W to placebo in overall study population during the 16-week placebo controlled period (Period 2)	• Proportion of patients who achieve ASAS20, ASAS40, ASAS5/6, and partial remission by ASAS criteria • Change from baseline in the individual components of the ASAS criteria • Change from baseline in BASDAI • Proportion of patients reaching BASDAI50 • Change from baseline in ASDAS • Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline ≥1.1), major improvement (change of ASDAS from baseline ≥2.0 or achievement of the lowest possible score), inactive disease (ASDAS score <1.3) and ASDAS<2.1 • Change from baseline in the measure of high sensitivity C-reactive protein (CRP) • Change from baseline in BASFI • Change from baseline in mobility ○ Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components

Objectives	Endpoints
	○ Chest expansion ○ Change from baseline in occiput to wall distance • Change from baseline in MRI of the SIJ (Spondyloarthritis Research Consortium of Canada Score [SPARCC]) • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) • Incidence rate of anterior uveitis or uveitis flares • Change from baseline in the following health outcomes measures: Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale, Work Productivity Activity Impairment—Spondyloarthritis (WPAI-SpA) scores, SF-36 (both PCS and mental component scores [MCS]) and Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16) score.
• To determine if the effect of ixekizumab is maintained through Week 52	All endpoints assessed at Week 16 (above) and during the 16-week placebo-controlled period (above) will continue to be assessed through Week 52. In addition, the following endpoint is added: • NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)
• To measure ixekizumab exposure and assess the relationship between exposure and immunogenicity	• Serum trough concentrations of ixekizumab • Ixekizumab serum trough concentrations associated with ADA titer sub groups
Exploratory • To evaluate time to first response	• Onset of action and treatment response (ASAS20, ASAS40, ASDAS) during the placebo-controlled period
• To compare ixekizumab regimen 80 mg Q4W to placebo during the 16-week placebo-controlled period (Period 2)	• Change from baseline in SPARCC SIJ Structural Score (SSS) • Change from baseline in ASAS HI score
• To evaluate the incidence of anti-ixekizumab antibodies and their relationship to efficacy of ixekizumab	• Efficacy response rates listed below at Weeks 16 and 52 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status ○ Proportion of patients achieving ASAS40 ○ Proportion of patients achieving ASAS20 ○ Proportion of patients achieving ASDAS inactive disease

5. Study Design

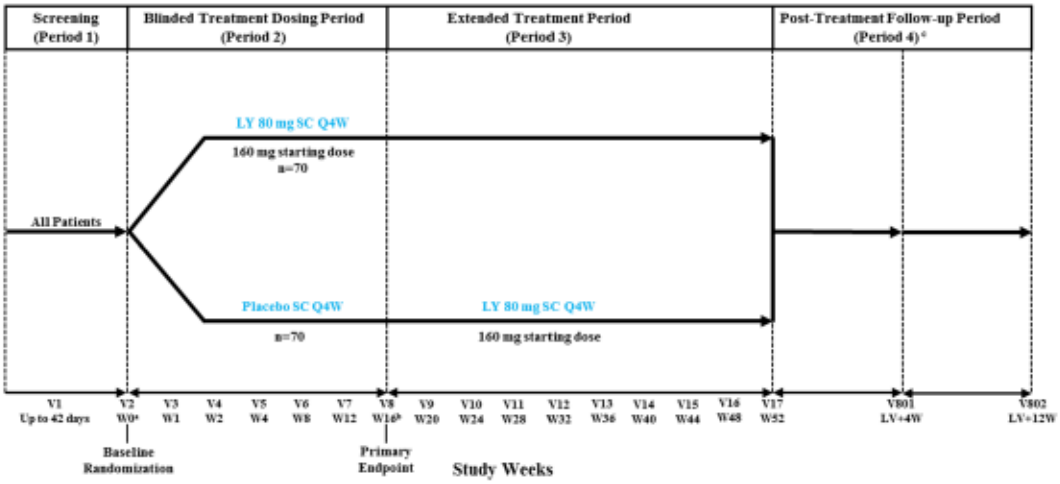
This section contains the summary of study design, the method of treatment assignment, and the sample size determination from the protocol for Study I1F-MC-RHCH.

5.1. Summary of Study Design

Study I1F-MC-RHCH (RHCH) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study to evaluate the efficacy and safety of ixekizumab 80 mg Q4W SC, as compared to placebo SC in patients with r-axSpA, during a 16-week Blinded Treatment Dosing Period.

Study RHCH will also evaluate long-term efficacy and safety of ixekizumab during the Extended Treatment Period (Period 3) for a total treatment duration of 1 year (52 weeks).

Figure RHCH.5. 1 illustrates the study design.



Abbreviations: LV = last visit; LY = ixekizumab; n = number; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week

[a] All patients will receive 2 injections at baseline, as detailed in Protocol Section 7.1. Patients randomized to the ixekizumab regimen will receive a 160 mg starting dose.

[b] All patients will receive 2 injections at Week 16, as detailed in Protocol Section 7.1. Patients randomized to placebo at Week 0 will begin ixekizumab 80 mg Q4W at Week 16 with a 160 mg starting dose, and patients randomized to ixekizumab at Week 0 will receive 1 ixekizumab 80 mg injection and 1 placebo injection at Week 16 to maintain the blinding (Protocol Section 7.1).

[c] Patients who discontinue from study treatment for any reason and who have received at least 1 dose of investigational product will continue to the early termination visit (ETV) before entering the Post-Treatment Follow-Up Period. V801 and V802 are required for all patients (Protocol Section 9.4.10).

Figure RHCH.5. 1 Illustration of study design for Clinical Protocol I1F-MC-RHCH.

5.2. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Week 0 (Visit 2). 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 double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS.

To achieve between-group comparability, the randomization will be stratified by baseline CRP (non-elevated or elevated) and TNF inhibitors experienced or naïve. The study will enroll approximately 60% of patients with baseline CRP elevated (>5.00 mg/L) and approximately 40% of patients with non-elevated baseline CRP. At least 61 bDMARD-naïve patients will be enrolled per arm.

Once a specific stratum is fully enrolled, the sponsor may stop further enrollment of patients fitting the criteria of that stratum.

5.3. Determination of Sample Size

Approximately 140 patients will be randomized at a 1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q4W with a starting dose 160 mg and placebo.

For 90% power to test the superiority of ixekizumab Q4W to placebo for ASAS40 at Week 16 in bDMARD-naïve patients, at least 61 patients per treatment group would be needed. The following assumptions were used for the power calculations for ASAS40 response rates: 44% for ixekizumab 80 mg Q4W treatment group and 16% for the placebo group in bDMARD naïve patients.

For the key secondary efficacy endpoint ASAS40 response at Week 16 compared to placebo group in overall study population, the power would be >90%. The assumptions are 42% response rate for ixekizumab 80 mg Q4W treatment group and 15% for the placebo group in overall study population.

These assumptions are based on the review of historical clinical studies in AS (etanercept, adalimumab, infliximab, certolizumab, and golimumab [Davis et al. 2003; van der Heijde et al. 2005, 2006; Inman et al. 2008, Landewé et al. 2014]) and recent secukinumab trials including both TNF inhibitor experienced patients and naïve patients (Baeten et al. 2014b; Sieper et al. 2014).

A 2-sided Fisher's exact test at the 0.05 level is assumed. Sample size and power estimates were obtained from nQuery® Advisor 7.0.

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 9.4 or higher.

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 continuous data, at visits of interest, change from baseline will be calculated as the observed value - the baseline value. Percent change (or percent improvement) is calculated as $100 \times \frac{Baseline\ value - Observed\ value}{Baseline\ value}$. If the baseline value or observed value is missing, the change from baseline and percent change (or percent improvement) from baseline will be missing.

All confidence intervals (CIs) and statistical tests will be 2-sided unless otherwise specified. P-values which are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to 3 decimal places. All other p-values which are less than 0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals will be presented to 1 more decimal place than the raw data.

Age, sex, and race will be reported on all by-patient listings unless otherwise specified. Sex will be abbreviated as follows: female (F) and male (M). Race will be abbreviated as follows: Asian (AS).

Not all displays described in this SAP will necessarily be included in the clinical study report (CSR). Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools such as Spotfire instead of, or in addition to, a static display. Any display described in this SAP and not included in the CSR would be available upon request.

6.1.1. General Considerations for Analyses during the Blinded Treatment Dosing Period (Period 2)

Comparisons between ixekizumab regimen 80 mg Q4W and placebo will be performed for all analyses in Period 2.

Period 2 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 8) or the ETV (between Weeks 0 and 16). If a patient has Visit 8 but does not receive injection at Week 16 (Visit 8), the last recorded time for Visit 8 is used as the end time for Period 2.

Baseline will be defined as the last available value before the first injection for efficacy, health outcome, and safety analyses. 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. Change from baseline will be calculated as the visit value of interest minus the baseline value. 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.

The randomization to treatment groups is stratified by baseline CRP status (nonelevated versus elevated) and TNF inhibitors experience (experienced or naïve) as described in Section 5.2. Unless otherwise specified, the statistical analysis models will adjust for baseline CRP status, and prior TNF inhibitors experience(if applicable).

The primary analysis method for treatment comparisons of categorical efficacy and health outcomes variables at specific time points will be made using a logistic regression analysis with treatment, baseline CRP status, and TNF inhibitors experience (if applicable) in the model. The proportions, odds ratio and 95% confidence intervals (CIs) will be reported; treatment difference and 95% CIs will also be reported. Secondary analysis will be conducted using a Fisher's exact test. In the case when logistic regression model does not produce statistical results due to sparse data, Fisher's exact test will be used.

As a secondary analysis for the primary and major secondary categorical efficacy measures, a categorical, pseudo-likelihood based mixed-effects model of repeated measures (categorical MMRM) estimating the percentage of patients achieving response across postbaseline visits will be used. The model will include treatment, baseline CRP status, TNF inhibitors experience (if applicable), visit, and treatment-by-visit as fixed factors. The binomial distribution and the logit link will be used. The restricted maximum likelihood (REML) will be used. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The probability of response, the corresponding 2-sided 95% CI, and the p-value for treatment comparisons at Week 16 (Visit 8) and all other postbaseline visits will be reported.

If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The sandwich estimator (Diggle et al. 1994) for the covariance estimation will be used by specifying the EMPIRICAL option in SAS PROC MIXED. When sandwich estimation is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, DDFM= BETWITHIN option will be used to estimate denominator degrees of freedom.

The primary analyses for continuous efficacy and health outcome variables will be made using Mixed Model for Repeated Measures (MMRM). The primary analyses for MRI endpoints will be made using analysis of covariance (ANCOVA). A secondary analysis for selected continuous efficacy and health outcome variables will also be made using analysis of covariance (ANCOVA).

When the MMRM is used, the model will include treatment, baseline CRP status, TNF inhibitors experience, baseline value, baseline value-by-visit, visit, and treatment-by-visit interaction as fixed factors (except for the analysis of CRP, see paragraph below). The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry, will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. The restricted maximum likelihood (REML) will be used. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparison with placebo at Week 16 (Visit 8) and all other visits will be reported.

For the analysis of CRP, the MMRM model will include treatment, baseline CRP status, TNF inhibitors experience, visit, and treatment-by-visit interaction as fixed factors.

When the ANCOVA is used, the model will include treatment, baseline CRP status, TNF inhibitors experience, and baseline value. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analyses (Andersen and Millen 2013). However, the data will still be used in other analyses, including shift analyses, or modified baseline observation carried forward (mBOCF) endpoint analyses, and other categorical analyses.

For selective efficacy measures, percent improvement will be calculated as 100 x (baseline score – observed scores)/baseline score, unless specified otherwise. If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening, this measure will be negative.

Figures showing the proportion of patients achieving a categorical clinical response at each scheduled visit within each treatment group may be provided.

Time to first clinical response (for example, ASAS40) will be assessed based on the intent-to-treat (ITT) Population in Period 2. Unless specified otherwise, time to first clinical response (for example, ASAS40) is defined as:

Time to first clinical response (days) = Date of first clinical response during Period 2 – Date of randomization + 1

If a patient has not met the criteria for response by completion or early discontinuation of Period 2, the patient will be censored at the date of their last visit during Period 2.

The number of patients at risk and experiencing a response by each scheduled visit during Period 2 will be presented by treatment group. The Kaplan-Meier estimate of the proportion of patients achieving the clinical response will be presented for each visit. Treatment group comparisons will be performed using the log-rank test and the log-rank test stratified by baseline CRP status and TNF inhibitors experienced or naïve. A Kaplan-Meier plot of the time to first clinical response by treatment group will also be provided.

Fisher's exact test will be used for all adverse event (AE), baseline, discontinuation, and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

6.1.2. General Considerations for Analyses during the Extended Treatment Period (Period 3)

Unless otherwise specified, Period 3 starts at the first injection of study treatment at Week 16 (Visit 8) and ends on the date of Week 52 (Visit 17) or the ETV (between Weeks 16 and 52).For the efficacy and health outcome analyses, baseline is defined as the last available value before the first injection in Period 2 and, in most cases, this will be the value recorded at Week 0 (Visit 2).

Unless otherwise specified, for the safety analyses during Period 3, baseline is defined as the last available value before first injection of ixekizumab in Period 3. In most cases, this will be the measure recorded at Week 16 (Visit 8). For treatment-emergent adverse events (TEAEs), baseline is the events ongoing just prior to the first injection of the study drug injection at Week 16 (for placebo and ixekizumab patients).

The number and percentage of patients having categorical efficacy response (for example, ASAS40) will be summarized for all scheduled visits (Nonresponder Imputation, NRI), including Week 52 (Visit 17) during Period 3.

In addition, the number and percentage of patients achieving response on ASAS20 for those who did not achieve response at Week 16, and the number and percentage of patients maintaining response for those who achieved response at Week 16, will be summarized for all scheduled visits (NRI), including Week 52 (Visit 17) during Period 3. Similar summary will be provided for ASAS40.

Each continuous efficacy and health outcome score and change from baseline (or percent improvement) will be summarized at all scheduled visits, including Week 52 (Visit 17) using descriptive statistics (n, mean, SD, median, minimum and maximum). Missing data will be imputed using mBOCF method (Section 6.3.2).

The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized at all scheduled visits.

6.1.3. General Considerations for Analyses during Combined Blinded Treatment Dosing Period and Extended Treatment Period (Combined Periods 2 and 3)

Selective efficacy and health outcome analyses will be performed for Combined Periods 2 and 3 for ITT Population who are randomized to ixekizumab at Week 0 (Visit 2). These analyses included the primary endpoint, all major secondary endpoints, as well as ASDAS<1.3, ASDAS clinically important improvement and major improvement, and MRI SIJ SPARCC score.

Unless otherwise specified, Combined Periods 2 and 3 starts at the first injection of study treatment at Week 0 (Visit 2) and ends on the date of Week 52 (Visit 17) or the ETV (between Weeks 0 and 52).

For the efficacy and health outcome analyses, baseline is defined as the last available value before the first injection in Period 2 and, in most cases, this will be the value 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.

The number and percentage of patients achieving a categorical response (for example ASAS40) will be summarized by treatment group for all scheduled visits (NRI), including Week 52 (Visit 17).

Continuous measure and change from baseline will be summarized by treatment group at all scheduled visits, including Week 52 (Visit 17) using descriptive statistics (n, mean, SD, median, minimum and maximum). Missing data will be imputed using mBOCF method (Section 6.3.2).

Selective safety analyses will be performed for Combined Periods 2 and 3 for the Safety Population who are randomized to ixekizumab at Week 0 (Visit 2).

For above safety analyses, baseline will be defined as the last available value before the first injection at Week 0. In most cases, this will be the measure recorded at Week 0 (Visit 2). For TEAEs, baseline is defined as the time from Visit 1 to the date/time of the first injection.

Additional categorical safety analyses will be conducted in the All Ixekizumab Exposures Safety Population (defined in Section 6.1.5.), for each patient, only periods in which ixekizumab is administrated are included. Exposure-adjusted incidence rates of AE during Week 0-52 will be provided. For these safety analyses, baseline is defined as below:

- If ixekizumab is dispensed at Week 0, baseline will be defined as the last available value before the first injection at Week 0. In most cases, this will be the measure recorded at Week 0 (Visit 2). For TEAEs, baseline is defined as the time from Visit 1 to the date/time of the first injection.
- If placebo is dispensed at Week 0, then the baseline is the last non-missing value up to the visit (V8) that the patient first receives an injection of ixekizumab.

6.1.4. General Considerations for Analyses during the Post-Treatment Follow-Up Period (Period 4)

For the safety analyses during Period 4, baseline is defined as the last non-missing assessment on or prior to entering Period 4, that is, on or prior to Week 52 (Visit 17), or ETV.

Safety data collected will be summarized using descriptive statistics.

