Statistical Analysis Plan: I1F-MC-RHBW (Version 4)

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

NCT02696798

Approval Date: 28-Feb-2019

1. Statistical Analysis Plan: I1F-MC-RHBW: A Multicenter, Randomized, Double-Blind, Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in TNFi-Experienced Patients with Radiographic Axial Spondyloarthritis

Ixekizumab (LY2439821) Axial Spondyloarthritis

Study I1F-MC-RHBW is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab (LY2439821) compared to placebo over 16 weeks in tumor necrosis factor (TNF) inhibitor-experienced patients with radiographic axial spondyloarthritis (rad-axSpA). Patients will be randomized to subcutaneous (SC) placebo, or 1 of 2 treatment regimens of ixekizumab (80 mg every 2 weeks [Q2W] or every 4 weeks [Q4W]). 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 be rerandomized to ixekizumab 80 mg Q2W or Q4W.

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Statistical Analysis Plan Version 1 electronically signed and approved by Lilly
07 April 2016
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly
12 June 2018
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly
18 June 2018

Statistical Analysis Plan Version 4 electronically signed and approved by Lilly on date provided below

Approval Date: 28-Feb-2019 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on April 07, 2016, prior to first patient visit.

SAP Version 2 was approved on June 12, 2018.

SAP Version 3 was approved prior to first unblinding on June 19, 2018.

SAP Version 4 was approved prior to Week 52 database lock on Febrary 28, 2019

Changes from Version 3:

Section	Action
Section 6.1.2, 6.1.3	Updated analysis for Period 3 and the combined periods 2 and 3
Section 6.1.5	Added All Ixekizumab Exposures Safety Population
Table 6.1	Added two columns for the ITT (Safety) Population Who are Initially Randomized to Ixekizumab at Week 0 and All Ixekizumab Exposures Safety Population
Table 6.2 and other sections	Updated the text according to the updates in Section 6.1.2, 6.1.3 and 6.1.5.
Appendix 6.	Updated norm for Week 52 DBL to use 2009 US population, and updated the term for the domain scores from 'raw' to 'transformed'
Table 6.4	Updated the derivation of ASDAS major improvement by adding the restriction of the minimum score of 0.6361.

Changes from Version 2:

Section	Action
Section 6.10 Table 6.4	Two rows were shifted from MASES all the way down to the bottom. Those were fixed in Version 3.
Section 6.14 Protocol Deviation Table 6.12	Fixed format of Table 12. When deleting a column from Version 1 to Version 2, some rows were accidently deleted. Those were brought back in Version 3
Entire document	Fixed some minor formatting issues

The overall changes and rationale for the changes incorporated in Version 2 from Version 1 are as follows:

Section	Action
Section 4 Objectives	Updated per protocol amendment (d) Changed the major secondary endpoint of ASDAS inactive disease to ASDAS <2.1 Changed the major secondary endpoint of BASDAI50 to BASDAI CFB
Section 5	Clarified stratification factor
Section 6.1.1 General Considerations for Period 2	Clarified analysis for CRP, ASDAS disease states, included analysis for ASDAS <2.1

Section	Action
Section 6.1.2 General Considerations for Period 3	Clarified baseline definition for TEAE for Period 3 per program safety analysis plan (PSAP 8.0 language; added additional safety analyses for combined period 2 and 3
Section 6.2. Adjustments for Covariates	Modified geographic regions for statistical analysis. Polished languages.
Section 6.3.5 Tipping Point Analysis	Updated methodology to 2-D analysis
Section 6.5 multiple comparison	Revised weights for graphical multiplicity testing procedure
Section 6.6 Patient disposition	Adding log-rank test for time to discontinuation
Section 6.7 Patient characteristics	Updated/clarified some baseline variables , adding spine SPARCC per protocol amendment
Section 6.7.2 Historical Illness and Preexisting Conditions	Updated analyses for pre-existing conditions for Period 2 and 3
Section 6.8 Treatment compliance	Updated population for treatment compliance analyses
Section 6.9.1 Previous Therapy	Removed Previous therapy due to redundancy to previous axSpA therapy
Section 6.9.2 Concomitant therapy	Removed summary of concomitant therapy for PSFU period
Section 6.10 Efficacy analyses Table 6.4	Changed the major secondary endpoint of ASDAS ID to ASDAS <2.1 activity Added change from Baseline for BASDAI 6 individual items Added variable for Good ASAS HI and improvement from Baseline ≥3 updated calculation for BASMI tragus to wall distance; clarified how to handle 'non-evaluable' for MASES; added additional descriptions and analysis for TJC/SJC; updated MRI related scores per protocol amendment; updated analysis for anterior uveitis;
Section 6.10 Efficacy analyses Table 6.5	Change major secondary endpoint of ASDAS ID to ASDAS <2.1 and updated the analysis Changed the major secondary endpoint of BASDAI50 to BASDAI CFB and updated the analysis Updated analyses for MRI related scores per protocol amendment a; Added additional analyses for TJC/SJC; Updated language for anterior uveitis Revised analysis for ASDAS disease activity states Updated analysis population for enthesitis and TJC/SJC, ASAS-NSAID score Added analysis for BASDAI 6 individual items Removed % improvement analysis for CRP, fatigue and JSEQ Removed time of 1st event analysis
Section 6.10.2 Major Secondary Efficacy Analyses	Updated MRI score per protocol amendment a
Section 6.10.4.1 Analyses on NSAID Intake	Added NSAID equivalent scoring system from reference and from medical input
Section 6.10.6 Health Outcome Tables 6.6 and 6.7	moved description of QIDS from Section 6.17.4 to this section
Section 6.11 Bioanalytical and PK methods	Updated text for PK analyses
Section 6.12.1 and 6.12.2.	Added exposure and AE for combined period 2 and 3 analysis

Section	Action
6.12.3.1 AESI Table 6.8	Text updates for definition/derivation of AESIs to be consistent with PSAP Removed duplicated or unnecessary analyses Changed Covance to performing lab reference range Wording updates per most recent PSAP for hepatic (T.Bili), infections, Allergic Reactions/Hypersensitivities, injection-site reactions, CV, malignancies, IBD)
6.12.4 Clinical Laboratory Evaluation	Added Grade 1-4 designations to each of the WBC parameters Clarified the reference ranges for WBC parameters and hepatic parameters
6.12.8 Immunogenicity	Updated text to be consistent with PSAP, clarified analyses for combined periods 2 and 3
6.13 and 6.14	Removed due to redundance in PKPD section
6.14 Subgroup analyses	Added subgroup analysis for TNFi, Baseline ASDAS, Baseline BASDAI and more
6.15 Protocol Deviations	Updated category/subcat/study spec for INC8, 12, 14, 35 due to protocol amendment Updated condition for exclusion from PPS for INC6, 30, 31, 37, EX-CM Removed statistical programming guidance to an external document
6.17.4 Planned Exploratory Health outcome analyses	Minor wording update
6.17.4 Tables 6.14 and 6.15	Moved the QIDS descriptions and analyses to Tables 6.6 and 6.7, respectively
Appendices 7-10	Updated per most recent PSAP
Appendix 11	Added per PSAP
Appendix 12, 13	Added ATC codes/terms for drug of specified interest; medical guidance on clinically meaningful change
Entire document	Made minor grammatical or formatting changes as needed