6.1.5. Analysis Populations

The following major analysis populations will be used (additional analysis populations for specific analysis will be defined in the corresponding analysis section):

Intent-to-Treat Population (ITT Population): Unless otherwise specified, efficacy and health outcomes analyses for Period 2 will be conducted on the ITT Population, defined as all randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned.

Per-Protocol Set (PPS): In addition, the primary efficacy analysis will be repeated using the PPS, which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoint (Section 6.13), and whose investigator site does not have significant good clinical practice (GCP) issues that require a report to the regulatory agencies prior to Week 16 (Visit 8). Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses (all injections at an injection week are counted as 1 dose), and not have any occurrence of over-dosing (that is, took more injections at the same time point than specified in the protocol) during Period 2. Patients will be analyzed according to the treatment to which they were assigned.

Safety Population: Safety analyses for Period 2 will be conducted on the Safety Population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which they were assigned in that period.

Extended Treatment Period Population: Efficacy, health outcomes, and safety analyses for Period 3 will be conducted on the Extended Treatment Period Population, defined as all patients who received at least 1 dose of ixekizumab treatment during Period 3.

All Ixekizumab Exposures Safety Population: Safety analyses for combined Blinded Treatment Dosing Period and Extended Treatment Period will be conducted on the All Ixekizumab Exposures Safety Population, defined as all patients who received at least one dose of ixekizumab during the study. For each patient, only periods in which ixekizumab is administrated are included.

Follow-Up Population: Safety analyses for Period 4 will be conducted on the Follow-Up Population, defined as all randomized patients who received at least 1 dose of study treatment and have entered the Period 4. Patients will be analyzed according to the treatment they received before entering the Follow-up Period.

Table RHCH.6.1 summarizes the major analysis purposes intended for each analysis population.

Table RHCH.6.2 describes the treatment groups and the comparisons for each study period and analysis population.

Table RHCH.6.1. Major Analysis Purposes Intended for Each Analysis Population

	ITT Population	Per-Protocol Set	Safety Population	Extended Treatment Period Population	ITT Population Who are Initially Randomized to Ixekizumab at Week 0	All Ixekizumab Exposures Safety Population	Follow-Up Population
Disposition	For Period 2			For Period 3			For Period 4
Baseline Characteristics [a]	For baseline			For baseline			
Treatment Compliance			For Period 2	For Period 3			
Concomitant Medication	For Period 2			For Period 3			
Protocol Deviation	For Period 2			For Period 3			
Exposure			For Period 2	For Period 3		For Periods 2 and 3, on ixekizumab treatment only	
Efficacy and Health Outcome Analyses	For Period 2	For ASAS40, ASAS20 in Period 2		For Period 3	For primary and major secondary objectives, and selective measures in Combined Periods 2 and 3		
Safety Analyses			For Period 2	For Period 3		For Periods 2 and 3, on ixekizumab treatment only	For Period 4
Subgroup Analyses on Efficacy	For Period 2						

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ITT = intent-to-treat; TEAE = treatment-emergent adverse event.

[a] including patient demographics and other baseline characteristics, historical illness, preexisting conditions, prespecified medical history, previous therapy.

Table RHCH.6.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment Group	Abbreviation	Comparison [a]
Blinded Treatment Dosing Period (Period 2)	Intent-to-Treat Population; Per Protocol Set; Safety Population	Placebo Ixekizumab 80 mg Q4W Total	PBO IXE80Q4W Total	IXE80Q4W vs. PBO
Extended Treatment Period (Period 3)	Extended Treatment Period Population	Placebo/Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q4W/Ixekizumab 80 mg Q4W Total	PBO/IXE80Q4W IXE80Q4W/IXE80Q4W Total	No Between-Group Comparison
Combined Periods 2 and 3	Intent-to-Treat Population Who are Initially Randomized to Ixekizumab; Safety Population Who are Initially Randomized to Ixekizumab	Ixekizumab 80 mg Q4W	IXE80Q4W	Not applicable
Combined Periods 2 and 3 (on Ixekizumab treatment only)	All Ixekizumab Exposures Safety Population [c]	Placebo/Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q4W/Ixekizumab 80 mg Q4W Total	PBO/IXE80Q4W IXE80Q4W/IXE80Q4W Total	No Between-Group Comparison
Post-Treatment Follow-up Period (Period 4) [b]	Follow-Up Population	Placebo Ixekizumab 80 mg Q4W Total	PBO IXE80Q4W Total	No Between-Group Comparison

Abbreviations: IXE80Q4W = ixekizumab 80 mg every 4 weeks; PBO = placebo; Q4W = every 4 weeks.

[a] The between-group comparison will be conducted for concomitant therapy, compliance, disposition, safety and efficacy.

[b] Treatment group refers to the treatment regimen that the patient received prior to entering Period 4.

[c] defined as all patients who received at least one dose of ixekizumab during the study

6.2. Adjustments for Covariates

Unless otherwise specified, the statistical analysis models will adjust for baseline CRP status (nonelevated or elevated, elevated defined as >5.00mg/L) and TNF inhibitors experience.

In general, when an MMRM is to be used for analyses, baseline value and baseline-by-visit interactions will be included as covariates; when an ANCOVA is to be used for analyses, baseline value will be included as a covariate.

6.3. Handling of Dropouts or Missing Data

In accordance with precedent set with other Phase 3 axSpA trials (van der Heijde et al. 2006; Inman et al. 2008), the following methods for imputation of missing data will be used.

6.3.1. Nonresponder Imputation

Analysis of categorical efficacy and health outcome variables will be assessed using a NRI method. Patients will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the primary analysis time point. 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 nonresponders for the NRI analysis at Week 16. Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

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

6.3.2. Modified Baseline Observation Carried Forward

An mBOCF analysis will be performed on continuous efficacy and health outcome variables in the major and other secondary objectives. For patients discontinuing study drug due to an AE, the baseline observation will be carried forward to the corresponding time point for evaluation. For patients discontinuing study drug for any other reason, the last nonmissing observation before discontinuation 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 with the exception of patients discontinuing study treatment because of an AE.

6.3.3. Multiple Imputation

Multiple imputations (MIs) are used to replace missing outcomes. *m* imputed complete datasets will be created. For each completed dataset, use the model as would have been applied had the data been completed. The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules, as implemented in SAS® PROC MI ANALYZE.

6.4. Multiple Comparisons/Multiplicity

The following is a list of primary and major secondary outcomes to be tested at Week 16:

> **Primary** - proportion of patients achieving an ASAS40 response in bDMARD-naïve patients [ASAS40 naïve]

Secondary 1 - proportion of patients achieving an ASAS40 response in overall population [ASAS40 overall]
Secondary 2 - proportion of patients achieving an ASAS20 response in overall population [ASAS20]
Secondary 3 - change from baseline in ASDAS score in overall population [ASDAS CFB]
Secondary 4 - change from baseline in BASDAI in overall population [BASDAI CFB]
Secondary 5 - change from baseline in BASFI in overall population [BASFI CFB]
Secondary 6 - proportion of patients achieving ASDAS<2.1 in overall population [ASDAS<2.1]
Secondary 7 - change from baseline in MRI of the spine in overall population [MRI spine CFB]
Secondary 8 - change from baseline in SF-36 PCS score in overall population [SF-36 PCS CFB].

A graphical multiple testing procedure (Bretz et al. 2011) will be used to control the family-wise type I error rate at a 2-sided α level of 0.05. The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate (Alosh et al. 2014). Each hypothesis is represented as a node in a graph. Directed arrows between the nodes with associated weights represent how alpha is passed from its initial allocation to other nodes. The testing scheme will be fully specified by the graph (including nodes, arrows and weights) along with the initial alpha allocation. Figure RHCH.6. 1 shows the graphical testing scheme with initial α allocation and weights. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses..

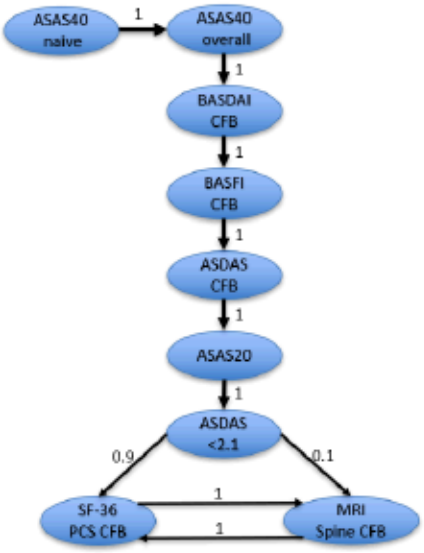


Figure RHCH.6. 1 Illustration of graphical multiple testing procedure with initial α allocation and weights.

6.5. Patient Disposition

The number and percentage (where applicable) of patients randomized at Week 0 (Visit 2), completing Week 16 (Visit 8), completing the study at Week 52 (Visit 17), and completing Follow-Up Visits 801, 802, will be summarized by the initial randomized treatment group (Analysis population: ITT).

For Period 2 (ITT Population), Period 3 (Extended Treatment period Population), and Period 4 (Follow-Up Population), the number and percentage of patients completing each period and the number and percentage of patients discontinuing from each period will be summarized by treatment group (Period 2 only) and primary reason for discontinuation. Fisher's exact test will be used to test for difference between treatment groups in Period 2.

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 during treatment periods, the date of completion or discontinuation of each period, and the primary reason for discontinuation if applicable. The number of days in Period 2 will also be calculated as defined above and presented in the listing (Analysis population: ITT).

6.6. Patient Characteristics

6.6.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized for ITT Population in Period 2 and Extended Treatment Period Population in Period 3. The continuous variables will be summarized using descriptive statistics (number of patients, mean, SD, minimum, median and maximum), categorical variables will be summarized using frequency counts and percentages. Treatment group comparisons in Period 2 will be conducted using Fisher's exact test for categorical data and an analysis of variance (ANOVA) with treatment as a factor for continuous data. Table RHCH. 6.1. shows the details of patient characteristics variables that will be summarized.

By-patient listings of demographic and baseline characteristics for the ITT population will be provided.

Table RHCH. 6.1. Patient Characteristics (and Variables for Subgroup Analysis)

Variable	Summary	Efficacy Subgroup Analysis For Categories
Demographics and baseline characteristics		
Age [a]	quantitative summary (in years)	
	<40 years, ≥40 years	Yes
	<50 years, ≥50 years	Yes
	<65 years, ≥65 years	
Sex	male, female	Yes

Race	Asian	
Height	quantitative summary (in cm)	
Weight	quantitative summary (in kg)	
	<70 kg, ≥70 kg	Yes
	<70 kg, ≥70 kg and <90 kg, ≥90 kg	
BMI [b]	quantitative summary (in kg/m^2)	
	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), extreme obese (≥40 kg/m^2)	Yes
Age at axSpA onset	quantitative summary (in years)	
Duration of symptoms since axSpA onset [c]	<10 years, ≥10 years	Yes
	<5 years, ≥5 years	Yes
	<3 years, ≥3 years	Yes
Duration of disease since axSpA diagnosis [d]	quantitative summary (in years)	
HLA-B27 positivity	yes, no	Yes
History of inflammatory back pain	yes, no	Yes
History of anterior uveitis	yes, no	Yes
History of psoriasis	yes, no	Yes
History of IBD	yes, no	Yes
History of dactylitis	yes, no	Yes
History of arthritis	yes, no	Yes
History of enthesitis	yes, no	Yes
Baseline C-Reactive Protein (CRP) level		
Baseline CRP	quantitative summary (mg/L)	
	≤3.00 mg/L, >3.00 mg/L	Yes
	≤5.00 mg/L, >5.00 mg/L	Yes
	≤10.00 mg/L, >10 mg/L	Yes
	≤15.00 mg/L, >15.00 mg/L	Yes
Baseline disease activity level, pain, function, and mobility		
Baseline ASDAS	quantitative summary	
	Inactive disease (<1.3), Low disease activity (≥1.3, <2.1), High disease activity (≥2.1, ≤3.5), Very high disease activity (>3.5)	
Baseline BASDAI	quantitative summary	
	<4, ≥4 and <6, ≥6	
Baseline Patient global assessment of disease activity NRS	quantitative summary	
Baseline Inflammation (mean of questions 5 and 6 of BASDAI)	quantitative summary	
Baseline Spinal pain (BASDAI question 2)	quantitative summary	
Baseline spinal pain at night due to AS (Pain NRS)	quantitative summary	
Baseline spinal pain due to AS (Pain NRS)	quantitative summary	
Baseline BASFI	quantitative summary	
Baseline BASMI Linear	quantitative summary	
Baseline Chest expansion	quantitative summary (in cm)	
Baseline Occiput-to-wall measurement	quantitative summary (in cm)	

Baseline enthesitis		
Baseline MASES	quantitative summary	
	=0, >0	
Baseline heel enthesitis	=0, >0	
Baseline health outcome measures		
Baseline ASAS HI	quantitative summary	
	<3, ≥3	
	≤5, >5	
Baseline FACIT-F score	quantitative summary	
Baseline EQ-5D-5L	quantitative summary	
Baseline WPAI-SpA	quantitative summary	
Baseline SF36 PCS	quantitative summary	
Baseline SF36 MCS	quantitative summary	
Baseline QIDS-SR16	quantitative summary of total score	
	Item12: 0, 1, 2, 3	
Baseline concomitant therapy use		
Baseline cDMARDs use [e]	yes, no	Yes
Baseline methotrexate use	quantitative summary	
	yes, no	
Baseline sulfasalazine use	quantitative summary	
	yes, no	
Baseline hydroxychloroquine use	quantitative summary	
	yes, no	
Baseline oral corticosteroid use [e]	yes, no	
Previous therapy: axial spondyloarthritis		
Previous non-biologic systemic agent for r-axSpA	yes, no	
Previous non-biologic non-systemic agent for r-axSpA	yes, no	
Previous TNF inhibitor for r-axSpA	yes, no	Yes
Habit		
Tobacco use	never, current, former	Yes
Cigarette use	≤10 per day, > 10 per day	
Alcohol consumption	never, current, former	
Caffeine/xanthine ingestion	never, current, former	
Baseline NSAID (including COX-2 inhitors) use		
Baseline ASAS-NSAID score	quantitative summary	
Baseline NSAIDs use [e]	yes, no	
Baseline Imaging of Sacroiliac Joints and Spine		
Baseline SPARCC SIJ MRI	quantitative summary	
	<2, ≥2	Yes
Baseline SPARCC SIJ SSS MRI for fat metaplasis	quantitative summary	
Baseline SPARCC SIJ SSS MRI for erosion	quantitative summary	
Baseline SPARCC SIJ SSS MRI for backfill	quantitative summary	

Baseline SPARCC SIJ SSS MRI for anklyosis	quantitative summary	
Baseline SPARCC spine MRI	quantitative summary	
	<2, ≥2	Yes

Abbreviations: BMI= body mass index; HLA-B27= Human leukocyte antigen B27; IBD= inflammatory bowel disease; CRP= C-Reative Protein; ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; BASMI= Bath Ankylosing Spondylitis Metrology Index; MASES= Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC= Spondyloarthritis Research Consortium of Canada; ASAS HI= ASAS Health Index; EQ-5D-5L= European Quality of Life-5 Dimensions-5 Level; WPAI-SpA= Work Productivity and Activity Impairment Questionnaire-Spondyloarthritis; SF36 = Short Forms (36 items) Health Survey; PCS= Physical Component Summary Score; MCS= Mental Component Summary Score; QIDS-SR 16= Quick Inventory of Depressive Symptomatology–Self-Report 16 items.

[a] Age will be calculated as: Age = floor((intck('month', brthdtc, rfstdtc) – (day(rfstdtc) < day(brthdtc)))/12). Here brthdtc = Imputed date of birth (July 1st in the year of birth collected in the eCRF), and rfstdtc = subject reference start date (that is, the date when patient is first exposed to study treatment).

[b] BMI will be calculated as BMI (kg/m^2) = Weight (kg) / (Height (m))^2.

[c] Duration of symptoms since axSpA onset = (date of informed consent – date of axial spondylitis onset)/365.25, where the date of axial spondylitis onset is recorded on the *Prespecified Medical History – Axial Spondyloarthritis* eCRF page.

[d] Duration of disease since axSpA diagnosis = (date of informed consent – date of axial spondylitis diagnosis)/365.25, where the date of axial spondylitis diagnosis is recorded on the *Prespecified Medical History – Axial Spondyloarthritis* eCRF page.

[e] Definition of DMARDs, Oral Corticosteroids, NSAIDS (including COX-2) are in Appendix 3.

6.6.2. Historical Illness and Preexisting Conditions

Historical illnesses and preexisting conditions will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Historical illness/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 an end date prior to the date of informed consent.

Preexisting condition for Period 2 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. Pre-existing condition for subsequent treatment period is defined as those pre-existing conditions and AEs which are ongoing at the treatment period baseline. Notice 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 onwards.