Abbreviations: AE = adverse event; AESI = adverse events of special interest; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASDAS ID = ASDAS Inactive Disease ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = ASAS Health Index; ASAS-NSAID = Assessment of SpondyloArthritis international Society Nonsteroidal Anti-inflammatory Drug; ATC = anatomical therapeutic chemical; axSpA = radiographic axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = an improvement of ≥50% of the BASDAI score from baseline (that is, if the value of % improvement from baseline is ≥50, BASDAI50 is met); BASMI = Bath Ankylosing Spondylitis Metrology Index; CFB = change from baseline; CRP = C-reactive protein; CV = cardiovascular; EX-CM = Excluded Con-meds ; IBD = Inflammatory Bowel Disease; JSEQ = Jenkins Sleep Evaluation Questionnaire; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score ; MRI = magnetic resonance imaging; PD = pharmacodynamics; PK -= pharmacokinetics; PSAP = program safety analysis plan ; QIDS = Quick Inventory of Depressive Symptomatology–Self Report; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; T.Bili = total bilirubin; TEAE = treatment-emergent adverse event; TJC = tender joint count; TNFi = tumor necrosis factor inhibitor.

4. Study Objectives

Objectives	Endpoints
Primary The primary objective is to compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active radiographic axial spondyloarthritis (rad-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 both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo at Week 16	• 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 Short Form 36 (SF-36) physical component score (PCS) • Change from baseline in ASAS Health Index (ASAS HI) • Change from baseline in magnetic resonance imaging (MRI) of the spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score). (This endpoint applies to MRI addendum only.)

Objectives	Endpoints

Other secondary objectives are:
• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo 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), inactive disease (ASDAS score <1.3) or 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
	  o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components
	  o Chest expansion
	  o Change from baseline in occiput to wall distance
	• Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
	• Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Score
	• Change from baseline in MRI of the spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity–Berlin Score [ASSpiMRI-Berlin]; this endpoint applies to MRI addendum only)
	• Incidence and severity of peripheral arthritis by tender (TJC) and swollen joint count (SJC) scores of 46/44 joints
	• Incidence rate of anterior uveitis or uveitis flares
	• Change from baseline in the following health outcomes measures: Fatigue Numeric Rating Scale (NRS) score, ASAS HI score, Jenkins Sleep Evaluation Questionnaire (JSEQ), 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.

Objectives	Endpoints
• To determine if the effect of either ixekizumab regimen 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 (with the exception of MRI-related endpoints). In addition, the following endpoint is added: • NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)
• To explore effect of starting dose (160 mg compared to 80 mg)	• Onset of action and treatment response (ASAS and CRP) during the placebo-controlled period
• To evaluate the incidence of anti-ixekizumab antibodies and their relationship to the 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: o Proportion of patients achieving ASAS40 o Proportion of patients achieving ASAS20 o Proportion of patients achieving ASDAS <2.1
• To measure ixekizumab exposure and assess the relationship between exposure and efficacy, and exposure and immunogenicity	• Serum trough concentrations of ixekizumab • Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, ASAS20, ASAS40) at Weeks 16 and/or 52 • Ixekizumab serum trough concentrations associated
CCI	

Abbreviations: CRP = C-reactive protein; DNA – deoxyribonucleic acid; mRNA = messenger ribonucleic acid; NSAID = nonsteroidal anti-inflammatory drug; Q2W = every 2 weeks; Q4W = every 4 weeks; TE-ADA = treatment-emergent anti-drug antibody.

5. Study Design

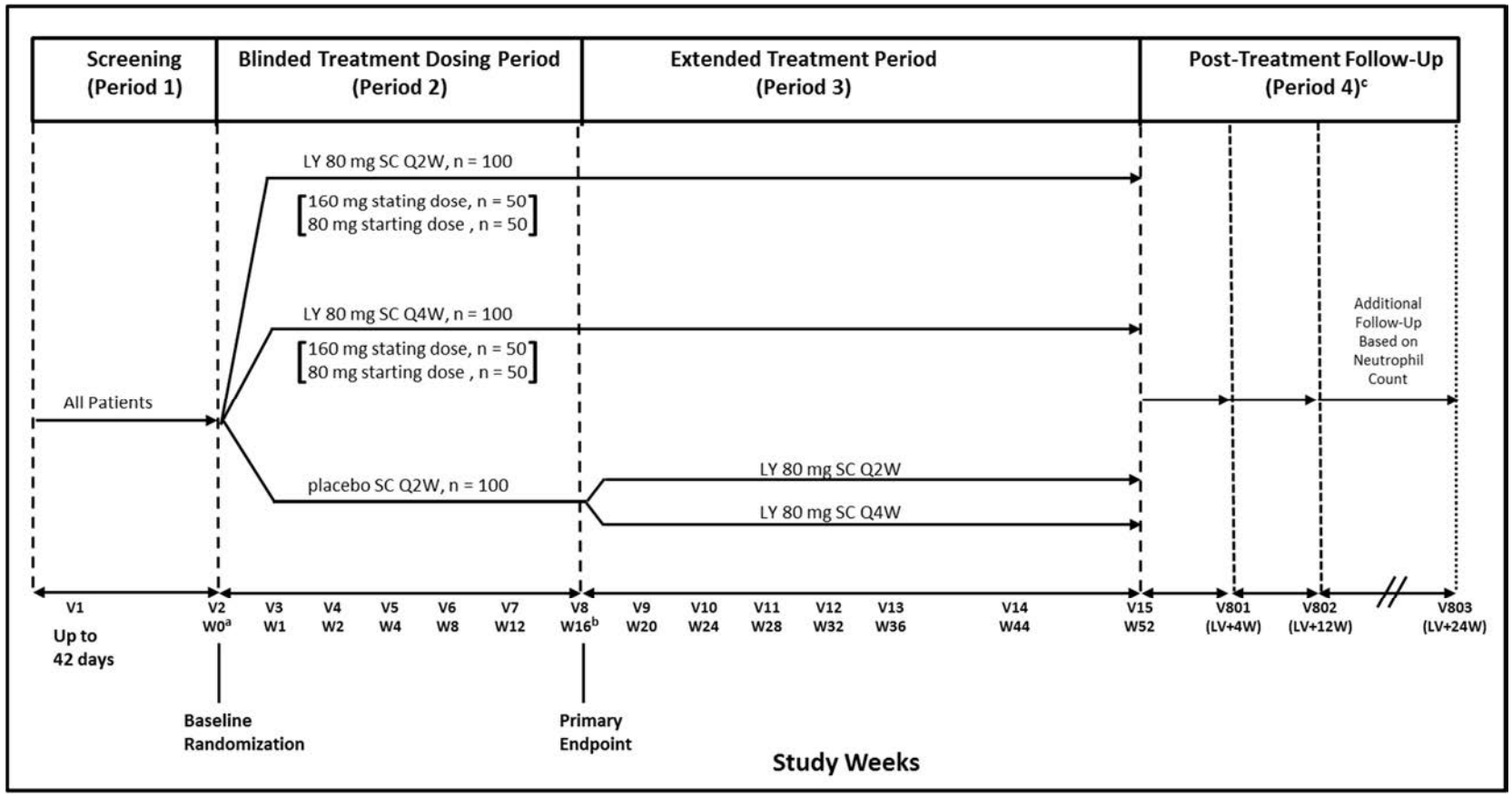
This section contains the summary of study design, the method of treatment assignment, and the sample size determination from the protocol for Study I1F-MC-RHBW (RHBW).