The following summaries will be provided for Period 2 (ITT Population) and/or Period 3 (Extended Treatment Period Population):

- The number and percentage of patients with historical illnesses by treatment group and overall, by System Organ Class (SOC) and preferred term (ITT Population in Period 2 only).

- The number and percentage of patients with preexisting conditions and adverse events prior to first dose by treatment group and overall, by SOC and preferred term (ITT Population in Period 2 only).
- The number and percentage of patients with preexisting conditions and adverse events prior to first dose of extended period, by SOC and preferred term (Extended Treatment Period Population in Period 3 only).
- The number and percentage of patients with prespecified medical history (hypertension; diabetes mellitus, Type I; diabetes mellitus, Type II insulin dependent; diabetes mellitus, Type II non-insulin dependent; coronary artery disease; history of stroke; dyslipidemia; psoriatic arthritis) by treatment group and overall.

For 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.

6.7. Treatment Compliance

By-patient listings of randomization schedule for the ITT Population and study drug dispensed (include the CT Lot number) for the Safety Population will be provided.

Throughout treatment periods, randomized patients will record information in a Study Drug Administration Log (captured in the *Exposure as Collected* 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 per period will be calculated as:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ expected}$$

- For patients who complete Period 2, the number of injections expected during Period 2 will be equal to 5 (2 injections at Week 0 and 1 injection every 4 weeks from Week 4 to Week 12).
- For patients who complete Period 3, the number of injections expected during Period 3 will be equal to 10 (2 injections at Week 16 and 1 injection every 4 weeks from Week 20 to Week 48).
- For patients who discontinue during the treatment period, the number of injections expected during that period can be derived by considering the IWRS study drug dispense dataset and the treatment disposition date.
- The total number of injections administered will be derived using the response to the question "Was dose administered?" on the *Exposure as Collected* eCRF page.

A patient will be considered overall compliant with study treatment within each treatment period if he/she misses no more than 20% of the expected doses, does not miss 2 consecutive doses (all injections at an injection week are counted as 1 dose), and does not over-dose (that is, take more injections at the same time point than specified in the protocol).

Patient treatment compliance by treatment week and overall will be summarized for the Safety Population for Period 2 and for the Extended Treatment Period Population for Period 3.

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.

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 Period 2. 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 Period 2. If there is clear evidence to suggest that the therapy stopped prior to the first dose of study treatment in Period 2, the therapy will be assumed to be previous only.

The following summaries will be provided for the ITT population:

- Previous spondyloarthritis therapy captured in the *Prior Therapy: Axial Spondyloarthritis eCRF* page to be summarized according to type (non-biologic systemic agent, non-biologic non-systemic agent, TNF inhibitor) and therapy.
- The number and percentage of patients with each reason for discontinuation of previous spondyloarthritis therapy to be summarized by type and therapy.

6.8.2. Concomitant Therapy

Concomitant therapy for each treatment period is defined as the therapy that starts before, on, or after the first day of study treatment in the defined 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. 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.

The following summaries will be provided for Period 2 (ITT Population) and Period 3 (Extended Treatment Period Population):

- General concomitant therapy by WHO ATC Level 4 and WHO preferred term.
- Concomitant DMARDs, systemic corticosteroids, NSAID (including COX-2 inhibitors) and opioids. The definition of above medications is provided in Appendix 3.

6.9. Efficacy Analyses

Table RHCH.6.3 includes the description and derivation of the primary and secondary efficacy outcomes.

Sections 6.9.1, 6.9.2, 6.9.3, and 6.9.4 summarize the analyses for primary and secondary efficacy measures.

Table RHCH.6.4 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for major secondary outcomes.

Table RHCH.6.3. Description and Derivation of Primary and Secondary Efficacy Outcomes

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Assessment of Spondyloarthritis International Society 40 (ASAS40), ASAS20, ASAS Partial Remission, ASAS5/6: ASAS40, ASAS20, ASAS Partial Remission and ASAS5/6 are clinical responses derived based on the following ASAS domains (Sieper et al. 2009, ASAS Handbook): 1) Patient Global 2) Spinal Pain 3) Function 4) Inflammation (mean of BASDAI Q5 and Q6) 5) CRP 6) Spinal mobility (lateral spinal flexion)	ASAS40 **Primary Outcome**	The ASAS40 is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0–10) in ≥3 of the following 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain.	See Appendix 1 for derivation of observed response.
	ASAS20 **major secondary outcome**	An ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 units (range 0–10) in ≥3 of the following 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) and no worsening of 20% and ≥1 unit (range 0-10) in the remaining domain.	
	ASAS Partial Remission	ASAS partial remission is defined as a value not above 2 units (range 0-10, NRS) in each of the following 4 domains: Patient Global, Spinal Pain, Function, and Inflammation.	
	ASAS5/6	ASAS5/6 includes assessment of all 6 individual ASAS domains (Patient Global, Spinal Pain, Function, Inflammation, CRP, Spinal mobility) and represents improvement of ≥20% in at least 5 domains.	
Patient Global (Assessment of Disease Activity): From the ASAS handbook (Sieper et al. 2009), the patient is asked to respond to the following question: "How active was your spondylitis on average during the last week?"	Patient Global, NRS	Range: 0 to 10 "0" (not active) and "10" (very active).	Single item, missing if missing
Spinal Pain: From the ASAS handbook (Sieper et al. 2009), the patient is asked to respond to the following 2 questions (on average, last week):	Spinal Pain, NRS	Range: 0 to 10 "0" (no pain) and "10" (most severe pain). This question is used to derive response for ASAS40, ASAS20, ASAS5/6 and ASAS partial remission.	Single item, missing if missing

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
1. "How much pain of your spine due to ankylosing spondylitis do you have?" 2. "How much pain of your spine due to ankylosing spondylitis do you have at night?"	Spinal Pain at night, NRS	Range: 0 to 10 "0" (no pain) and "10" (most severe pain).	Single item, missing if missing
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): The BASDAI is an instrument consisting of 6 questions that relate to 5 major symptoms relevant to r-axSpA (Garrett et al. 1994; Sieper et al. 2009): 1) Fatigue 2) Spinal pain 3) Peripheral arthritis 4) Enthesitis 5) Intensity of morning stiffness 6) Duration of morning stiffness. Patients need to score each item with a score from 0 to 10 (NRS).	Inflammation	Calculated as: (Q5+Q6)/2 Range: 0 to 10 Q5: "0" (none) and "10" (very severe). Q6: "0" (0 hours) and "10" (≥2 hours).	Missing if both Q5 and Q6 are missing; If Q6 is missing, then use Q5 as inflammation score.
	BASDAI score BASDAI change from baseline – **major secondary outcome**	BASDAI = (Q1+Q2+Q3+Q4+inflammation)/5 Range: 0 to 10 "0" (none) and "10" (very severe).	If only Q6 is missing, BASDAI is average of the other 5 questions; missing BASDAI if more missing than just Q6.
	BASDAI50	BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline, ie, if the value of % improvement from baseline is ≥50, BASDAI50 is met.	Missing if observed value is missing (note: baseline BASDAI is part of inclusion criteria therefore should not be missing)
Bath Ankylosing Spondylitis Functional Index (BASFI): The BASFI establishes a patient's functional baseline and subsequent response to treatment (Calin et al. 1995). To complete the BASFI, a patient will be asked to rate the difficulty associated with 10 individual basic functional activities. Patients respond to each question using a NRS (range 0 to 10), with a higher score indicating worse functioning.	BASFI score BASFI change from baseline – **major secondary outcome**	BASFI score is the mean of the 10 item scores completed on a NRS Range: 0 to 10 "0" (easy) and "10" (impossible).	Missing if >20% scores (ie, >2 of the 10 item scores) are missing
High Sensitivity C-Reactive Protein (CRP):	CRP value	Lab values obtained from central lab	Missing if missing

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
High sensitivity CRP will be the measure of acute phase reactant. It will be measured with a high sensitivity assay at the central laboratory to help assess the effect of ixekizumab on disease activity.			

<table>
<tr><th>Measure / Description</th><th>Variable</th><th>Derivation / Comment</th><th>Imputation Approach if with Missing Components</th></tr>
<tr><td>Bath Ankylosing Spondylitis Metrology Index—Spinal Mobility (BASMI)
BASMI is a combined index comprising the following 5 clinical measurements of spinal mobility in patients with AS (Jenkinson et al. 1994).
• Lateral Spinal Flexion
• Tragus-to-wall distance
• Lumbar Flexion (modified Schober)
• Maximal intermalleolar distance
• Cervical rotation</td><td>BASMI Linear</td><td>The BASMI includes these 5 measurements which are each scaled to a score of 0-10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives the BASMI linear result (van der Heijde et al. 2008; Sieper et al. 2009).
<table><tr><th>Function</th><th>For</th></tr><tr><td>S = (21.1cm- A) / 2.1cm</td><td>Lateral Lumbar flexion (mean right/left)</td></tr><tr><td>S = (A-8cm) / 3cm</td><td>Tragus to wall distance</td></tr><tr><td>S = (7.4cm –A)/0.7 cm</td><td>Lumbar flexion (modified Schober)</td></tr><tr><td>S= (124.5 cm –A) /10cm</td><td>Maximal intermalleolar distance</td></tr><tr><td>S = (89.3° –A)/8.5°</td><td>Cervical rotation angle (mean right/left)</td></tr></table>The average score of the five assessments gives the BASMI linear result. The additional condition $0 \leq S \leq 10$ is always applied. A is the result of an assessment. When 2 readings are taken for each of above measures, the better of the two will be used (for tragus, the smaller number is better; for the other 4 measurements, the bigger number is better).</td><td>Missing if >20% measurements (ie >1 of the 5 clinical measurements) are missing.
If only 1 of 5 measurements missing, then averaging the other 4 nonmissing ones.
In some individual component (eg, lateral lumbar flexion) with left and right measurements, if one side (either left or right) is missing, the other nonmissing side will be used as the mean.</td></tr>
<tr><td>Chest Expansion:
While patients have their hands resting on or behind the head, the assessor will measure the chest encircled length by centimeter (cm) at the</td><td>Chest Expansion score</td><td>One score measured in centimeter (cm).
When 2 readings are taken, the better of the two numbers (bigger one) will be used.</td><td>Single item, missing if missing</td></tr>
</table>

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
fourth intercostal level anteriorly. The maximal inspiration and expiration in cm will be recorded. Two tries will be recorded in the source documents and will be entered into case report form (CRF).			
Occiput to Wall Distance: The patient is to make a maximum effort to touch the head against the wall when standing with heels and back against the wall. Then the distance from occiput to wall is measured. The better (smaller) measurement of two tries in cm (eg, 10.2 cm) is reported.	Occiput to Wall Distance score	One score measured in centimeter (cm). When 2 readings are taken, the better of the 2 numbers (smaller one) will be used.	Single item, missing if missing
Ankylosing Spondylitis Disease Activity Score (ASDAS): The ASDAS is a composite index to assess disease activity in AS (Machado et al. 2011a, 2011b; Zochling 2011). The parameters used for the ASDAS (with CRP as acute phase reactant): 1) Total back pain (BASDAI Q2) 2) Patient global 3) Peripheral pain/swelling (BASDAI Q3) 4) Duration of morning stiffness (BASDAI Q6) 5) CRP in mg/L	$ASDAS_{crp}$ $ASDAS_{crp}$ change from baseline - **major secondary outcome**	$ASDAS_{crp}$ (Sieper et al. 2009): 0.121 × total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(CRP+1) (Machado et al. 2015). C-reactive protein is in mg/liter, the range of other variables is from 0 to 10; Ln represents the natural logarithm.	Missing if any of the components is missing. If CRP <2 mg/L or below the limit of detection, then use 2 mg/L in the calculation (Machado et al. 2015).

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	ASDAS Disease Activity States	Four (4) disease activity states have been defined by ASAS consensus (Machado et al. 2011c, Machado 2018): • ASDAS <1.3 defines inactive disease • 1.3 ≤ ASDAS <2.1 defines low disease activity • 2.1 ≤ ASDAS ≤3.5 defines high disease activity • ASDAS >3.5 defines very high disease activity.	Set the disease activity state to worst state (ie, very high) if observed ASDAS score is missing
	ASDAS<2.1	Defined as ASDAS <2.1 (low or inactive disease activity)	
	Clinical important improvement	Defined as at least 1.1 unit change in ASDAS from baseline	Missing if baseline or observed ASDAS score is missing
	Major improvement	Defined as at least 2.0 unit change in ASDAS from baseline or reached the minimum of ASDAS score (0.6361) at postbaseline visit	
Maastricht Ankylosing Spondylitis Enthesitis Score (MASES): The MASES is an index used to measure the severity of enthesitis (Heuft-Dorenbosch et al. 2003). The MASES assesses 13 sites for enthesitis using a score of "0" for no activity, or "1" for activity. Sites assessed include: costochondral 1 (right/left), costochondral 7 (right/left), spinal iliaca anterior superior (right/left), crista iliaca (right/left), spinal iliaca posterior (right/left), processus spinosus L5, and Achilles tendon proximal insertion (right/left).	MASES	The MASES is the sum of all site scores. Range: 0 to 13, higher scores indicate more severe enthesitis 0 = no activity and not evaluable 1 = activity	Missing if >20% (ie, ≥3) sites are missing. If ≤20% missing, then imputed sum = sum of scores from nonmissing sites x 13/ no. of nonmissing sites
	MASES score = 0	MASES score = 0 refers to complete resolution in enthesitis. Analysis of MASES score = 0 only applies to patients with baseline enthesitis (MASES >0).	Missing if observed value is missing
	Heel Enthesitis score = 0	Heel Enthesitis score = 0 refers to Achilles tendon proximal insertion (right/left) = 0. Analysis of Heel Enthesitis score = 0 only applies to patients with baseline Heel Enthesitis score >0.	Missing if observed value is missing

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Non-Steroidal Anti-Inflammatory Drug (NSAID) Intake: Information regarding NSAIDs (including COX-2 inhibitors) intake will be collected in the eCRF and the ASAS-NSAID score will be calculated (Dougados et al. 2011).	Proportion of patients taking NSAID	Proportion of patients taking NSAID (including COX-2 inhibitors) at specified visit	NA
	ASAS -NSAID score	See Section 6.9.4.1 and Appendix 2 for details of deriving ASAS-NSAID score. ASAS-NSAID = 0 if no NSAID use	If NSAID dose is missing, the maximum efficacy dose (Appendix 2) is assumed. If frequency is missing, 'every day' intake is assumed.
	ASAS-NSAID50	$100 \times \frac{\text{Baseline ASAS-NSAID} - \text{Observed ASAS-NSAID}}{\text{Baseline ASAS-NSAID}}$ Proportion of patients with at least 50% decrease from baseline in ASAS-NSAID score. Derivation only applies to patients whose ASAS-NSAID is not equal to 0 at baseline.	
	ASAS-NSAID 10	Proportion of patients with ASAS-NSAID score <10	
	ASAS-NSAID 0	Proportion of patients with ASAS-NSAID score = 0	
SPARCC MRI score for Spine: All 23 disco-vertebral units (DVU) of the spine (from C2 to S1) are scored for bone marrow edema. A single DVU has 18 scoring units, and each has score of 0 or 1, bringing the maximum total score to 414, with higher scores reflecting worse disease (Maksymowych et al. 2005). Scoring will be performed by a central reader.	SPARCC Spine Score SPARCC spine score change from baseline – **major secondary outcome**	The SPARCC spine score is a sum of 414 scoring units over 23 DVUs; the sum ranges from 0 to 414.	see 'MRI Data Programming Guidance for AxSpA Studies' for missing rule and imputation method.
MRI Sacroiliac Joint (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] Score): Both left and right SIJ are scored for bone marrow edema. Each side has 6 slices and each slice has 6 scoring units, and each scoring unit has a score of 0 or 1. Total SIJ SPARCC scores	SPARCC SIJ Score	The SPARCC SIJ Score is sum of 72 scoring units; the sum ranges from 0 to 72;	see 'MRI Data Programming Guidance for AxSpA Studies' for missing rule and imputation method

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
can range from 0 to 72 with higher scores reflecting worse disease. Scoring will be performed by a central reader.			
Spondyloarthritis Research Consortium of Canada – SIJ Structure Score (SSS): Structural lesions in MRIs of the SIJ are assessed using the SPARCC SSS method for both left and right side. Each side has 5 slices. For fat metaplasia and bone erosion, each slice has 1 scoring unit in each of the 4 quadrants; for backfill and ankyloses, each slice has 1 scoring unit in each of the upper and lower half. Each scoring unit has score of 0 or 1. (Maksymowych et al. 2015). Scoring will be performed by central readers.	SPARCC SIJ SSS Score	For each feature, sum all corresponding scoring units. The sum ranges are fat metaplasia (0 to 40), erosions (0 to 40), backfill (0 to 20), and ankylosis (0 to 20).	see 'MRI Data Programming Guidance for AxSpA Studies' for missing rule and imputation method

Abbreviations: CRP = C-reactive protein; no. = number; NRS = numeric rating scale; Q = question; r-axSpA = radiographic axial spondyloarthritis; V = visit.