5.1. Summary of Study Design

Study RHBW is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of 2 ixekizumab treatment regimens (80 mg every 2 weeks [Q2W] and 80 mg every 4 weeks [Q4W] subcutaneous [SC]), as compared to placebo SC in patients with active radiographic axial spondyloarthritis (rad-axSpA) who are tumor necrosis factor (TNF) inhibitor-experienced, during a double-blind, 16-week treatment period (Period 2). Starting doses of 80 mg and 160 mg (at Week 0) will be evaluated for each ixekizumab regimen.

Study RHBW 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). Patients who complete Study RHBW may be eligible to enroll into a long-term study (Study I1F-MC-RHBY [RHBY]) for up to 2 additional years. Patients who do not enroll into Study RHBY will complete the Post-Treatment Follow-Up Period (Period 4) in Study RHBW.

Figure RHBW.5.1 illustrates the study design.



Abbreviations: LV = last visit; LY = ixekizumab; n = number of patients; Q2W = every 2 weeks; 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 6.1. Patients randomized to an ixekizumab regimen will be randomized to a 160 mg starting dose or 80 mg starting dose at a 1:1 ratio (within each ixekizumab regimen).

b All patients will receive 2 injections at Week 16, as detailed in Protocol Section 6.1. Patients randomized to placebo at Week 0 will begin ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at Week 16 with a 160 mg starting dose (Protocol Section 6.1).

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; V803 may be needed depending on neutrophil counts (Protocol Section 6.1).

Figure RHBW.5.1. Illustration of study design for Clinical Protocol I1F-MC-RHBW.

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 country, baseline C-reactive protein (CRP) (nonelevated or elevated, elevated defined as >5.00 mg/L) and number of prior tumor necrosis factor (TNF) inhibitor used (1 or 2). Due to operational feasibility, stratification by CRP is based on the most recent CRP before randomization, (that is, screening CRP). The study will enroll approximately 60% of patients with elevated screening CRP (>5.00 mg/L) and approximately 40% of patients with nonelevated screening CRP (≤5.00 mg/L), and approximately 60% of patients with 1 prior TNF inhibitor and approximately 40% of patients with 2 prior TNF inhibitors.

5.3. Determination of Sample Size

Approximately 300 patients will be randomized at a 1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo. With 100 patients per treatment group, CCI [redacted] hese assumptions are based on the review of historical clinical studies in rad-axSpA (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 data in patients who are TNF inhibitor experienced (Baeten et al. 2014; Sieper et al. 2014).

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The statistical analyses will be performed using SAS® Version 9.2 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.

All confidence intervals (CIs) and statistical tests will be 2-sided unless otherwise specified. P-values which are ≥ 0.001, and ≤ 0.999, will be presented to 3 decimal places. All other p-values which are <0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals (CIs) 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: American Indian or Alaska Native (AI), Asian (AS), Black or African American (BL), Native Hawaiian or other Pacific Islander (NH), White (WH), and Multiple (MU).

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

Comparisons between each ixekizumab regimen (80 mg Q2W or 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 before the first injection of study treatment at Week 16 (Visit 8) or the early termination visit (ETV) (between Weeks 0 and 16).

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 before 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 country, screening CRP status (nonelevated versus elevated), and number of prior TNF inhibitors used (1 or 2) as described in Section 5.2. The countries will be categorized into geographic regions for analysis. Geographic regions are defined in Section 6.2. Unless otherwise specified, the statistical analysis models will adjust for geographic region, baseline CRP status, and number of prior TNF inhibitors used.

Unless otherwise specified, treatment groups of ixekizumab 80 mg Q2W and Q4W groups will be analyzed without regard to starting dose.

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, geographic region (Europe and non-Europe), number of prior TNF inhibitors used, and baseline CRP status in the model using PROC Logistic with a Wald test. The odds ratio and 95% CIs will be reported; treatment difference and 95% CI will also be reported. Secondary analysis will be conducted using a Fisher's exact test. In the case when the 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 mixed-effects model of repeated measures [MMRM]) estimating the percentage of patients achieving response across postbaseline visits may be used. The model will include treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, 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 outcomes variables will be made using MMRM, except for magnetic resonance imaging (MRI) endpoints, which will be made using analysis of covariance (ANCOVA). A secondary analysis for continuous efficacy and health outcomes variables will be made using ANCOVA.

When the MMRM is used, the model will include treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, baseline value, visit, baseline value-by-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. The REML will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. 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 comparisons with placebo at Week 16 (Visit 8) and all other visits will be reported. If the unstructured covariance matrix results in a lack of convergence, the similar approach specified above for categorical MMRM will be used.

For the analysis of CRP, the MMRM model will include treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, visit, and treatment-by-visit interaction as fixed factors. Note, for the ratio of postbaseline to baseline in CRP, analysis will be performed on the natural log transformed ratio. When the ANCOVA is used, the model will include treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, and baseline value (except for the analysis of CRP; see paragraph below). Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For the analysis of CRP, the ANCOVA model will include treatment, geographic region, number of prior TNF inhibitors used, and baseline CRP status. Note, for the ratio of postbaseline to baseline in CRP, analysis will be performed on the natural log transformed ratio.

For the analysis of Ankylosing Spondylitis Disease Activity Score (ASDAS) disease activity states (that is, inactive, low, high, and very high disease states), the repeated measures proportional odds model will include treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, visit, and treatment-by-visit interaction.