Table RHCH.6.4. Description of Primary and Secondary Efficacy Analyses

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
ASAS40	ASAS40 - **Primary**	Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM	ITT Population in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16	Primary analysis is logistic regression analysis with NRI for ITT Population in bDMARD-naïve patients comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.1). Other analyses are additional analyses of primary outcome (Section 6.9.3)
		Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2); Other analyses are additional analyses of primary outcome (Section 6.9.3)
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Per Protocol Set in bDMARD naïve patients; Per Protocol Set	IXE80Q4W vs. placebo at Week 16	Additional analyses of primary outcome (Section 6.9.3).
		KM analysis of time to first ASAS40 Response	ITT Population	IXE80Q4W vs. placebo during Period 2	Additional analyses of primary outcome (Section 6.9.3).
		Subgroup analyses	ITT Population	IXE80Q4W vs. placebo at Week 16	Subgroup Analysis (Section 6.12.1)
		Descriptive statistics of ASAS40 response rate	Extended Treatment Period Population	No comparison during period 3	Other secondary efficacy analyses for primary outcome (Section 6.9.4) This summary includes Extended Treatment Period Population overall and by ASAS40 response status (responder vs nonresponder) at Week 16 (Visit 8) (NRI)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics of ASAS40 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses for primary outcome (Section 6.9.4)
ASAS20	ASAS20 – **Major Secondary**	Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM	ITT Population;	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2). Other secondary efficacy analyses (Section 6.9.4).
		Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		KM analysis of time to first ASAS20 Response	ITT Population	IXE80Q4W vs. placebo during Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Subgroup analyses	ITT Population	IXE80Q4W vs. placebo at Week 16	Subgroup Analysis (Section 6.12.1)
		Descriptive statistics of ASAS20 response rate	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4). This summary includes Extended Treatment Period Population overall and by ASAS20 response status (responder vs nonresponder) at Week 16 (Visit 8) (NRI)
		Descriptive statistics of ASAS20 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
ASDAS	$ASDAS_{crp}$ change from baseline **(Major Secondary)**	MMRM	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is MMRM analysis for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2). Other secondary efficacy analyses (Section 6.9.4).
		ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4).
ASDAS	ASDAS Inactive Disease	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		KM analysis of time to first ASDAS inactive disease response	ITT Population	IXE80Q4W vs. placebo during Period 2	Other secondary efficacy analyses (Section 6.9.4).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics of ASDAS inactive disease response rate	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of ASDAS inactive disease response rate	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4)
	ASDAS <2.1 – **Major Secondary**	Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM	ITT Population;	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2). Other secondary efficacy analyses (Section 6.9.4)
		Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4)
		KM analysis of time to first ASDAS < 2.1	ITT Population	IXE80Q4W vs. placebo during Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of ASDAS <2.1 response rate	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics of ASDAS <2.1 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4)
	ASDAS clinical important improvement; major improvement	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of response rate	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of response rate	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4).
BASDAI	BASDAI50	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2). Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of BASDAI50 response rate	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics of BASDAI50 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4)
BASDAI	BASDAI change and % improvement from baseline (inclu. Inflammation) BASDAI change from baseline – **Major Secondary**	MMRM	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
BASFI	BASFI change from baseline **(Major Secondary)** and % improvement from baseline	MMRM	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is MMRM mean change analysis for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2). Other secondary efficacy analyses (Section 6.9.4).
		ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.9.4).
SPARCC Spine Score	SPARCC-Spine change from baseline - **Major Secondary**	ANCOVA with observed case analysis	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is ANCOVA with observed case analysis for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2).
		ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison at Week 52	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	ITT Population Who are Initially Randomized to Ixekizumab	No comparisons at Weeks 16 and 52	Other secondary efficacy analyses (Section 6.9.4).
SPARCC SIJ Score	SPARCC SIJ score change from baseline	ANCOVA with observed case analysis; ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison at Week 52	Other secondary efficacy analyses (Section 6.9.4).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
SPARCC SIJ Structural Score (SSS)	SPARCC SIJ SSS score change from baseline for each of the 4 features: fat metaplasia, bone erosion, backfill and ankylosis.	ANCOVA with observed case analysis; ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparisons at Week 52	Other secondary efficacy analyses (Section 6.9.4).
ASAS	ASAS5/6 and ASAS partial remission	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of ASAS5/6 response rate and ASAS partial remission	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
Patient Global	Patient Global change and % improvement from baseline	MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
Spinal Pain	Spinal Pain and Spinal Pain at night change and % improvement from baseline	MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
CRP	CRP change from baseline	MMRM	ITT Population; ITT Population in bDMARD-naïve patients; Per Protocol Set; Per Protocol Set in bDMARD-naïve patients	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
Mobility related measures	BASMI linear (incl. 5 components); chest expansion, occiput to wall distance change from baseline	MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
Enthesitis Scores	MASES change from baseline	MMRM	ITT Population with Baseline MASES >0	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of change from baseline	Extended Treatment Period Population with Baseline MASES >0	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.9.4).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
	MASES score = 0	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population with Baseline MASES >0	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of MASES = 0	Extended Treatment Period Population with Baseline MASES >0	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
	Heel Enthesitis Score = 0	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population with Baseline Heel Enthesitis Score >0	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.9.4).
		Descriptive statistics of MASES = 0	Extended Treatment Period Population with Baseline Heel Enthesitis Score >0	No comparison during Period 3	Other secondary efficacy analyses (Section 6.9.4).
NSAID (including COX-2 inhibitors) Intake	Proportion of patients taking NSAID (including COX-2 inhibitors)	Descriptive statistics	Extended Treatment Period Population	At Weeks 16, 20, 24, 28, 32, 36, 44, 52.	Analyses on NSAID intake (Section 6.9.4.1)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
	Change from baseline in ASAS-NSAID	Descriptive statistics	Extended Treatment Period Population who have NSAID (including COX-2 inhibitor) intake at baseline	At Weeks 16, 20, 24, 28, 32, 36, 44, 52.	Analyses on NSAID intake (Section 6.9.4.1)
	ASAS-NSAID50; ASAS-NSAID 10; ASAS-NSAID 0	Descriptive statistics	Extended Treatment Period Population who have NSAID (including COX-2 inhibitor) intake at baseline	At Weeks 16, 20, 24, 28, 32, 36, 44, 52.	Analyses on NSAID intake (Section 6.9.4.1)

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = C-reactive protein; ITT = intent-to-treat; IXE80Q4W = ixekizumab 80 mg every 4 weeks; KM = Kaplan-Meier; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; NSAID = nonsteroidal anti-inflammatory drug.

6.9.1. Primary Outcome and Methodology

The primary outcome is the proportion of patients achieving ASAS40 at Week 16 (Visit 8) in bDMARD-naïve patients. The primary outcome related to improvement in symptomatic feature of AxSpA are assessed at Week 16 (Visit 8) prior to placebo patients being switched to ixekizumab during Period 3 (Extended Treatment Period).

The primary analysis will be based on the ITT Population in bDMARD-naïve patients for the Blinded Treatment Dosing Period (Period 2) comparing the ixekizumab treatment group and placebo at Week 16 (Visit 8). The primary analysis is a logistic regression analysis with treatment and baseline CRP status in the model (Section 6.1.1).

Table RHCH.6.4 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for primary outcome.

6.9.2. Major Secondary Efficacy Analyses

The major secondary outcomes at Week 16 (Visit 8) are:

- Proportion of patients achieving an ASAS40 response in overall population
- Proportion of patients achieving an ASAS20 response in overall population
- Change from baseline in ASDAS in overall population
- Change from baseline in BASDAI in overall population
- Change from baseline in BASFI in overall population
- Proportion of patients achieving ASDAS < 2.1 in overall population
- Change from baseline in MRI SPARCC spine score in overall population
- Change from baseline in SF-36 PCS in overall population*

*Detailed descriptions and analyses on SF-36 PCS are described in Table RHCH.6.5 and Table RHCH.6.6.

The major secondary analysis will be based on the ITT Population for Period 2 comparing the ixekizumab treatment group and placebo at Week 16 (Visit 8).

The primary analysis for categorical major secondary outcomes is a logistic regression analysis with treatment, baseline CRP status and TNF inhibitor experience in the model (only in overall population, Section 6.1.1). Missing data will be imputed using the NRI method (Section 6.3.1).

The primary analysis for continuous major secondary outcomes (except MRI SPARCC spine score) is an MMRM analysis with treatment, baseline CRP status, TNF inhibitor experience, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors (Section 6.1.1).

The primary analysis for change from baseline in MRI SPARCC spine score is an observed case analysis using ANCOVA with treatment, baseline CRP status, TNF inhibitor experience, and baseline value in the model (Section 6.1.1). Only patients with both baseline and Week 16 SPARCC spine score will be included in the analysis.

These major secondary comparisons will be tested based on the graphical multiple testing procedure detailed in Section 6.4.

Table RHCH.6.4 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for major secondary outcomes.

6.9.3. Additional Analyses of the Primary Outcome

There will be no adjustment for multiple comparisons for additional analyses of the primary outcome, ASAS40.

To support the primary outcome analysis, ASAS40 will be analyzed based on the PPS Population in bDMARD-naïve and overall patients for Period 2 at Week 16 (Visit 8) using a logistic regression analysis with treatment, baseline CRP status, and TNF inhibitor experienced or naïve (only in overall patients) in the model (Section 6.1.1). Missing data will be imputed using the NRI method (Section 6.3.1).

Figures showing the proportion of patients achieving an ASAS40 response at each scheduled visit during Period 2 within each treatment group will be provided.

Time to first ASAS40 response will be assessed based on the ITT Population during Period 2 as described in Section 6.1.1.

Please see Table RHCH.6.4 for details of the additional analyses on primary outcome.

6.9.4. Other Secondary Efficacy Analyses

There will be no adjustment for multiple comparisons for other secondary efficacy analyses.

The other secondary efficacy variables for secondary objectives will be done on:

- ASAS40, ASAS20, ASAS5/6 and partial remission, BASDAI50
- ASDAS inactive disease, ASDAS<2.1, cinically important improvement and major improvement
- Change from baseline in:
    - individual components of the ASAS criteria (patient global, spinal pain, function, inflammation, CRP, and spinal mobility [lateral spinal flexion])
    - BASDAI and inflammation (mean of Q5 and Q6 on BASDAI)
    - ASDAS, BASFI, CRP
    - mobility (BASMI linear and individual components, chest expansion, occiput to wall distance)
    - MRI SPARCC spine score; MRI SPARCC SIJ structural score (SSS) for each of the 4 features: fat metaplasia, bone erosion, backfill and ankyloses; MRI SPARCC SIJ score; enthesitis score (MASES)
    - ASAS-NSAID score (apply to Period 3 analysis only, Section 6.9.4.1)

Treatment comparisons of ixekizumab treatment group and placebo at Week 16 (Visit 8) and all other postbaseline visits during Period 2 will be provided.

Descriptive statistics (that is, no inferential testing) will be provided during Period 3, or Combined Periods 2 and 3, as applicable.

Table RHCH.6.4 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for other secondary outcomes.

6.9.4.1. Analyses on NSAID Intake

ASAS-NSAID score is used to present the NSAID (including COX-2 inhibitor) intake by considering the type of NSAID, the total daily dose, and the number of days on which NSAID has been taken during a period of interest (Dougados et al. 2011). Appendix 2 provides the equivalent dose of each NSAID compared to 150 mg diclofenac (Dougados et al. 2011), additional equivalent scores are listed below:

For the NSAID equivalent scoring system, 0 = no intake, 100 = 150 mg diclofenac, 1000 mg naproxen, 200 mg aceclofenac, 400 mg celecoxib, 600 mg etodolac, 90 mg etoricoxib, 200 mg flurbiprofen, 2400 mg ibuprofen, 150 mg indometacin, 200 mg ketoprofen, 15 mg meloxicam, 200 mg nimesulide, 400 mg phenylbutazone, 20 mg piroxicam, 20 mg tenoxicam (Dougados et al. 2011). Additionally, 100 = 180 mg acemetacin, 3600 mg acetylsalicylic acid, 3600 mg salicylic acid, 32 mg lornoxicam, 360 mg loxoprofen, 1000 mg mefenamic acid, 2000 mg nabumetone, 1000 mg niflumic acid, 600 mg tiaprofenic acid, 90 mg pelubiprofen, 240 mg zaltoprofen, 120 mg ketorolac tromethamine (if used intramuscularly [IM] or intravenous [IV]), 40 mg ketorolac tromethamine (if used orally), 120 mg ketorolac (if used intramuscularly [IM] or intravenous [IV]), 40 mg ketorolac (if used orally), 400 mg sulindac, 1200 mg dexibuprofen, 75 mg dexketoprofen, 1110 mg talniflumate. For Vimovo, esomeprazole strontium w/naproxen, esomeprazole w/naproxen and naproxen w/omeprazole, use the score for naproxen; for caffeine with ibuprofen, CAROL-F, and famotidine w/ibuprofen, use the score for ibuprofen; for Dioxaflex Protec and Arthrotec, use the score for diclofenac; for anacin/00141001/, use the score for acetylsalicylic acid; for paynocil, use the score for salicylic acid.
The general formula for calculating ASAS-NSAID score is:
(equivalent NSAID score)x (days of intake during period of interest) x (days per week)/(period of interest in days).

A score is assigned depending on the frequency of NSAID use per week (Dougados et al. 2011): 7/7: everyday use; 6/7: >5 days/week; 4/7: >3 to ≤5 days/week; 2/7: >1 to ≤3 days/week; 0.5/7: ≤1 day/week; 0: no intake.

For example (Dougados et al. 2011), if during a period of interest (between two visits) of 6 months, if the patient has taken piroxicam 20 mg during the first 4 months on 3-5 days per week and has used 10 mg piroxicam during the remaining 2 months on 2 days a week, the ASAS-NSAID score for the first 4 months is:
100 (20 mg piroxicam score) × 120 (4 months) × 4/7 (3–5 days/ week)/180 (6 months) = 38.1

the ASAS-NSAID score for the remaining 2 months is:
50 (10 mg piroxicam score) ×60 (2 months) × 2/7 (2–3 days/week)/180 (6 months) = 4.8

The total score for the 6 month period is 42.9 (38.1 plus 4.8).

ASAS-NSAID score will be summarized for the following endpoints at baseline Week 0 (when applicable) and each scheduled visit of interest, which includes the timeframe after the date of previous visit to the date of current visit:

- Change from baseline in ASAS-NSAID
- ASAS-NSAID50, ASAS-NSAID 10, ASAS-NSAID 0.

In addition, proportion of patients taking NSAID at specified visit will be summarized.

6.9.5. Sensitivity Analyses

6.9.5.1. Multiple Imputation

The primary and key categorical secondary endpoints at Week 16 (Visit 8) may be analyzed based on the ITT Population and ITT Population in bDMARD-naïve patients using the multiple imputation (MI) method, as described in Section 6.3.3. Analyses for categorical endpoints will be based on the logistic regression analysis with include treatment, baseline CRP status and TNF inhibitors experience in the model (Section 6.1.1).

6.9.6. Additional Exploratory Analyses

Exploratory analyses like including additional covariates (e.g. pooled sites) in the logistic regression, MMRM or categorical MMRM analysis may be explored. Potential protocol deviations that might have impact on treatment effect including but not limited to the ones in IPD list may also be considered for further excluding from PPS for sensitivity analysis.

6.9.7. Health Outcomes/Quality-of-Life Analyses

The health outcomes and quality of life (QOL) measures are ASAS-HI, SF-36, FACIT-Fatigue, WPAI-SpA and EQ-5D-5L.

The analyses of health outcomes and QOL measures for Period 2 will be based on the ITT Population. Descriptive statistics will be provided for Period 3 based on the Extended Treatment Period Population.

Table RHCH.6.5 includes the description and derivation of the health outcomes and QOL measures.

Table RHCH.6.6 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for health outcomes and QOL analyses.

Table RHCH.6.5. Description and Derivation of Health Outcomes and Quality-of-Life Measures

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
ASAS Health Index: The ASAS-Health Index (ASAS-HI) is a disease specific health-index instrument designed to assess the impact of interventions for SpA, including axSpA. The 17 item instrument has scores ranging from 0 (good Health) to 17 (poor Health) (Kiltz et al. 2013). Each item consists of 1 question that the patient needs to respond to with either "I agree" (score 1) or "I do not agree (score 0)." A score of "1" is given where the item is affirmed, indicating adverse health.	ASAS-HI	All item scores are summed to give a total score or index. Range: 0 to 17 0 (good health) and 17 (poor health) Note, items # 7 and #8 may not be applicable for some patients. For those patients who ticked the response "not applicable", the sum score is analyzed based on n=16 or n=15, respectively.	If ≥ 4 items (>20%) have missing response, then ASAS-HI is missing. If <4 items (≤20%) missing, then imputed sum = sum of scores from nonmissing items x n/ (n - no. of missing items), where n is the total number of applicable items, e.g. 15, 16, or 17. [ASAS Health Index User Manual (WWW)].
Medical Outcomes Study 36-item Short-Form Health Survey: The SF-36 is a 36-item patient-administered measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role – physical, role – emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the Mental Component Summary and Physical Co mponent Summary scores. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute version) will be used, which utilizes a 1-week recall period (Ware [2000]).	8 associated domain scores: • Physical Functioning, • Role Physical, • Bodily Pain, • General Health, • Vitality, • Social Functioning, • Role Emotional, • Mental Health 2 component Scores: • MCS Score • PCS Score PCS change from baseline – **Major Secondary**	Per copyright owner, the Quality Metric Health Outcomes™ Scoring Software will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will re-calibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (t-scores) using the 1-week recall period. The summary scores range from 0 to 100.	If an item is missing, there will be imputation conducted by the Scoring Software.

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Functional Assessment of Clinical Illness Therapy Fatigue (FACIT-Fatigue) Scale: The FACIT-Fatigue scale (Cella and Webster 1997) is a 13-item symptom-specific questionnaire that assesses the self-reported severity of fatigue and its impact upon daily activities and functioning.	FACIT-Fatigue total score	The FACIT-Fatigue uses 0 ("not at all") to 4 ("very much") numeric rating scales to assess fatigue and its impact in the past 7 days. Scores range from 0 to 52 with higher scores indicating less fatigue. The FACIT-Fatigue Scoring Guidelines (Version 4) will be used to calculate the Total Score. Reversals are needed for all items except An5 and An7, as described in scoring manual. http://www.ser.es/wp-content/uploads/2015/03/FACIT-F_INDICE.pdf	Missing items are acceptable as long as more than 50% of the items are answered (i.e., a minimum of 7 out of 13 items), the sum of available items will be divided by the number of items answered to obtain the total score. If less than 7 items are answered, the FACIT-Fatigue total score will be set to missing.
Work Productivity and Activity Impairment Questionnaire—Spondyloarthritis: The Work Productivity and Activity Impairment—Spondyloarthritis (WPAI-SpA) consists of 6 questions to determine employment status, hours missed from work because of spondyloarthritis, hours missed from work for other reasons, hours actually worked, the degree to which spondyloarthritis affected work productivity while at work, and the degree to which spondyloarthritis affected activities outside of work. The WPAI-SpA has been validated in the AS patient population (Reilly et al. 2010). Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment.	percentage of absenteeism	% work time missed due to problem: (Q2/(Q2 + Q4))*100	if Q2 or Q4 is missing, then missing
	percentage of presenteeism	% impairment while working due to problem: (Q5/10)*100	if Q5 is missing, then missing
	overall work impairment score	% overall work impairment due to problem: (Q2/(Q2+ Q4) + [(1-Q2/(Q2+Q4))*(Q5/10)])*100	if any of Q2, Q4, or Q5 is missing, then missing
	percentage of impairment	% activity impairment due to problem: (Q6/10)*100	if Q6 is missing, then missing

Measure / Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
European Quality of Life – 5 Dimensions 5 Level: EQ-5D-5L: is a standardized measure of health status used to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: item 1: mobility item 2: self-care item 3: usual activities item 4: pain/discomfort item 5: anxiety/depression The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled 100 = "best imaginable health state" and 0 = "worst imaginable health state".	EQ-5D mobility EQ-5D self-care EQ-5D usual activities EQ-5D pain/discomfort EQ-5D anxiety/depression	Five health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems 5 = extreme problems It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a primary score	Each dimension is a single item, missing if missing
	EQ-5D-5L UK Population based index score	Derive EQ-5D-5L UK Population-based index score according to the link by using the UK algorithm (Szende et al. 2007) to produce a patient-level index score between -0.59 and 1.0 (continuous variable): https://euroqol.org/wp-content/uploads/2018/02/EQ-5D-5L_Crosswalk_Value_Sets.xls	If any of the items is missing, the index score is missing
	EQ-5D-5L Chinese Population based index score	Derive EQ-5D-5L Chinese Population-based index score (Luo et al. 2017) to produce a patient-level index score between 0 and 1: https://ars.els-cdn.com/content/image/1-s2.0-S1098301516341250-mmc1.xls	If any of the items is missing, the index score is missing
	EQ-5D VAS	Range from 0 = "worst imaginable health state" to 100 = "best imaginable health state". Note: higher value indicates better health state.	Single item, missing if missing

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; MCS = mental component summary; NRS = numeric rating scale; PCS = physical component summary.

Table RHCH.6.6. Description of Health Outcomes and Quality-of-Life Analyses

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
36 item Short Form Health Survey (SF-36)	PCS change from baseline **Major Secondary**	MMRM; ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Major secondary analysis is MMRM analysis for ITT Population comparing IXE80Q4W vs. placebo at Week 16 (Section 6.9.2). Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics of change from baseline	ITT Population Who are Initially Randomized to Ixekizumab	No comparison during Combined Periods 2 and 3	Health Outcomes/QOL analyses (Section 6.9.7).
	MCS and domain scores change from baseline	MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).
ASAS Health Index (ASAS-HI)	change from baseline	MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale	change from baseline	MMRM	ITT Population	IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics	Extended Treatment Period Population	No comparison during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).
Work Productivity and Activity Impairment Questionnaire—Spondyloarthritis	Change from baseline in: • percentage of absenteeism • percentage of presenteeism • overall work impairment score • percentage of impairment	ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16 in Period 2	Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparison during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).
European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L)	EQ-5D mobility, EQ-5D self-care, EQ-5D usual activities, EQ-5D pain/discomfort, EQ-5D anxiety/depression	For category "no problem": Logistic regression with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q4W vs. placebo at Week 16 in Period 2	Health Outcomes/QOL analyses (Section 6.9.7).
		Descriptive statistics of each category and proportion of patients with "no problems"	Extended Treatment Period Population	No comparison during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
	Change from baseline in EQ-5D-5L UK EQ-5D-5L Chinese index	ANCOVA with mBOCF	ITT Population	IXE80Q4W vs. placebo at Week 16 in Period 2	Health Outcomes/QOL analyses (Section 6.9.7).
	Population-based index scores, EQ-5D VAS	Descriptive statistics of change from baseline	Extended Treatment Period Population	No comparision during Period 3	Health Outcomes/QOL analyses (Section 6.9.7).

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; IXE80Q4W = ixekizumab 80 mg every 4 weeks; ITT = intent-to-treat; mBOCF = modified baseline observation carried forward; MCS = mental component summary; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; PCS = physical component summary; QOL = quality of life.

6.10. Pharmacokinetic/Pharmacodynamic Methods

Details of pharmacokinetic/pharmacodynamics (PK/PD) analyses can be found in a separate PK/PD analysis plan.

6.11. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, QIDS-SR16, and C-SSRS. The duration of treatment exposure will also be summarized.

Safety analyses will be conducted for each period separately, including Period 4 (Follow-up Period). In addition, safety data on ixekizumab will be summarized for All Ixekizumab Exposures Safety Population who had at least 1 dose of ixekizumab.

For safety analyses, the following baselines will be used:

- Treatment-emergent adverse events (TEAEs): baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Change from baseline to last observation and each scheduled postbaseline visit for laboratory and vital signs: baseline will be last non-missing assessment recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Treatment-emergent abnormal laboratory and vital signs: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Change from baseline to minimum or maximum: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).

6.11.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group for Safety Population during Period 2 and Extension Period Population for Period 3 using descriptive statistics. Exposure for All Ixekizumab Exposures Safety Population during Combined Periods 2 and 3 will be provided.

The duration of exposure will be calculated as:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ Treatment\ Period \\ &\quad - Date\ of\ first\ dose\ in\ Treatment\ Period + 1 \end{aligned}$$

The number and percentage of patients in each of the following categories will be included in the summaries:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days (for Period 3, add ≥150 days, ≥183 days, ≥210 days, and ≥273 days; for Combined Periods 2 and 3, add ≥150 days, ≥183 days, ≥365 days). Note that patients may be included in more than 1 category.
- >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 days (for Period 3, change ≥120 days to ≥120 to <150 days, add ≥150 to

<183 days, ≥183 to <210 days, ≥210 to <273 days, and ≥273 days; for Combined Periods 2 and 3, change ≥120 days to ≥120 to <150 days, add ≥150 to <183 days, ≥183 to <365 days, ≥365 days).

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

$$Total\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ of\ exposures\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

- Mean and median total dose. Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose. For those randomized to ixekizumab 80 mg Q4W, the total dose (in mg) taken during Period 2 or 3 will be calculated as follows:

$$Total\ Period\ 2\ or\ 3\ dose\ for\ patients\ on\ \text{ixekizumab}\ 80\ mg\ Q4W = Total\ number\ of\ active\ injections\ (including\ loading\ doses, if\ any)\ received\ in\ Period\ 2\ or\ 3 \times 80$$

- Total number of injections received will be derived using the response to the question "Was dose administered?" on the *Exposure as Collected* eCRF page and the actual dose description from IWRS study drug dispense dataset.

6.11.2. Adverse Events

Adverse events (AEs) will be classified based upon the latest version of the MedDRA. Adverse events will be recorded at every study visit. Any condition starting on or after the date of informed consent will be considered an AE. Any preexisting condition which worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the *Adverse Event (AE)* eCRF page from the date of worsening onwards.

A treatment-emergent adverse event (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 defined treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. Treatment-emergent AEs will be assigned to the study period to which it's considered treatment-emergent:

- The MedDRA lowest level term (LLT) will be used when classifying AEs as treatment-emergent.
- The maximum severity recorded for each LLT prior to the first dose date/time in the treatment Period will be used as the pre-treatment severity for that LLT. If an event during the baseline period has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the postbaseline level of severity. Events with a missing severity during the treatment period will be considered treatment-emergent.

- AEs with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date/time in the treatment period (ie, a patient has no preexisting conditions with that lowest level term), or if the severity is greater than the pre-treatment severity for that lowest level term. If a partial AE start date/time is present, the date/time will be compared as far as possible to the treatment start date/time in order to determine whether the event is treatment-emergent or not. If there is any doubt, the event will be flagged as treatment-emergent.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Visit 17 (that is, Week 52) or the ETV:

- The MedDRA LLT will be used when classifying AEs as follow-up emergent.
- For AEs that are ongoing at the date of Visit 17 or ETV, the maximum severity recorded for each LLT on or prior to the date of Visit 17 or ETV will be used as the follow-up baseline severity for that LLT.

Adverse events and TEAEs will be summarized for the following study periods and analysis populations:

- Period 2 (Safety Population)
- Period 3 (Extended Treatment Period Population)
- Combined Periods 2 and 3 on ixekizumab treatment only (All Ixekizumab Exposures Safety Population)

The following summaries/analyses will be performed for all the populations above:

- An overall summary of AEs including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, SAE, TEAE possibly related to study treatment, discontinuations from the treatment due to an AE, and TEAEs of special interest.

The following summaries will be provided for selective populations above:

- TEAE by system organ class (SOC) and preferred term (PT).
- TEAE by PT.
- TEAE by maximum severity, SOC, and PT.

Follow-up emergent adverse events will be summarized for the Follow-Up Population for Period 4:

- FEAE by PT.

In general, for all AE-related summaries, the number and percentage of patients experiencing the events will be presented by treatment group. In general, events will be ordered by decreasing frequency in the ixekizumab Q4W, and then in placebo (when applicable) group, within SOC and/or PT for sorting. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

A by-patient listing of all AEs for safety population will be provided.

6.11.2.1. Common Adverse Events

Common TEAEs are those TEAEs that occurred in ≥1% before rounding of total ixekizumab treated patients.

The following summaries will be provided for common TEAEs based on the Safety Population for Period 2:

- Common TEAEs by PT

6.11.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

By-patient listings of deaths, SAEs, and AEs leading to discontinuation will be provided, respectively.

All deaths will be included, regardless of the investigator's or the sponsor's judgment about causality, including:

- any deaths occurring during participation in the study in the database for which data are being presented
- any deaths occurring after a patient leaves (is discontinued from or completed) the study in the database for which data are being presented if the death is:
    - the result of a process initiated during the study, regardless of when it actually occurred, or
    - occurs during the Period 4 after discontinuation of study drug.

An SAE is any AE that results in one of the following outcomes: death, life-threatening, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly or birth defect, or any other serious/important medical events.

The following summary tables will be provided for the Safety Population for Period 2, and for the Extended Treatment Period Population for Period 3, as well as Combined Periods 2 and 3 for All Ixekizumab Exposures Safety Population:

- SAEs by PT
- AEs that lead to treatment discontinuation (including death) by PT.

A follow-up emergent serious adverse event (FESAE) is defined as an SAE that first occurred or worsened in severity after the date of Visit 17 (that is, Week 52) or the ETV. The following summary tables will be provided for the Follow-Up Population for Period 4:

- FESAE by PT

6.11.3.1. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AEs of special interest (AESI) will be presented by treatment group and by study period. Table RHCH.6.7 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. For final analysis, the most current version of PSAP will be used, including PSAP released after SAP finalization but before database lock.

For Period 3, summaries will be provided for the Extended Treatment Period Population. In addition, for Combined Periods 2 and 3 on ixekizumab treatment only, selective summaries will be provided for the All Ixekizumab Exposures Safety Population.

In general, AESI summary will not be provided for Follow-Up Population during Period 4 except hepatic laboratory tests.

Table RHCH.6.7. Definitions and Analyses of Special Safety Topics including Adverse Events of Special Interest

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 Medical Dictionary for Regulatory Activities (MedDRA) PTs contained in any of the following standardized MedDRA query (SMQ) or sub-SMQ as defined in MedDRA: • 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)	**Period 2 (Fisher's exact test), Period 3 (Summary), Combined Periods 2 and 3 (Summary):** TEAE by PT within SMQ or sub-SMQ. **Listing:** TEAE (included in the same listing with cytopenia, depression and interstitial lung disease AESIs)
	Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using Performing Lab Reference Ranges are defined as: • Include scheduled visits, unscheduled visits, and repeat measurements. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST): maximum postbaseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing Lab upper limit of normal (ULN) for all patients with a postbaseline value. o The analysis of 3× ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN, or missing. o The analysis of 5× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN, or missing. o The analysis of 10× ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN, or missing. o The analysis of 20× ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN to <20× ULN, ≥20× ULN, or missing. • Total bilirubin: maximum postbaseline measurement ≥1.5 times (1.5×), and ≥2 times (2×) the Performing Lab ULN for all patients with a postbaseline value o The analysis of 1.5× ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN, or missing.	**Period 2 (Fisher's exact test), and Period 3 (Summary):** Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum postbaseline category

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	○ The analysis of 2× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN to <2× ULN, ≥2× ULN, or missing. • Alkaline phosphatase (ALP): maximum postbaseline measurement >1.5 times (1.5×) the Performing Lab ULN for all patients with a postbaseline value, and divided into 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to ≤1.5× ULN, >1.5× ULN, or missing.	
	Shift for ALT, AST, ALP and total bilirubin from maximum baseline to maximum postbaseline will be produced with the requirements using Performing Lab Reference Ranges: • Include scheduled visits, unscheduled visits, and repeat measurements. • Use the maximum non-missing value in the baseline period. • Use the maximum non-missing postbaseline value within each study period. • Categories are: ○ 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× ULN, ≥2× ULN ○ ALP: ≤1× ULN, >1 to ≤1.5× ULN, >1.5× ULN • With additional categories: ○ Decreased: postbaseline category < baseline category ○ Increased: postbaseline category > baseline category ○ Same: postbaseline category = baseline category	**Period 2, Period 3 (Summary)** : Shifts from maximum baseline to maximum postbaseline category
	Elevated hepatic criteria: maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN using Performing Lab Reference Ranges. Listing of patients who meet any of the following criteria: • Elevated hepatic criteria: defined as maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN • An ALT or AST ≥3× ULN • An alkaline phosphatase (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.	**Period 2 (Fisher's exact test), Period 3, and Period 4 (Summary)**: Elevated hepatic criteria **Listing**: Elevations in hepatic laboratory tests

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot: use maximum ALT measurement and maximum total bilirubin measurement with patients having at least one postbaseline ALT and total bilirubin, which contributes one point to the plot. The measurements do not need to be taken at the same blood draw.	**Period 2**: eDISH plot (to be prepared in Spotfire)
Cytopenias	Cytopenias are defined using the PTs from the following 2 sub-SMQs of the Haematopoietic cytopenias SMQ (20000027) as specified in MedDRA: • Broad and narrow terms in the Haematopoietic leukopenia (20000030) • Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031)	**Period 2 (Fisher's exact test) and Period 3 (Summary)**: **Combined Periods 2 and 3 (Summary)**: TEAE by PT within sub-SMQ **Listing:** TEAE (included in the same listing with hepatic, depression and interstitial lung disease AESIs)
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, antivirals, antifungals, antiparasitic treatments).	**Period 2 (Fisher's exact test), Period 3 (Summary), Combined Periods 2 and 3 (Summary)**: SAE by PT
	Anti-infective medications are defined in LY2439821 PSAP v8 Appendix 5 (or most current version) including antibiotics, antifungals, antivirals, or antiprotozoals. Listing of patients experiencing a TEAE of infections will be provided including the following additional information: anti-infective medications use (if treated) with medication start/end dates, indication for use, and route; minimum postbaseline value within treatment Period 2 for leukocytes, platelets, lymphocytes, and absolute neutrophils.	**Listing:** TEAE with anti-infective medications.