The impact of ixekizumab starting dose of 160 mg versus 80 mg on treatment response at Week 16 and time to onset of action will be summarized and evaluated. Response rates in categorical variables (including ASAS40 and ASAS20) and LS mean change in continuous efficacy measure of CRP at Week 16 will be presented for patients randomized to ixekizumab Q2W or Q4W treatment regimen with ixekizumab 160-mg starting dose and with ixekizumab 80-mg starting dose.

For response rates, starting dose comparisons within ixekizumab Q2W or Q4W treatment regimens will be based on a logistic regression model with treatment, starting dose, and treatment-by-starting-dose interaction (only ixekizumab Q2W and Q4W will be included in the analyses). Starting dose comparison combining ixekizumab Q2W and Q4W treatment regimens will be based on a logistic regression model with only starting dose in the model.

For mean change analysis, starting dose comparisons within ixekizumab Q2W or Q4W treatment regimens will be based on a MMRM model with treatment, starting dose, baseline value, visit, baseline value-by-visit, treatment-by-visit, treatment-by-starting dose, starting dose-by-visit, and treatment-by-starting dose-by-visit interactions as fixed factors. Starting dose comparison combining ixekizumab Q2W and Q4W treatment regimens will be based on a MMRM model with starting dose, baseline value, visit, baseline value-by-visit, and starting dose-by-visit

interaction as fixed factors. The differences in response rates and LS mean changes between starting doses and the corresponding 95% CI will be reported as well.

Time-to-onset analyses will focus on earlier time points (for example, Weeks 1, 2, 4, and so on) for abovementioned response variables in a similar fashion. For time-to-first-clinical-response analysis, starting dose comparisons within and across ixekizumab Q2W and Q4W treatment regimens will be based on a log-rank test.

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 and categorical MMRM analyses (Andersen and Millen 2013). However, the data will still be used in other analyses, including shift analyses, change from baseline to last-observation carried forward (LOCF) or modified baseline observation carried forward (mBOCF) endpoint analyses, and other categorical analyses.

For selective continuous efficacy variables, 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 Week 0 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 geographic region, number of prior TNF inhibitors used, and baseline CRP status. 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 events (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 15) or the ETV (between Weeks 16 and 52).

For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first injection in Period 2 and, in most cases, 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 considered as those events that are ongoing before the first injection of the study treatment at Week 16.

The number and percentage of patients having a categorical efficacy response (for example, ASAS40) will be summarized by treatment group for all scheduled visits (nonresponder imputation [NRI]), including Week 52 (Visit 15) during Period 3.

In addition, the number and percentage of patients achieving response on ASAS20 for those patients who did not achieve it at Week 16, and the number and percentage of patients maintaining response for those who achieved response at Week 16 will be summarized by treatment group for all scheduled visits (NRI), including Week 52 (Visit 15) during Period 3. Similar summary will be provided for ASAS40.

Each continuous efficacy and health outcomes score and change from baseline (or percent improvement) will be summarized by treatment group at all scheduled visits, including Week 52 (Visit 15) 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 outcomes analyses will be performed for Combined Periods 2 and 3 for the ITT population who are randomized to ixekizumab at Week 0 (Visit 2). These analyses include the primary endpoint, all major secondary endpoints, as well as BASDAI50, ASDAS inactive disease, ASDAS clinically important improvement and major improvement.

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 15) or the ETV (between Weeks 0 and 52).

For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first injection in Period 2 and, in most cases, 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 before 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 15).

Continuous measure score and change from baseline will be summarized by treatment group at all scheduled visits, including Week 52 (Visit 15) using descriptive statistics (n, mean, SD, median, minimum, and maximum). Missing data will be imputed using mBOCF method (Section 6.3.2).

Selected 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 the 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, and will include only periods in which ixekizumab is administrated. Exposure-adjusted incidence rates of AEs during Week 0-52 timeframe will be provided. For these safety analyses, baseline is defined as follows:

- 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 nonmissing value up to visit (V8) that the patient receives first 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 nonmissing assessment on or before entering Period 4, that is, on or before Week 52 (Visit 15), or ETV.

Safety data collected will be summarized using descriptive statistics.

Efficacy data collected during Period 4 will be summarized as described in Section 6.10.5.

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 do not have a subset of important protocol deviations that impact the primary efficacy endpoint (Section 6.14). For example, patients who are not compliant with therapy during the double-blind period will be excluded from the PPS. Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses (all injections in 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 1 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 Period 4. Patients will be analyzed according to the treatment they received before entering the Follow-up Period. Table RHBW.6.1 summarizes the major analysis purposes intended for each analysis population.

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

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

	ITT Population	Per-Protocol Set	Safety Population	Extended Treatment Period Population	ITT Safety 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 Combined Periods 2 and 3	For Periods 2 and 3, on ixekizumab treatment only	
Efficacy and Health Outcomes Analyses	For Period 2; For Period 4, only ASAS40	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 Combined Periods 2 and 3	For Periods 2 and 3, on ixekizumab treatment only	For Period 4
Subgroup Analyses on Efficacy Outcome	For Period 2						
Subgroup Analyses on Safety Outcome			For Period 2				

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ITT = intent-to-treat.

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

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

Study Period	Analysis Population	Treatment Group	Abbreviation	Comparison
Blinded Treatment Dosing Period (Period 2)	Intent-to-Treat Population; Per Protocol Set; Safety Population	Placebo Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q2W Total Ixekizumab Total Add the following treatment groups for analyses evaluating the impact of ixekizumab starting dose: Ixekizumab 80 mg Q4W/80 mg Starting Dose Ixekizumab 80 mg Q4W/160 mg Starting Dose Ixekizumab 80 mg Q2W/80 mg Starting Dose Ixekizumab 80 mg Q2W/160 mg Starting Dose Total Ixekizumab/80 mg Starting Dose Total Ixekizumab/160 mg Starting Dose	PBO IXE80Q4W IXE80Q2W Total IXE Total IXE80Q4W/80S[b] IXE80Q4W/160S[b] IXE80Q2W/80S[b] IXE80Q2W/160S[b] Total IXE/80S[b] Total IXE/160S[b]	IXE80Q4W vs. PBO IXE80Q2W vs. PBO Overall[a] IXE80Q4W/80S[b] vs. IXE80Q4W/160S[b] IXE80Q2W/80S[b] vs. IXE80Q2W/160S[b] Total IXE/80S[b] vs. Total IXE/160S[b]
Extended Treatment Period (Period 3)	Extended Treatment Period Population	Placebo/Ixekizumab 80 mg Q4W Placebo/Ixekizumab 80 mg Q2W Ixekizumab 80 mg Q4W/Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q2W/Ixekizumab 80 mg Q2W Placebo/Ixekizumab 80 mg Ixekizumab 80 mg/Ixekizumab 80 mg Total	PBO/IXE80Q4W PBO/IXE80Q2W IXE80Q4W/IXE80Q4W IXE80Q2W/IXE80Q2W PBO/IXE IXE/IXE Total	No Between-Group or Overall Comparisons
Combined Periods 2 and 3	Intent-to-Treat Population Who are Initially Randomized to Ixekizumab	Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q2W Total Ixekizumab	IXE80Q4W IXE80Q2W Total IXE	No Between-Group or Overall Comparisons
Combined Periods 2 and 3	Safety Population Who are Initially Randomized to Ixekizumab	Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q2W Total Ixekizumab	IXE80Q4W IXE80Q2W Total IXE	No Between-Group or Overall Comparisons