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	The list of MedDRA terms used to identify infections that are predefined as potential OIs are found in the LY2439821 PSAP v8 Appendix 10 (or most current version). This list contains PTs as contained within categories (narrow or broad) from the Infections and infestations SOC and the Investigations SOC which can assist in identifying potential OIs. The narrow terms are considered OIs 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. Listing of patients experiencing a TEAE of OIs will be provided including the following additional information: type of infection, causative pathogen(s) identified through laboratory testing (Yes/No).	**Period 2 (Fisher's exact test) , Period 3 and Combined Periods 2 and 3 (Summary):** TEAE of OIs by maximum severity by PT **Listing:** TEAE of OIs
	The duration of each common (≥1% of total ixekizumab) TEAE PT of Infections, and duration of narrow terms for Opportunistic infections are defined as: Duration of treatment-emergent AE Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7. Only TEAEs of infections beginning during treatment Period 2 or Period 3 will be included in the summary. If an AE has not ended by the date of completion of the treatment periods 2or 3, or date of early discontinuation, it will be censored as of that date (last visit within the treatment period 2 or treatment period 3, or date of early discontinuation). 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.	**Period 2 (Summary):** Duration of Common TEAE – Infections
Allergic Reactions/Hy-persensitivities	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. Allergic Reactions/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 criteria: 1) designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). 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	**Period 2 (Fisher's exact test), and Period 3 (Summary):** TEAE by maximum severity by PT within Category, SAE by PT within Category, **Combined Periods 2 and 3 (Summary):** TEAE by maximum severity by PT within Category

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• Kounis Syndrome • Type 1 hypersensitivity 2) to identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 2 for anaphylaxis requires having TEAEs from two or more of four categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident; based on recording of events on CRFs. All qualifying event 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 the LY2439821 PSAP v8 Appendix 6 (or most current version). 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.	

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	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. 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 (or overall) treatment-emergent anaphylactic AE will be based on the maximum severity within Criterion 1 and/or Criterion 2. 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 the LY2439821 PSAP v8 Appendix 7 (or most current version) and excluding the anaphylactic events as defined above.	
	A by-patient listing will be provided for all patients experiencing TEAE of allergic reactions/hypersensitivities at any time, including status/criterion of anaphylaxis or non-anaphylaxis, and the associated information collected on *Hypersensitivity and Anaphylactic Reaction* eCRF page if identified by the investigator.	**Listing:** TEAE including information collected on *Hypersensitivity and Anaphylactic Reaction* eCRF page
Injection Site Reactions	Injection site reaction is defined using the PTs from the MedDRA HLT of injection site reactions as specified by MedDRA excluding the following 10 PTs: 1) Embolia cutis medicamentosa 2) Injection site joint discomfort 3) Injection site joint effusion 4) Injection site joint erythema 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. These TEAEs will be summarized within the MedDRA HLT by maximum severity or category. If more than one TEAE of injection site reaction occurs, the event with the worst value (within the individual categories: redness, swelling and pain) will be used. Redness (Scored 0-4) • [0] Subject's normal skin color, no increased redness • [1] Noticeable, but very mild redness • [2] Clearly red	**Period 2 (Fisher's exact test) and Period 3 (Summary)**: TEAE by maximum severity by PT within HLT, SAE by PT within HLT, TEAE identified by the investigator PT within HLT: by maximum severity, by maximum redness category, by maximum swelling category, by maximum pain category **Combined Periods 2 and 3 (Summary)**: TEAE by maximum severity by PT within HLT SAE by PT within HLT **Listing:**

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• [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 • [4] Clear bump 2 mm thick or more Pain (including burning) (Scored 0-3) • [0] None • [1] Mild • [2] Moderate • [3] Severe	TEAE including information collected on *Injection Site Reaction* eCRF page

Cerebro-cardiovascular Events	Cerebro-cardiovascular events will be externally adjudicated by the Central Events Committee (CEC) at the Cleveland Clinic, as outlined in the Manual of Operations. 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), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient documentation for confirmation of an event. All events which qualify for CEC adjudication will be used for the analysis of cerebro-cardiovascular events. The categories and subcategories of adjudicated events used for the analysis will include the following:
	• Cardiovascular
	  o Death (Cardiovascular)
	  o Cardiac Ischemic Event: Myocardial Infarction and Hospitalization for Unstable Angina
	  o Serious Arrhythmia
	  o Hospitalization for Heart Failure
	  o Hospitalization for Hypertension
	  o Resuscitated Sudden Death
	  o Cardiogenic Shock
	  o Coronary Revascularization
	• Neurologic
	  o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Hemorrhagic, Ischemic and Undetermined)
		Period 2 (Fisher's exact test), Period 3 and Combined Periods 2 and 3 (Summary):
		TEAE by PT within Subcategory
		
		Listing:
		TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing

	• Peripheral Vascular Events
	  o Peripheral Arterial Event
	  o Peripheral Revascularization
	Events will be analyzed using MedDRA PT nested within the CEC assessment (confirmed event, no event, or insufficient documentation for event determination) and the subcategory. Subtypes of stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed in the analyses nested within Cerebrovascular Event. Subtypes of Serious Arrhythmia (Atrial Arrhythmia, Ventricular Arrhythmia, Heart Block, Other, Unknown) will be displayed nested within Serious Arrhythmia.	

Major Adverse Cerebro-Cardiovascular Events (MACE)	MACE (requiring adjudication as defined above) is defined as: • Vascular Death (including cardiovascular and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system) • Non-fatal myocardial infarction • Non-fatal stroke (subtypes: hemorrhagic stroke, ischemic stroke, undetermined stroke type) Where, • Vascular death should be captured as an Event on *Adjudication - Death* eCRF page with Adjudication Death Type = 'Cardiovascular'. • Non-fatal myocardial infarction should be captured as an Event on *Adjudication - Cardiac Ischemic Event* eCRF page with Type of Ischemic Event = "Myocardial Infarction" and the Event is NOT on *Adjudication - Death* eCRF page. • Non-fatal strokes (ischemic, hemorrhagic) should be captured as an Event on *Adjudication - Cerebrovascular Event* eCRF page with Stroke Cerebrovascular Event Subtype in one of the following categories: hemorrhagic stroke, ischemic stroke, undetermined stroke type, and the Event is NOT on *Adjudication - Death* eCRF page. Subcategories of non-fatal stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed nested within non-fatal stroke category.	**Period 2 (Fisher's exact test), Period 3 and Combined Periods 2 and 3 (Summary):** TEAE by maximum severity by PT within category **Listing:** TEAE
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as specified 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]	**Period 2 (Fisher's exact test), Period 3 and Combined Periods 2 and 3 (Summary):** TEAE by PT within category **Listing:** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing

	Events will be summarize by the following categories:
	• Nonmelanoma Skin Cancer (NMSC)
	  o Basal Cell Carcinoma, PTs include:
	  ▪ Basal cell carcinoma
	  ▪ Basosquamous carcinoma
	  ▪ Basosquamous carcinoma of skin
	  o Squamous Cell Carcinoma, PTs include:
	  ▪ Squamous cell carcinoma of skin
	  ▪ Bowen's disease
	  ▪ Lip squamous cell carcinoma
	  ▪ Skin squamous cell carcinoma metastatic
	  ▪ Keratoacanthoma
	• Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	

Depressions	Depression is defined using the PTs from the Depression and suicide/self-injury SMQ as specified in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excl suicide and self-injury)]).	**Period 2 (Fisher's exact test), Period 3 and Combined Periods 2 and 3 (Summary)**: TEAE by PT within SMQ and sub-SMQ **Listing:** TEAE (included in the same listing with hepatic, cytopenia and interstitial lung disease AESIs)
Inflammatory Bowel Disease (IBD)	IBD will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered 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 (Events That Can Occur with IBD (Broad Terms)): The PTs in this category are listed in the LY2439821 PSAP v8 Appendix 11 (or most current version)	**Period 2 (Fisher's exact test), Period 3 and Combined Periods 2 and 3 (Summary)**: TEAE by PT within subcategory **Listing:** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Interstitial Lung Disease (ILD)	ILD is defined using the following terms: • Broad and narrow terms in the Interstitial lung disease SMQ (20000042) • Additional 6 PTs from Eosinophilic pneumonia SMQ (20000157): o Angiolymphoid hyperplasia with eosinophilia (Narrow) o Eosinophilic bronchitis (Narrow) o Hypereosinophilic syndrome (Narrow) o Loeffler's syndrome (Narrow) o Pulmonary eosinophilia (Narrow) o Pulmonary vasculitis (Narrow)	**Listing**: TEAE (included in the same listing with hepatic, depression and interstitial lung disease AESIs)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; eCRF = electronic case report form; HLT = high-level term; OI =opportunistic infection; PT = preferred term; SAE = serious adverse event; TEAE = treatment emergent adverse event.

6.11.3.2. Anterior Uveitis

At each study visit, study health care providers will evaluate the patient for any symptoms of anterior uveitis. The incidence of anterior uveitis is identified using the preferred term 'iridocyclitis'. The incidence rate of anterior uveitis will be summarized for patients with or without prior anterior uveitis separately, for the following study periods and analysis populations:

- Period 2 (Safety Population)
- Period 3 (Extended Treatment Period Population)

6.11.4. Clinical Laboratory Evaluation

Clinical laboratory assessments include hematology, serum chemistry, urinalysis, and safety-related immune markers such as neutrophil counts. All laboratory tests will be presented using the international system of unit (SI) when applicable.

Continuous laboratory tests will be summarized as changes from baseline to last observation for patients who have both baseline and at least one postbaseline result for Period 2 and 3, respectively:

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- For the Safety Population for Period 2, the comparisons between treatment groups will be conducted using an ANCOVA with treatment group and baseline value in the model.
- Data will be analyzed based on original scale.

Laboratory test observed values at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients who have both a baseline and at least one postbaseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least one postbaseline result, mean, standard deviation, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.
- On the box plots of the laboratory test observed values, the lines of the reference ranges/limits (by using the performing laboratory reference ranges) will be added. In cases where limits vary across age and gender, the lowest of the high limits and the highest of the low limits will be used.

The number and percentage of patients with a treatment-emergent or follow-up emergent abnormal, high, or low for laboratory tests will be summarized by treatment group for each study period (Period 2 or 3 or 4). The comparisons between treatment groups will be conducted using Fisher's exact test for the Safety Population for Period 2.

- All scheduled, unscheduled and repeated measurements will be included.
- Performing laboratory will be used to defined the low and high limits reference ranges except for leukocyte, neutrophil, lymphocyte and platelet counts, where Lilly defined lower limit of normal will be used for these 4 labs.
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), neutrophils, leukocytes, platelets, and lymphocytes will not be included in the treatment-emergent abnormal, high, or low summary as a separate analysis addressing the risk of liver injury is described in Section 6.11.3.1 and a separate analysis addressing Leukocytes (WBC) and Platelets is described in Section 6.11.4.1.
- Note that the ranges are defined by a lower limit of normal (LLN) and an upper limit of normal (ULN). A result that is greater than or equal to the LLN and less than or equal to the ULN is considered to be within the normal ranges.
- For categorical laboratory tests:
    - Treatment-emergent abnormal value is defined as a change from normal at all baseline visits to abnormal at any time postbaseline during the treatment period.
    - Follow-up emergent abnormal result is defined as a change from normal at baseline to abnormal at any time during the follow-up period.
- For continuous laboratory tests:
    - Treatment-emergent high value is defined as a change from a value less than or equal to the ULN at all baseline visits to a value greater than the ULN 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 LLN at all baseline visits to a value less than the LLN at any time postbaseline during the treatment period.
    - Follow-up emergent high value is defined as a change from a value less than or equal to the ULN at baseline to a value greater than the ULN at any time postbaseline during the follow-up period.
    - Follow-up emergent low value is defined as a change from a value greater than or equal to the LLN at baseline to a value less than the LLN at any time postbaseline during the follow-up period.
    - By-patient listing of abnormal laboratory test results (criteria defined in the shift tables excluding the normal category) for parameters of special interest (hepatic, leukocytes and platelets) will be provided.

6.11.4.1. Leukocytes (WBC) and Platelets

Further analyses will be conducted for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils. Unless otherwise specified, neutrophils will be summarized as absolute neutrophils (derived by adding segmented neutrophils and band neutrophils).

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 for study Periods 2 and 3, respectively:

- Scheduled visits, unscheduled visits, and repeat measurements will be included.
- Baseline is defined as the minimum result during the defined baseline period or baseline.
- Use the minimum non-missing postbaseline value within each study period.
- The parameters and categories are:
    - Leukocytes: ≥1× LLN (Normal), < LLN to ≥3.0× 10^9/L (Grade 1), <3.0× 10^9/L to ≥2.0× 10^9/L (Grade 2), <2.0× 10^9/L to ≥1.0× 10^9/L (Grade 3), and <1.0× 10^9/L (Grade 4).
    - Neutrophils: ≥1× LLN (Normal), < LLN to ≥1.5× 10^9/L (Grade 1), <1.5× 10^9/L to ≥1.0× 10^9/L (Grade 2), <1.0× 10^9/L to ≥0.5× 10^9/L (Grade 3), and <0.5× 10^9/L (Grade 4)
    - Platelets: ≥1 × LLN (Normal), < LLN to ≥75.0 × 10^9/L (Grade 1), <75.0 × 10^9/L to ≥50.0 × 10^9/L (Grade 2), <50.0 × 10^9/L to ≥25.0 × 10^9/L (Grade 3), and <25.0 × 10^9/L (Grade 4).
    - Lymphocytes: ≥1× LLN (Normal), < LLN to ≥0.8× 10^9/L (Grade 1), <0.8× 10^9/L to ≥0.5× 10^9/L (Grade 2), <0.5× 10^9/L to ≥0.2× 10^9/L (Grade 3), and <0.2× 10^9/L (Grade 4).
- The above LLNs are defined as:
    - Leukocytes: LLN = 4.0× 10^9/L
    - Neutrophils: LLN = 2.0× 10^9/L
    - Platelets: LLN = 150× 10^9/L
    - Lymphocytes: LLN = 1.1× 10^9/L
- With additional categories:
    - Decreased; postbaseline category < baseline category
    - Increased; postbaseline category > baseline category
    - Same; postbaseline category = baseline category.

The change from minimum baseline to minimum postbaseline result for each of these leukocytes and platelets will be summarized graphically using a box plot for Periods 2 and 3, respectively.

6.11.4.2. Neutrophil Follow-Up

Neutrophil counts will be followed throughout the study. The neutrophil follow-up analysis 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× 10^9/L) at the last scheduled visit or early termination visit prior to entering Period 4 and less than the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0).

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 absolute neutrophil count prior to first study drug injection at Week 0. If a patient's neutrophil count has not recovered within 12 weeks after entering the follow-up period (Visit 802), the investigator will determine the appropriate management of the patient and the appropriate timing of additional contact(s).

The number and percentage of patients achieving neutrophil clinical recovery will be presented by treatment groups and week interval for the Neutrophil Follow-Up Population for Period 4. 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.

6.11.5. Vital Signs and Other Physical Findings

Analyses will be conducted on vital signs and physical characteristics including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (bpm), weight (kg), BMI (kg/m^2).

Change from baseline to last observation for vital signs and physical characteristics will be summarized for patients who have both baseline and at least one postbaseline result, for Periods 2, and 3, respectively:

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- For the Safety Population for Period 2, the comparisons between treatment groups will be conducted using an ANCOVA with treatment groups and baseline value in the model.
- Data will be analyzed based on original scale.

For vital signs and physical characteristics, the observed values at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients who have both a baseline and at least one postbaseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least one postbaseline result, mean, standard deviation, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.

To assess the effect of administration of study drug on vital signs (blood pressures and pulse rate) among patients, at weeks 0, and 16, vital signs will be measured before the first injection and 1 hour after the injection. The box plots will be produced for pre-dose and post-dose vital signs at Week 0 (Visit 2), and Week 16 (Visit 8)).