Treatment Groups and Comparisons for Each Study Period and Analysis Population

Combined Periods 2 and 3 (on Ixekizumab treatment only)	All Ixekizumab Exposures Safety Population [e]	Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q2W Total Ixekizumab	IXE80Q4W IXE80Q2W Total IXE	No Between-Group or Overall Comparisons
Post-Treatment Follow-up Period (Period 4) [d]	Follow-Up Population	Placebo Ixekizumab 80 mg Q4W Ixekizumab 80 mg Q2W Total Ixekizumab Total	PBO IXE80Q4W IXE80Q2W Total IXE Total	No Between-Group or Overall Comparisons

Abbreviations: IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; IXE = Ixekizumab including IXE80Q2W and IXE80Q4W; PBO = placebo.

[a] Overall comparison will be conducted for demographics, historical illness, medical history, pre-existing condition, and previous therapy. The between-group comparisons and the overall comparison will be conducted for concomitant therapy, compliance, disposition, and safety.

[b] S=Starting does; differences between starting dose groups and 95% CI will be provided.

[c] For Extended Treatment Period Population, 'Total Ixekizumab 80 mg Q4W' is a pooled group of 'Placebo/Ixekizumab 80 mg Q4W', and 'Ixekizumab 80 mg Q4W/Ixekizumab 80 mg Q4W'; similarly, 'Total Ixekizumab 80 mg Q2W' is a pooled group of 'Placebo/Ixekizumab 80 mg Q2W', and 'Ixekizumab 80 mg Q2W/Ixekizumab 80 mg Q2W'.

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

[e] Defined as all patients who received at least 1 dose of ixekizumab during the study

6.2. Adjustments for Covariates

The countries will be categorized into geographic regions for statistical analysis Table RHBW.6.3). Unless otherwise specified, the statistical analysis models will adjust for geographic region, baseline CRP status (nonelevated or elevated), and number of prior TNF inhibitors used (1 or 2).

Below are the initial country allocations.

Table RHBW.6.3. Geographic Regions for Statistical Analysis

Geographic Region	Country or Countries
Non-Europe	United States, Canada, Mexico, Korea, Argentina, Israel, Brazil
Europe	Finland, France, Poland, Germany, Italy, Spain, UK, The Netherlands

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 outcomes variables will be assessed based on treatment success/failure. This approach yields results numerically identical to NRI, but it is interpreted differently. Patients will be considered treatment failures if they do not meet the clinical response criteria or have missing clinical response data at the primary analysis time point. Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

With NRI, as the acronym implies, there is explicit imputation of missing ASAS40 outcomes. With treatment success/failure, discontinuation of study medication is considered a treatment failure because if patients cannot adhere to the medication, they will not have sustained benefit from it. Therefore, every patient will have an observation for treatment success/failure and there will be no missing data for this estimand, and hence inferences will not depend on missing data assumptions. These attributes also apply to other endpoints involving use of NRI.

6.3.2. Modified Baseline Observation Carried Forward

An mBOCF analysis will be performed on continuous efficacy and health outcomes 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. Last Observation Carried Forward

An LOCF analysis will be performed on continuous efficacy and health outcomes variables in the major secondary objectives. This approach is identical to the mBOCF approach, with 1 exception: for patients discontinuing study drug because of an AE, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding time point for evaluation. Randomized patients without any postbaseline observation will not be included for evaluation.

6.3.4. Placebo Multiple Imputation

The placebo multiple imputation (pMI) method will be used for the analyses of primary efficacy endpoints ASAS40, major secondary efficacy endpoints ASAS20, and ASDAS change from baseline at Week 16 (Visit 8). Appendix 1 presents the detailed scientific justification of the pMI method.

Placebo multiple imputation assumes that the statistical behavior of drug- and placebo-treated patients after discontinuing study medication becomes that of placebo-treated patients. Multiple imputations (MIs) are used to replace missing outcomes for drug- and placebo-treated patients who discontinued, utilizing multiple draws from the posterior predictive distribution estimated from the placebo arm.

Data are processed sequentially by repeatedly calling SAS® PROC MI to impute missing outcomes at visits t=1,.., T.

1. *Initialization*. Set t=0 (baseline visit).
2. *Iteration*. Set t=t+1. Create a dataset combining records from drug- and placebo-treated patients with columns for covariates **X** and outcomes at visits 1,..,t with outcomes for all drug-treated patients set to missing at visit t and set to observed or imputed values at visits 1,..,t-1.
3. *Imputation*. Run Bayesian regression in SAS® PROC MI on this data to impute missing values for visit t using previous outcomes for visits 1 to t-1 and baseline covariates. Note that only placebo data will be used to estimate the imputation model since no outcome is available for drug-treated patients at visit t.
4. Replace imputed data for all drug-treated patients at visit t with their observed values, whenever available. If t<T, then go to Step 2, otherwise proceed to Step 5. Repeat Steps 1 to 4 m times with different seed values to create m imputed complete datasets.
5. *Analysis*. For each completed dataset, use the model as would have been applied had the data been completed for continuous outcome. For the efficacy endpoints, ASAS20 and ASAS40, the missing binary outcomes will be imputed directly for each patient before fitting into the analysis model. A logistic regression model will be applied.

The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules, as implemented in SAS® PROC MI ANALYZE.

Thus, in the effectiveness context, pMI assumes no pharmacological benefit of the drug after dropout but is a more reasonable approach than mBOCF because, unlike BOCF and mBOCF, pMI accounts for uncertainty of imputation, and therefore does not underestimate standard errors and limits bias by taking into account study/placebo effects. In the efficacy context, pMI is a specific form of a missing-not-at-random (MNAR) analysis expected to yield a conservative estimate of efficacy.

6.3.5. Tipping Point Analyses

To evaluate the robustness of statistical analyses of key efficacy data and assumptions inherent in missing data imputation methods, tipping point analyses will be used for the missing data of ASAS40, ASAS20, as well as mean change from baseline in ASDAS at the primary time point of Week 16. Appendix 2 presents the detailed scientific justification of the tipping point method.

For continuous variable (mean change in ASDAS at Week 16), a 2-step MI method is used to impute missing data independently by treatment group.