The number and percentage of patients with treatment-emergent or follow-up emergent high or low vital sign and weight at any time for Periods 2, 3, and 4 (for vital signs only in Period 4), respectively, will be summarized. The comparisons between and among treatment groups will be conducted using Fisher's exact test for the Safety Population for Period 2.

- Table RHCH.6.8 defines the high and low baseline values as well as the limits that are specified as treatment-emergent and follow-up emergent. Note that weight does not have an abnormal baseline; therefore, the treatment-emergent and follow-up emergent values are determined by change from baseline.
- All postbaseline scheduled, unscheduled and repeated measurements will be included.

- To assess increases, change from the maximum value during the baseline period or baseline to the maximum value during each study period will be used.
- To assess decreases, change from the minimum value during the baseline period or baseline to the minimum value during each study period will be used.
- For treatment-emergent high and low:
  - A treatment-emergent **high** result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria 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 baseline to a value less than the low limit at any time that meets the specified change criteria during the treatment period.
- For follow-up emergent high and low:
  - A follow-up emergent **high** result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the follow-up period.
  - A follow-up emergent **low** result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the follow-up period.

Table RHCH.6.8. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressures and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg) [a] (supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) [a] (supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) [a] (supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg)	(Loss) decrease from baseline ≥7%	(Gain) increase from baseline ≥7%

Abbreviations: BP = blood pressure; bpm = beats per minute; kg = kilogram; mm Hg = millimeters of mercury.

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

6.11.6. Quick Inventory of Depressive Symptomatology–Self Report 16 Items (QIDS-SR16)

The QIDS-SR16 is a self-administered 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's (APA's) *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* (APA 1994). The QIDS-SR16 scale is used to assess the potential impact of treatment on new onset or changes in depression, thoughts of death, and/or suicidal ideation severity. A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are

summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS resource page ((http://www.ids-qids.org/).

The 9 domains assessed by the instrument are defined as:

1) Sleep disturbance (initial, middle, and late insomnia or hypersomnia): the highest score recorded for the four sleep items: #1 (falling asleep), #2 (sleep during the night), #3 (waking up too early) and #4 (sleeping too much). Domain is missing if all items are missing.
2) Sad mood: Item #5 (feeling sad). Domain is missing if the item is missing.
3) Decrease/increase in appetite/weight: the highest score recorded for the appetite/weight items: #6 (decreased appetite), #7 (increased appetite), #8 (decreased weight within the last two weeks), and #9 (increased weight within the last two weeks). Domain is missing if all items are missing or not applicable.
4) Concentration: Item #10 (concentration / decision making). Domain is missing if the item is missing.
5) Self-criticism: Item #11 (view of myself). Domain is missing if the item is missing.
6) Suicidal ideation: Item #12 (thoughts of death or suicide). Domain is missing if the item is missing.
7) Interest: Item #13 (general interest). Domain is missing if the item is missing.
8) Energy/fatigue: Item #14 (energy level). Domain is missing if the item is missing.
9) Psychomotor agitation/retardation: the highest score recorded for the two psychomotor items: #15 (feeling slowed down) and #16 (feeling restless). Domain is missing if all items are missing.

The QIDS-SR16 total score is the sum of the above domain scores. The total score will be missing if any domain score is missing. The QIDS-SR16 total scores are categorized as: None (no depression) (0 – 5), Mild (6 – 10), Moderate (11 – 15), Severe (16 – 20) and Very severe (21 – 27).

For both Period 2 and 3 QIDS-SR16 analyses, baseline is defined as the last non-missing assessment recorded on or prior to the date of first injection of study treatment at Week 0 (Visit 2), as for QoL measures. In most cases, this will be the measure recorded at Week 0 (Visit 2).

Summaries will be done by treatment groups for Safety Population in Period 2 and Extended Treatment Period Population in Period 3, respectively.

The following summaries will be produced for QIDS-SR16 total score category:

- The number and percentage of patients falling into each QIDS-SR16 total score category at each scheduled visit.
- Shift from maximum baseline to each postbaseline visit in QIDS-SR16 total score category.

- The number and percentage of patients falling into the following categories based upon the maximum postbaseline QIDS-SR16 total score:
    - Improved; maximum postbaseline category < maximum baseline category.
    - Worsened; maximum postbaseline category > maximum baseline category.
    - Same; maximum postbaseline category = maximum baseline category.

In addition, the number and percentage of patients falling into the following groups based upon the maximum postbaseline QIDS-SR16 item 12 (Thoughts of Death or Suicide) score will be summarized:

- Improved; maximum postbaseline item 12 score < maximum baseline item 12 score.
- Worsened; maximum postbaseline item 12 score > maximum baseline item 12 score.
- Same; maximum postbaseline item 12 score = maximum baseline item 12 score.

6.11.7. 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://www.cssrs.columbia.edu.

Specifically, the following outcomes are C-SSRS categories and have binary responses (yes/no).

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:** answered 'yes' to any one of Categories 1-5 questions.
- **Suicidal behavior:** answered 'yes' to any one of Categories 6-10 questions.
- **Suicidal ideation or behavior:** answered 'yes' to any one of Categories 1-10 questions.

C-SSRS will be listed by patient and visit using Spotfire. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed. However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be displayed, even if not positive. Note, missing data should not be imputed.

The Self-Harm Supplement Form is a one-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. 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 CRF '*Self Harm Questionnaire Supplement.*'

6.11.8. Immunogenicity

6.11.8.1. Definitions and Terms

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

6.11.8.1.1. 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.
- **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.
- **ADA/NAb Inconclusive sample:** when ADA/NAb is not detected in a sample but drug is present in the same sample at a level that can cause interference in the ADA/NAb detection method, then the negative ADA/NAb result cannot be confirmed and the sample should be considered inconclusive.
    - Confirmation of a negative ADA or NAb result was based on ixekizumab concentrations.

6.11.8.1.2. 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.

6.11.8.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses during Period 2, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment (Week 0). Unless otherwise specified, the baseline for Period 3 is defined as the last non-missing observation on, or prior to, the date of first injection of ixekizumab. For patients originally randomized to ixekizumab during Period 2, baseline is the last non-missing observation on, or prior to, the date of the first injection of study treatment for Period 2 (Week 0). For patients who are not originally randomized to ixekizumab in Period 2, baseline is the last non-missing observation on, or prior to, the date of the first injection of ixekizumab. See Table RHCH.6.9 for further details.

Table RHCH.6.9. Baseline Definition for Immunogenicity Analyses for Extended Treatment Period

Treatment Assignment for Blinded Treatment Dosing Period (Period 2)	Treatment Assignment for Extended Treatment Period (Period 3)	Baseline for Extended Treatment Period Analysis[a]
Ixekizumab	Ixekizumab	Week 0
Placebo	Ixekizumab	Week 16

[a] Last non-missing observation on, or prior to, the date of the first injection of study treatment at the defined week.

- **Baseline ADA positive (preexisting antibody) patient:** ADA detected in a sample collected at baseline.
- **Baseline ADA-negative patient:** ADA is not detected in a sample collected at baseline.
- **TE-ADA positive patient:** a) a patient with a ≥4-fold increase over a positive baseline antibody titer (Tier 3); or b) for a negative baseline titer, a patient with an increase from the baseline to a level of ≥1:10.
- **TE-ADA inconclusive patient:** A patient without a TE-ADA positive sample and with at least one sample for which drug levels may interfere with the ADA assay.
- **TE-ADA negative patient:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.
- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment period. 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 patient:** A patient where a NAb positive result is detected for ≥1 TE-ADA positive samples.
- **NAb-inconclusive patient:** A patient without a NAb positive sample and with at least one sample for which drug levels may interfere with the NAb assay.
- **NAb-negative patient:** A patient who is evaluable for NAb and is not either NAb positive sample or NAb inconclusive.

Please see the LY2439821 PSAP v8 section 5.6.4.1.3 (or most current version) for details on the definitions for clinical interpretation of assay results.

6.11.8.2. 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 6.11.8.1.2 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; and
- 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 <1:1,280; and
  - High Titer: TE-ADA titer value (LOCF) ≥1:1,280.

Time-Varying TE-ADA Status Groups:

Individual ADA samples will be ascribed into 3 different dichotomous variables as explained in Table RHCH.6.10. 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 RHCH.6.10. 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 anti-drug antibody.
Note: For purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive."
Note: 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 <1:1,280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1,280.

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 RHCH.6.10. 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 used.

For each TE-ADA status dichotomous variable, 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.

6.11.8.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of ADA effects will be conducted on all evaluable patients within the defined Safety Population for Blinded Treatment Dosing Period (Period 2), and Combined Blinded Treatment Dosing and Extended Treatment Periods (Combined Periods 2 and 3).

Baseline definition for immunogenicity analyses for the Combined Treatment Period is the same as Table RHCH.6.9.

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, they will be censored at the date of the last immunogenicity assessment.

Descriptive statistics, including 25th percentile, 50th percentile (median), 75th percentile, and corresponding 95% CIs as well as proportion of TE-ADA/NAb positive by endpoint summarized by treatment group, will also be provided if sufficient data is present. A Kaplan-Meier plot of the time to development of treatment-emergent ADA/NAb will be presented by treatment group, also if sufficient data is present.

For each TE-ADA status dichotomous variable (as defined in Table RHCH.6.10), 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, ADA and NAb inconclusive results will also be provided, for patients with any one sample of ADA (or NAb) positive or inconclusive.

6.11.8.2.2. Analyses of ADA Effects on Efficacy

Efficacy analyses for Period 2 and Period 3 will be conducted on all evaluable patients within the ITT Population and Extended Treatment Period Population.

The ASAS40, ASAS20, ASDAS inactive disease and ASDAS < 2.1 at week 16 with NRI will be summarized by the TE-ADA status groups as described in Section 6.11.8.2.

A logistic regression model with treatment group, TE-ADA status group (excluding patients in the TE-ADA inconclusive category for TE-ADA, excluding TE-ADA positive and co-occurring NAb inconclusive subgroups for NAb), and the interaction of treatment group-by-TE-ADA status group included as factors will be used to test the interaction of treatment group-by-TE-ADA status group for ITT Population during Period 2. The p-value associated with the interaction term will be used to assess if the treatment groups effect is consistent across the TE-ADA status group. When the interaction term is statistically significant, the association between responder status and treatment depends, in some manner, on the TE-ADA status group. The interaction will be tested at the 10% significance level. Treatment differences will be evaluated within each subgroup using Fisher's exact test regardless of whether the interaction is statistically significant.

Response rates for ASAS40, ASAS20, ASDAS inactive disease and ASDAS < 2.1 at Week 16 will be provided and compared among the TE-ADA status (and TE-ADA tiers) and NAb status groups for the ITT Population who were treated with ixekizumab.

Descriptive statistics for ASAS40 and ASAS20 at Week 52 based on the TE-ADA status (and TE-ADA tiers) and NAb status group will be provided for the Extended Treatment Period Population. No inferential statistics will performed.

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

The analyses of TE-ADA effects on safety will be conducted on all evaluable patients within the defined Safety Population for Blinded Treatment Dosing Period (Period 2) and Combined Blinded Treatment Dosing and Extended Treatment Periods (Combined Periods 2 and 3).

Baseline definition for immunogenicity analyses for the Combined Treatment Period is the same as Table RHCH.6.9.

AESIs 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 RHCH.6.10), 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 one 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 of patients with TE-ADA who experience a treatment-emergent allergic reaction/hypersensitivity reaction or an injection site reaction.

6.12. Subgroup Analyses

6.12.1. Efficacy Subgroup Analyses

Subgroup analysis will be conducted for the primary endpoint of proportion of patients achieving an ASAS40 response at Week 16 (NRI) using the ITT Population for the Period 2. The major secondary efficacy endpoint, the proportion of patients achieving ASAS20 (NRI) at Week 16, will also be conducted. Subgroup analysis using the ITT Population in bDMARD-naïve patients may be explored.

For categorical response variables (ASAS20, ASAS40), a logistic regression analysis with treatment, subgroup, and treatment-by-subgroup interaction as factors will be used. The treatment-by-subgroup interaction will be tested at the 10% significance level. Treatment group differences will be evaluated within each subgroup using the Fisher's exact test, regardless of whether the interaction is statistically significant. If any group within the subgroup (for example, yes, no) is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

Forest plots may be created to illustrate the treatment differences with 95% CIs between each of the ixekizumab treatment groups and placebo group, by each subgroup category.

Please see Table RHCH. 6.1. for subgroups of baseline characteristics that will be analyzed.

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

6.13. Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those violations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

A separate document (known as the trial issue management plan) will be used to define the categories and subcategories of important protocol deviations, whether or not these deviations will result in the exclusion of patients from PPS, and the source of identification for the deviations.

The number and percentage of patients having important protocol deviations (s) will be summarized within category and subcategory of deviations by treatment group for:

- Period 2 (ITT Population);
- Period 3 (Extended Treatment Period Population).

A by-patient listing of important protocol deviations will be provided. A listing of protocol deviation due to COVID-19 will also be provided.

6.14. Interim Analyses

An interim database lock and unblinding will occur, and interim analyses will be performed at the time (that is, a cutoff date) the last patient completes Visit 8 (Blinded Dosing Treatment Period [Period 2], Week 16) or ETV. This interim database lock will include all data collected by the cutoff date including the data from the Extended Treatment Period (Period 3) and follow-up data from patients that have begun the Post-Treatment Follow-Up Period (Period 4). The analyses from the Week 16 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

Additional analyses and snapshots of study data may be performed during the Period 3 or after completion of Period 4 to fulfill the need for regulatory interactions or publication purposes.

Please see a separate blinding and unblinding plan document for the details.

6.15. 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 summary of AEs, 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 such as the CSR.

7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

8. References

Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2014;33(4):693-713.

Andersen SW, Millen BA. On the practical application of mixed effects models for repeated measures to clinical trial data. *Pharm Stat*. 2013;12(1):7-16.

[ASAS] Assessment of Spondyloarthritis International Society. ASAS-Heath Index users manual. Available at http://www.asas-group.org/clinical-instruments/asas_health_index/asas_hi_english_um.pdf. Accessed 25 March 2016.

Baeten D, Braun J, Baraliakos X, Sieper J, Dougados M, Emery P, Deodhar A, Porter B, Martin R, Mpofu S, Richards H. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a 52-week phase 3 randomized placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing [abstract]. In: ACR/ARHP Annual Meeting Abstract Supplement. 14-19 Nov 2014; Boston, MA. *Arthritis Rheum.* 2014;66(S10):S360. Abstract 819.

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913.

Calin A, Jones SD, Garrett SL, Kennedy LG. Bath Ankylosing Spondylitis Functional Index. *Br J Rheumatol*. 1995;34(8):793-794.

Cella D, Webster K. Linking outcomes management to quality-of-life measurement. *Oncology*. (Willeston Park). 1997;11(11A):232-235.

Columbia University Medical Center. Columbia–Suicide Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed April 21, 2011.

Davis JC Jr, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, Kivitz A, Fleischmann R, Inman R, Tsuji W; Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum*. 2003;48(11):3230-3236.

Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. Analysis of longitudinal data. Oxford: Oxford University Press; 1994.

Dougados M, Simon P, Braun J, Burgos-Vargas R, Maksymowych WP, Sieper J, van der Heijde D. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(2):249-251.

EuroQol Group. EQ-5D-5L user guide. Version 1.0. April 2011. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L. Accessed September 14, 2012.

Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21(12):2286-2291.

Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewé R, van ver Tempel H, Mielants H, Dougados M, van der Heijde D. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis.* 2003;62(2):127-132.

Inman RD, Davis JC Jr, van der Heijde D, Diekman L, Sieper J, Kim SI, Mack M, Han J, Visvanathan S, Xu Z, Hsu B, Beutler A, Braun J. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum.* 2008;58(11):3402-3412.

Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol.* 1994;21(9):1694-1698.

Kiltz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, Maksymowych WP, Marzo-Ortega H, Reveille J, Stebbings S, Bostan C, Braun J. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis.* 2013;74(5):830-835.

Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, Reveille JD, Rudwaleit M, van der Heijde D, Stach C, Hoepken B, Fichtner A, Coteur G, de Longueville M, Sieper J. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis.* 2014;73(1):39-47.

Luo N, Liu G, Li M, Guan H, Jin X, Rand-Hendriksen K. Estimating an EQ-5D-5L value set for China. *Value in Health*. 2017 Apr 1;20(4):662-9.

Machado P, Castrejon I, Katchamart W, Koevoets R, Kuriya B, Schoels M, Silva-Fernández L, Thevissen K, Vercoutere W, Villeneuve E, Aletaha D, Carmona L, Landewé R, van der Heijde D, Bijlsma JW, Bykerk V, Canhão H, Catrina AI, Durez P, Edwards CJ, Mjaavatten MD, Leeb BF, Losada B, Martín-Mola EM, Martinez-Osuna P, Montecucco C, Müller-Ladner U, Østergaard M, Sheane B, Xavier RM, Zochling J, Bombardier C. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 2011a;70(1):15-24.