1. The first step is to create a monotone missing pattern using a Markov chain Monte Carlo method (using SAS® Proc MI with MCMC option) to handle intermittent missing data.
2. The second step is to use a set of Bayesian regressions (using Proc MI with MONOTONE option, 20 imputed data sets) for the imputation of monotone dropouts. The regression models are fit sequentially starting from the first visit with at least 1 missing response using treatment as a fixed effect and values (observed or imputed) from the previous visits as covariates. All patients in the ITT Population with a baseline value are included in the analyses, and all observed data are utilized from each patient, regardless of adherence to randomized treatment. A delta score is added to all imputed scores (at the primary time point) for patients in any ixekizumab treatment group to evaluate a scenario in which patients treated with ixekizumab would have worse outcomes than patients treated with placebo. An independent delta score will be added to the placebo group and is capped for individual patients based on the range of the outcome measure being analyzed. The delta score will not be added to the observed values.

Analyses using the principal analysis model are aggregated across the *m* imputed data sets using SAS® PROC MI ANALYZE to compute a p-value for the treatment comparison for a given value of the delta score.

Sensitivity of the analysis conclusion to the choice of delta score is determined by repeating the aforementioned MI steps and analyses by gradually increasing the delta score, thus evaluating scenarios with increasingly worse imputed values for missing data for patients treated with ixekizumab. The tipping point is identified as the delta score value, which leads to a loss of statistical significance when evaluating ixekizumab relative to the placebo group.,

The tipping point analysis will be used for categorical data (ASAS40 or ASAS20 at Week 16) in a similar fashion.

- For ixekizumab groups, a range of response probability (for example, probability = 0, 0.1, 0.2, …, respectively) will be used to impute the missing values for ASAS40 or ASAS20 (each probability is imputed based on 20 data sets). NRI will be used as the most extreme case.
- For placebo group, different response probability (for example, probability=0, 0.2, … 1, respectively) will be used to impute the missing values for ASAS40 or ASAS20 (each probability is imputed based on *m* data sets).
- Analyses using the principal analysis model are aggregated across the *m* imputed data sets using SAS® PROC MI ANALYZE to compute a p-value for the treatment comparison for a given value of the response probability.

Sensitivity of the analysis conclusion is determined by gradually increasing the response probability value, thus evaluating scenarios with increasingly imputed response rate for patients treated with placebo. The tipping point is identified as the probability value, which leads to a loss of statistical significance when evaluating ixekizumab relative to the placebo group.

6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. The countries will be categorized into geographic regions, as described in Section 6.2, for analysis.

For the analysis of the primary endpoint, the presence of a treatment-by-geographic region interaction will be tested at 10% significance level. Treatment group comparisons for the primary outcome will be presented separately for each geographic region. When there is evidence of an interaction ($p<.10$), descriptive statistics may be used to assess whether the interaction is quantitative (that is, the treatment effect is consistent in direction but not size of effect) or qualitative (the treatment is beneficial for some but not other geographic regions or countries).

6.5. Multiple Comparisons/Multiplicity

A multiple testing strategy for the primary and major secondary objectives will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05. The primary outcome will be tested by using the primary analysis method, logistic regression analysis with treatment, geographic region, number of prior TNF inhibitors used, and baseline CRP status in the model, with NRI missing data imputation approach.

A graphical multiple testing procedure (Bretz et al. 2011) will be used (Figure RHBW.6.1). The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate (Alosh et al. 2014). The following is a list of primary and major secondary outcomes to be tested for both ixekizumab 80 mg Q2W and Q4W regimen at Week 16:

Primary - proportion of patients achieving an ASAS40 response [ASAS40]
Secondary 1 - proportion of patients achieving an ASAS20 response [ASAS20]
Secondary 2 - change from baseline in ASDAS score [ASDAS change from baseline (CFB)]

Secondary 3 - change from baseline in BASDAI score [BASDAI CFB]
Secondary 4 - change from baseline in BASFI [BASFI CFB]
Secondary 5 - change from baseline in SF-36 PCS score [SF-36 PCS CFB]
Secondary 6 - proportion of patients achieving ASDAS <2.1 [ASDAS<2.1]
Secondary 7 - change from baseline in ASAS Health Index (ASAS HI) [ASAS HI CFB]
Secondary 8 - change from baseline in MRI of the spine [MRI spine SPARCC score CFB]

With the exception of secondary outcome 8 (MRI spine SPARCC score CFB), the remaining secondary outcomes are grouped into 2 tiers (Figure RHBW.6.1, Figure RHBW.6.2, and Figure RHBW.6.3) based on the clinical importance as well as statistical significance observed in historical axSpA studies.

Figure RHBW.6.1 shows the graphical testing scheme with initial α allocation and weights, and Figure RHBW.6.2 and Figure RHBW.6.3 show the graphical testing schemes used within the Tier 1 and Tier 2 groups of endpoints respectively. The testing steps are outlined below:

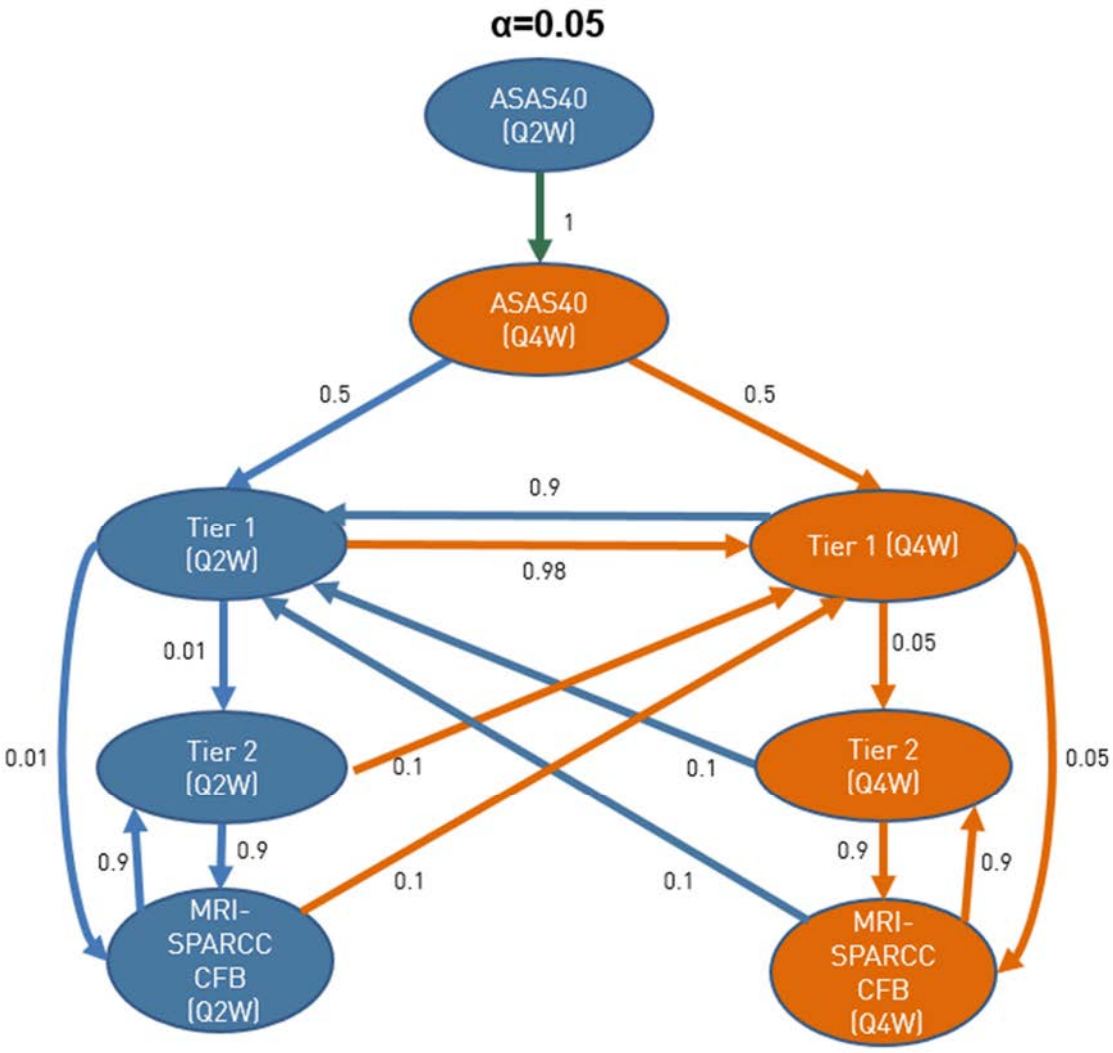
Step 1: The primary outcome of ASAS40 will be tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided α=0.05. If the null hypothesis is not rejected, no further testing is conducted as the α for that test is considered 'spent' and cannot be passed to other endpoints. If the null hypothesis is rejected, then move to Step 2.

Step 2: The primary outcome of ASAS40 will be tested for ixekizumab 80 mg Q4W versus placebo at a 2-sided α=0.05. If the null hypothesis is not rejected, no further testing is conducted as the α for that test is considered 'spent' and cannot be passed to other endpoints. If the null hypothesis is rejected, then move to Step 3.

Step 3: α=0.025 will be distributed to Tier 1 set of secondary outcomes for ixekizumab 80 mg Q2W (blue circles in Figure RHBW.6.2), and the remaining α=0.025 will be distributed to Tier 1 set of secondary outcomes for ixekizumab 80 mg Q4W (green circles in Figure RHBW.6.2).

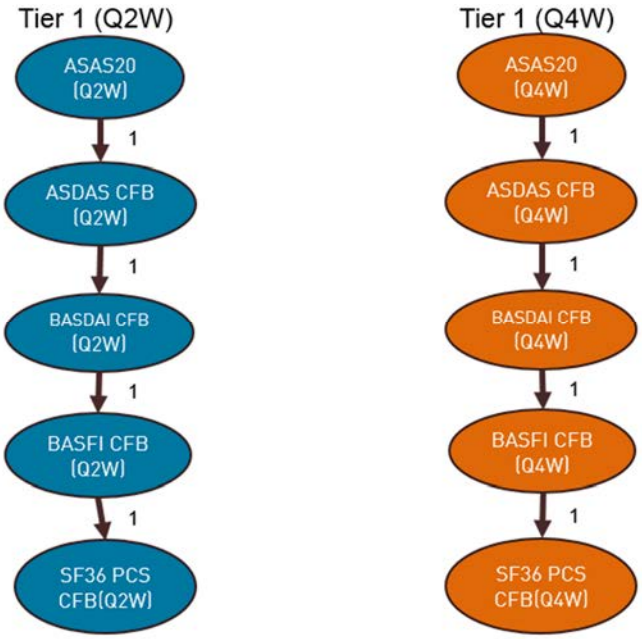
The major secondary endpoints for both doses will be tested according to the procedure specified by the graphs.

The testing process continues for the remaining outcomes by allocating the remaining α to the next set of outcomes as long as at least 1 hypothesis can be rejected. Each time a hypothesis is rejected, the graph is updated to reflect the reallocation of α, which is considered "recycled" (Alosh et al. 2014). This iterative process of updating the graph and reallocating α is repeated until all major secondary hypotheses have been tested or when no remaining hypotheses can be rejected at their corresponding α level. The weights along the edges for α allocation between ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W outcomes as well as within each of the tiers are prespecified in Figure RHBW.6.1, Figure RHBW.6.2, and Figure RHBW.6.3.



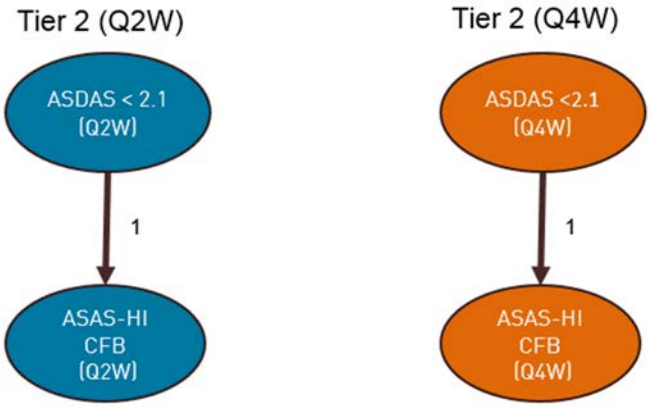
Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; CFB = change from baseline; Q2W = every 2 weeks; Q4W = every 4 weeks; SPARCC = Spondyloarthritis Research Consortium of Canada.

Figure RHBW.6.1. Illustration of graphical multiple testing procedure with initial α allocation and weights.



Abbreviations: 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; CFB = change from baseline; Q2W = every 2 weeks; Q4W = every 4 weeks; SF-36 PCS = Short Form 36 physical component score.

Figure RHBW.6.2. Graphical multiple testing scheme used within the Tier 1 group of endpoints.



Abbreviations: ASAS HI = ASAS Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; CFB = change from baseline; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure RHBW.6.3. Graphical multiple testing scheme used within the Tier 2 group of endpoints.

There will be no adjustment for multiple comparisons for any other analyses.