Machado PM, Landewé RB, van der Heijde DM. Endorsement of definitions of disease activity states and improvements scores for the Ankylosing Spondylitis Disease Activity Score: results from OMERACT 10. *J Rheumatol.* 2011b;38(7):1502-1506.

Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, van der Heijde D, Assessment of SpondyloArthritis International Society. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis*. 2011c;70(1):47-53.

Machado P, Navarro-Compán V,Landewé R, van Gaalen FA, Roux C, van der Heijde D. Calculating the ankylosing spondylitis disease activity score if the conventional c-reactive protein level is below the limit of detection or if high-sensitivity c-reactive protein is used: an analysis in the DESIR cohort. *Arthritis Rheumatol.* 2015;67(2):408-413.

Machado P, Landewé R, van der Heijde D. Ankylosing Spondylitis Disease Activity Score

(ASDAS): 2018 update of the nomenclature for disease activity states Ann Rheum Dis 2018;0:1–2.

Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Krishnananthan R, Stone M, Conner-Spady B, Palsat J, Lambert RGW. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. *Arthritis Rheum*. 2005a;53(4):502-509.

Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, Sampalis J, Conner-Spady B. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis*. 2009;68(6):948-953.

Maksymowych WP, Wichuk S, Chiowchanwisawakit P, Lambert RG, Pedersen SJ. Development and preliminary validation of the spondyloarthritis research consortium of Canada magnetic resonance imaging sacroiliac joint structural score. *J Rheumatol*. 2015;42(1):79-86.

Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. *Rheumatology (Oxford)*. 2010;49(4):812-819.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-397.

Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, Dougados M, Hermann KG, Landewé R, Maksymowych W, van der Heijde D. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 2009;68(suppl 2):ii1-ii44.

Sieper J, Braun J, Baraliakos X, Baeten D, Dougados M, Emery P, Deodhar A, Porter B, Andersson M, Mpofu S, Richards H. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a phase 3, randomized, placebo-controlled trial with subcutaneous loading and maintenance dosing [poster]. Poster presented at: American College of Rheumatology 2014 Annual Scientific Meeting; 14-19 November 2014; Boston, MA. Poster 536.

Szende A, Oppe M, Devlin N, eds. EQ-5D Value Sets: Inventory, Comparative Review and User Guide. Dordrecht, Netherlands: Springer; 2007. University of Pittsburgh Epidemiology Data Center. Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS). Available at: http://www.ids-qids.org/.2010.

van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, Braun J; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum*. 2005;52(2):582-591.

van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, Dougados M, Reveille JD, Wong RL, Kupper H, Davis JC Jr; ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2006;54(7):2136-2146.

van der Heijde D, Landewé R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis*. 2008;67(4):489-493.

Ware JE, Jr. SF-36 health survey update. *Spine*. 2000;25(24):3130-3139.

Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res (Hoboken)*. 2011;63(suppl 11):S47-S58.

9. Appendices

Appendix 1. Algorithm for Determining ASAS Response

The following ASAS domains are used to determine ASAS40, ASAS20, ASAS partial remission, and ASAS5/6 (Sieper et al. 2009, ASAS Handbook), detailed definitions of ASAS40, ASAS20, ASAS partial remission, and ASAS5/6 are provided in Table RHCH.6.3:

- Patient Global
- Spinal Pain
- Function
- Inflammation
- CRP and
- Spinal mobility (lateral spinal flexion).

The following variables will be derived for above domains as applicable:

Variables	Derivation / Comments	Imputation Approach with Missing Component
V1: Percent improvement from baseline	Calculated as: $$Percent\ improvement\ from\ baseline\ = 100 \times \frac{Baseline\ score\ - Observed\ score}{Baseline\ score}$$ If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	Missing if baseline or observed value is missing
V2: Absolute improvement	Calculated as: Baseline score – Observed Score If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	Missing if baseline or observed value is missing
V3: Any worsening	Yes if V2 'absolute improvement' is negative	Missing if V2 is missing
V4: Worsening of ≥20% and ≥1 unit	Yes if V1≤-20% and V2 ≤-1	Missing if V1 or V2 is missing

Algorithm to calculate the *observed* ASAS40 response at a visit:

- **Step 1:** among the above 4 domains (patient global, spinal pain, function, and inflammation), if at least 3 of them are ≥40 on variable 'percent improvement [V1])' AND ≥2 on variable 'absolute improvement [V2]' AND variable 'absolute improvement [V2]' is ≥0 for the remaining domain, assign ASAS40 response as responder;
- **Step 2:** else, among the 4 domains, if any of them are 'YES' on variable 'any worsening [V3]', or at least 2 of them have nonmissing 'percent improvement [V1] '<40 or nonmissing 'absolute improvement [V2]'<2, assign ASAS40 response as nonresponder;
- **Step 3:** For all other situations, assign ASAS40 response as missing.

Algorithm to calculate the *observed* ASAS20 response at a visit:

- **Step 1:** among the above 4 domains (patient global, spinal pain, function, and inflammation), if at least 3 of them are ≥20 on variable 'percent improvement [V1])' AND ≥1 on variable 'absolute improvement [V2]' AND variable 'Worsening of ≥20% and ≥1 unit [V4]' is 'NO' for the remaining domain, assign ASAS20 response as responder;
- **Step 2:** else, among the 4 domains, if any of them are 'YES' on variable 'Worsening of ≥20% and ≥1 unit [V4]', or at least 2 of them have nonmissing 'percent improvement [V1]' <20 or nonmissing 'absolute improvement [V2]' <1, assign ASAS20 response as nonresponder;
- **Step 3:** For all other situations, assign ASAS20 response as missing.

Algorithm to calculate the *observed* ASAS partial remission response at a visit:

- **Step 1:** among the above 4 domains (patient global, spinal pain, function, and inflammation), if the value for all of them are not missing and ≤2, then assign ASAS partial remission response as responder;
- **Step 2:** else, if at least one of the 4 domains have a value >2, assign ASAS partial remission response as nonresponder;
- **Step 3:** for all other situations, assign ASAS partial remission response as missing.

Algorithm to calculate the *observed* ASAS5/6 response at a visit:

- **Step 1:** among the 6 domains (Patient Global, Spinal Pain, Function, Inflammation, CRP, Spinal mobility), if at least 5 of them are ≥20 on variable 'percent improvement [V1]', then assign ASAS5/6 response as responder;
- **Step 2:** else, if any 2 or more domains have non-missing variable 'percent improvement [V1]' <20, then assign ASAS5/6 response as nonresponder;
- **Step 3:** for all other situations, assign ASAS5/6 response as missing.

Appendix 2. ASAS-NSAID Equivalent Score

NSAID	Dose comparable to 150 mg of diclofenac	Maximum dose used in AS	Consensus
Diclofenac	/	n=60* 150 (150–200)	150
Naproxen	n=57 1000 (1000–1000)	n=59 1000 (1000–1500)	n=47/50ǂ 1000
Aceclofenac	n=15 200 (200–200)	n=14 200 (200–200)	n=29/29 200
Celecoxib	n=61 400 (300–400)	n=60 400 (400–400)	n=47/50 400
Etodolac	n=15 600 (400–800)	n=13 600 (600–600)	n=17/20 600
Etoricoxib	n=36 90 (90–90)	n=37 120 (90–120)	n=42/46 90
Flurbiprofen	n=13 200 (200–300)	n=13 300 (200–300)	n=15/18 200
Ibuprofen	n=54 2400 (1600–2400)	n=54 2400 (2400–2400)	n=39/45 2400
Indometacin	n=57 150 (100–150)	n=58 150 (150–200)	n=42/47 150
Ketoprofen	n=26 200 (200–200)	n=25 200 (200–300)	n=21/23 200
Meloxicam	n=58 15 (15–15)	n=55 15 (15–22.5)	n=42/48 15
Nimesulide	n=8 200 (200–200)	n=9 200 (200–200)	n=16/16 200
Phenylbutazone	n=28 400 (200–500)	n=28 400 (250–600)	n=25/28 400
Piroxicam	n=51 20 (20–20)	n=50 20 (20–40)	n=46/46 20
Tenoxicam	n=17 20 (20–20)	n=16 25 (20–40)	n=18/18 20

Results of the survey evaluating the opinion of ASAS members about the comparable efficacy of each NSAID with 150 mg of diclofenac.

Values given are:

*first row, n=number of ASAS members giving an answer to the question; second row, median dose in mg (tertiles).

ǂ first row, n=number of ASAS members who have voted in favor of such a dose/the total number of ASAS members who have voted; second row, agreed dose.

AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; NSAID, non-steroidal anti-inflammatory drug. Source: Dougados 2011.

Appendix 3. Definition of DMARDs, Oral Corticosteroids, NSAIDs (including COX-2), and Opioids

DMARDs

The following ATC codes and WHO preferred terms are provided by Lilly Medical to select the possible DMARDs.

ATC codes: containing M01C, A07EC, L01BA, L04, L01BB, J04BA, P01BA, and

Preferred Terms: listed below, which were used to identify the specified DMARDs.

Medication	WHO Preferred Term
Methotrexate	METHOTREXATE, METHOTREXATE SODIUM
Sulfasalazine	SULFASALAZINE
Hydroxychloroquine	HYDROXYCHLOROQUINE SULFATE, HYDROXYCHLOROQUINE, HYDROXYCHLOROQUINE PHOSPHATE

If MESALAZINE (A07EC) is used for Primary Study Condition, then it is regarded as DMARD, otherwise it is not a DMARD.

Oral Corticosteroids

The following preferred terms are provided by Lilly Medical to select the possible corticosteroids use with route of Oral (CMROUTE="ORAL").

In analyses, corticosteroid doses need to be converted to prednisone equivalent doses. If additional WHO preferred terms and conversion factors are identified, they will be added to the SAP prior to database lock.

The following table should be used for converting oral corticosteroids to prednisone equivalent:

Multiply the dose of the corticosteroid taken by the patient (in milligrams) in Column 1 by the conversion factor in Column 2 to get the equivalent dose of prednisone (in milligrams).

Example: Patient is taking 25 mg of cortisone orally daily. To convert to prednisone: 25 mg cortisone x 0.2 = 5 mg prednisone. 25 mg cortisone taken orally daily is equivalent to 5 mg of prednisone taken orally daily.

Column 1 Corticosteroid Preferred Term	Column 2 Conversion factor for converting to an equivalent prednisone dose
CORTISONE	0.2
CORTISONE ACETATE	0.25
HYDROCORTISONE	0.25
HYDROCORTISONE ACETATE	0.25
HYDROCORTISONE SODIUM SUCCINATE	0.25
DEFLAZACORT	0.8333
CORTIVAZOL	16.67
PREDNISONE	1
PREDNISONE ACETATE	1
PREDNISOLONE	1
PREDNISOLONE ACETATE	1
PREDNISOLONE SODIUM PHOSPHATE	1
FLUOCORTOLONE	1
METHYLPREDNISOLONE	1.25
METHYLPREDNISOLONE ACETATE	1.25
METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
TRIAMCINOLONE	1.25
TRIAMCINOLONE ACETONIDE	1.25
TRIAMCINOLONE HEXACETONIDE	1.25
DEPO-MEDROL MED LIDOKAIN	1.25
MEPREDNISONE	1.25
PARAMETHASONE	2.5
BETAMETHASONE	8.34
BETAMETHASONE ACETATE	8.34

Column 1 Corticosteroid Preferred Term	Column 2 Conversion factor for converting to an equivalent prednisone dose
BETAMETHASONE DIPROPIONATE	8.34
BETAMETHASONE SODIUM PHOSPHATE	8.34
DEXAMETHASONE	6.67
DEXAMETHASONE ACETATE	6.67
DEXAMETHASONE PHOSPHATE	6.67
DEXAMETHASONE SODIUM PHOSPHATE	6.67
CELESTONA BIFAS	8.34
DIPROSPAN /00582101/	8.34

Systemic Corticosteroids:

defined as ATC code = H02AB, route in (INTRAMUSCULAR, INTRADERMAL, INTRAVENOUS, INTRAVENOUS CENTRAL VEIN, INTRAVENOUS PERIPHERAL VEIN, ORAL, SUBCUTANEOUS, SUBLINGUAL, PERIARTICULAR, TRANSDERMAL).

NSAIDs/COX-2 Inhibitors

The following ATC codes are provided by Lilly Medical to select the possible NSAIDs and COX-2 inhibitors.

ATC codes: containing M01A, M01B, N02BA, M01AH (already included in M01A), but excluding the following preferred terms:

Preferred Term
BENZYDAMINE HYDROCHLORIDE
CHONDROITIN W/GLUCOSAMINE /02118501/
GLUCOSAMINE HYDROCHLORIDE
GLUCOSAMINE SULFATE NOW
METHYLSULFONYLMETHANE
BENZYDAMINE HYDROCHLORIDE
SULFASALAZINE
HYDROXYCHLOROQUINE
GLUCOSAMINE W/METHYLSULFONYLMETHANE
GLUCOSAMINE SULFATE POTASSIUM CHLORIDE
CHONDROITIN SULFATE SODIUM
CHONDROITIN SULFATE
CURCUMIN
GLUCOSAMINE
HYDROXYCHLOROQUINE SULFATE
GLUCOSAMINE CHONDROITIN COMPLEX

Preferred Term
SHAKUYAKUKANZOTO
CURCUMA LONGA
GLUCOSAMINE CHONDROITIN COMPLEX /06278301/

Opioids

The following WHO preferred terms are provided by Lilly Medical to select the possible opioids use.

In analysis, opioid doses need to be converted to morphine equivalent doses. If additional preferred terms and conversion factors are identified, they will be added to the SAP prior to database lock.

The following table should be used for converting opioids to morphine equivalent:

If an opioid was taken with an oral or sublingual route: multiply the dose of the opioids taken by the patient (in milligrams) in Column 1 by the conversion factor in Column 2 to get the equivalent dose of morphine (in milligrams).

If an opioid was taken with an intravenous, intravenous central vein, intramuscular, transdermal, or nasal route: multiply the dose of opioids in Column 1 by the conversion factor in Column 3 to get the equivalent dose of morphine.*Example: Patient is taking 15 mg of codeine orally daily. To convert to morphine: 15 mg codeine x 0.15 = 2.25 mg morphine. 15 mg codeine taken orally daily is equivalent to 2.25 mg of morphine taken orally daily.*

Column 1	Column 2	Column 3
Preferred Term	Conversion factor PO (based on mg)	Conversion factor IV (based on mg)
ANCOUGLIN	0.15	0.23
BUPRENORPHINE	75	33.34
BUPRENORPHINE HYDROCHLORIDE	75	33.34
CHERACOL /00693301/	0.15	0.23
CO-DAFALGAN	0.15	0.23
CODATEN	0.15	0.23
CODEINE	0.15	0.23
CODEINE CONTIN	0.15	0.23
CODEINE PHOSPHATE	0.15	0.23
CODEINE PHOSPHATE HEMIHYDRATE	0.15	0.23
CODEINE W/GUAIFENESIN /08428801/	0.15	0.23
CODENAL /00467701/	0.15	0.23
CODEPINE /01488001/	0.15	0.23
FENTANYL	NA	300
FENTANYL CITRATE	NA	300
FENTANYL HYDROCHLORIDE	NA	300
FENTANYL W/CLONIDINE	NA	300
HYDROCODONE	1	NA
HYDROCODONE BITARTRATE	1	NA
HYDROCODONE COMPOUND /01224801/	1	NA
HYDROCODONE CP	1	NA

Column 1	Column 2	Column 3
Preferred Term	Conversion factor PO (based on mg)	Conversion factor IV (based on mg)
HYDROCODONE HYDROCHLORIDE	1	NA
HYDROMORPHONE	4	20
HYDROMORPHONE HYDROCHLORIDE	4	20
LENOLTEC WITH CODEINE NO 1	0.15	0.23
MORPHINE	1	1
MORPHINE HYDROCHLORIDE	1	1
MORPHINE SULFATE	1	1
MYPRODOL	0.15	0.23
OXYCOCET	1.5	4
OXYCODONE	1.5	4
OXYCODONE HYDROCHLORIDE	1.5	4
PANADEINE CO	0.15	0.23
PARACETAMOL W/TRAMADOL	0.1	0.3
PARAMOL-118	0.15	0.23
PERCOCET-5	1.5	4
PETHIDINE	0.1	0.3
PIRITRAMIDE	0.7	0.7
PROCET /01554201/	1	NA
PROMETHAZINE W/CODEINE	0.15	0.23
TAPENTADOL	0.3	NA
TARGIN	1.5	4
TRAMADOL	0.1	0.3
TRAMADOL HYDROCHLORIDE	0.1	0.3
TRIMEPERIDINE	0.5	0.5
ULTRACET	0.1	0.3
VICODIN	1	NA