6.6. Patient Disposition

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 6.1.5):

- 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 15), and completing Follow-Up Visits 801, 802, and 803 if they are not going to enter Study RHBY, by the initial randomized treatment group (Analysis population: ITT)
- The number and percentage of patients completing Period 2 (Blinded Treatment Dosing Period) and the number and percentage of patients discontinuing from Period 2, by treatment group and primary reason for discontinuation (Analysis population: ITT)
- Fisher's exact test will be used to test for difference between treatment groups in the proportion of patients discontinuing from Period 2 and in the proportion of patients discontinuing for each reason during Period 2.
- The number and percentage of patients completing Period 3 (Extended Treatment Period) and the number and percentage of patients discontinuing from Period 3, by treatment group and primary reason for discontinuation (Analysis population: Extended Treatment Period Population)
- The number and percentage of patients completing Period 4 and the number and percentage of patients discontinuing from Period 4, by treatment group and primary reason for discontinuation (Analysis population: Follow-Up Population)

- The time to discontinuation of the treatment period due to any reason (in weeks) will be summarized by treatment group and graphically presented using Kaplan-Meier techniques, for the Blinded Treatment Dosing period. The time to discontinuation of the treatment period will be calculated as:

$$\frac{Date\ of\ discontinuation\ of\ period - Date\ of\ first\ dose\ in\ period + 1}{7}$$

Patients completing the treatment period will be censored at the date of completion (that is, the date of the last scheduled visit in the period). Patients without a date of treatment period completion or discontinuation will be censored at the latest nonmissing date out of the following dates: date of last dose in the treatment period and date of last attended visit in the treatment period (scheduled or unscheduled) (Analysis population: ITT Population). The log-rank test will be used to test for differences in the time to discontinuation between the 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).

6.7. Patient Characteristics

6.7.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized for the ITT Population and Extended Treatment Period Population.

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.

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.

Demographics and baseline characteristics:

- Age (in years): calculated using an imputed date of birth of 01 July in the year of birth collected in the electronic case report form (eCRF). Age will be calculated as:

  Age = floor((intck('month', brthdtc, rfstdtc) - (day(rfstdtc) < day(brthdtc)))/12)

  where brthdtc = Imputed date of birth, and rfstdtc = subject reference start date (that is, the date when patient is first exposed to study treatment)

- Age category:
  - Age category: <40 years, ≥40 years
  - Age category: <50 years, ≥50 years
  - Age category: <65 years, ≥65 years
- Sex
- Race
- Ethnicity
- Geographic region:
  - United States (US, including Puerto Rico) or non-US
  - Europe or Non-Europe
  - North America (US, including Puerto Rico sites, Canada) or Rest of the World (ROW)
  - America, Asia, Europe or ROW
- Country
- Weight (kg)
- Weight category: <70 kg or ≥70 kg
- Weight category: <70 kg, ≥70 to <90 kg, ≥90 kg
- Body mass index (BMI) (kg/m^2) will be calculated as:

$$BMI\ (kg\ /\ m^2) = \frac{Weight\ (kg)}{(Height\ (m)\ at\ Visit\ 2)^2}$$

- BMI category:
  - 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)
- Age of onset of axSpA (in years)
- Duration of symptoms since axSpA onset (in years) will be calculated using the date of onset of spondylitis disease (as recorded on the *Prespecified Medical History: Axial Spondyloarthritis* eCRF page) as follows:

$$Duration\ of\ \text{symptoms}(years) = \frac{Date\ of\ informed\ consent - Date\ of\ onset\ of\ axial\ spondylitis}{365.25}$$

- Duration of symptom since axSpA onset category: <10 years, ≥10 years
- Duration of symptom since axSpA onset category: <5 years, ≥5 years
- Duration of symptom since onset category: <3 years, ≥3 years
- Duration of disease since axSpA diagnosis (in years) will be calculated using the date of diagnosis of spondylitis disease (as recorded on the *Prespecified Medical History: Axial Spondyloarthritis* eCRF page) as follows:

$$Duration\ of\ disease\ since\ diagnosis\ (years) = \frac{Date\ of\ informed\ consent - Date\ of\ \text{diagnosis o}f\ axial\ spondylitis}{365.25}$$

- Human leukocyte antigen B27 (HLA-B27) positivity: n (%)
- Inflammatory back pain: n (%)
- Current and/or history of extra-axial involvement separately for: n (%):
  - anterior uveitis
  - psoriasis
  - inflammatory bowel disease (including Crohn's disease or ulcerative colitis)
  - dactylitis
  - arthritis
  - enthesitis

Baseline CRP level:

- CRP (mg/L)
- CRP categories: n (%):
  - ≤3.00 mg/L, >3.00 mg/L ≤5.00 mg/L, >5.00 mg/L
  - ≤10.00 mg/L, >10 mg/L
  - ≤15.00 mg/L, >15.00 mg/L

Baseline disease activity level, pain, function, and mobility:

- Ankylosing Spondylitis Disease Activity Score (ASDAS) and ASDAS≤3.5 or ASDAS >3.5
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and 4≤ BASDAI <6 or BASDAI ≥6
- Patient global assessment of disease activity (numeric rating scale [NRS])
- Inflammation (mean of questions 5 and 6 of BASDAI)
- Fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness and duration of morning stiffness (BASDAI question 1-6)
- Pain, NRS: spinal pain at night due to AS
- Pain, NRS: spinal pain due to AS
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Metrology Index–Spinal Mobility (BASMI Linear)
- Chest expansion (in cm)
- Occiput-to-wall measurement (in cm)

Baseline peripheral arthritis and enthesitis:

- Tender Joint Count (TJC) based on 46 joints
  - TJC: mean (SD)
  - patients with >0 tender joint: n (%)

  - patients with current or historical peripheral arthritis
- Swollen Joint Count (SJC) based on 44 joints
  - SJC: mean (SD)
  - patients with >0 swollen joint: n (%)
  - patients with current or historical peripheral arthritis
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
  - MASES: mean (SD)
  - patients with MASES >0: n (%)
- Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis score
  - SPARCC: mean (SD)
  - patients with SPARCC score >0: n (%)

Baseline health outcomes measures:

- ASAS Health Index (ASAS HI), ASAS HI baseline ≥3 and ASAS HI baseline>5
- Fatigue Severity NRS
- Jenkins Sleep Evaluation Questionnaire (JSEQ)
- European Quality of Life–5 Dimensions–5 Level (EQ-5D-5L) (EuroQol Group 2011 [WWW])
- Work Productivity and Activity Impairment Questionnaire–Spondyloarthritis (WPAI-SpA)
- Short Form (36 items) Health Survey – SF36 Physical Component Summary (PCS) and Mental Component Summary (MCS) score
- QIDS-SR16 Total Score
- QIDS-SR16 Item 12

Baseline concomitant therapy use:

- Disease-modifying antirheumatic drugs (DMARDs) use: n (%)
  - Overall and separately for methotrexate, sulfasalazine, hydroxychloroquine
- Baseline dosage for methotrexate, sulfasalazine, hydroxychloroquine
- Oral corticosteroid use: n (%)

Previous therapy: axSpA: n (%)

- Biologic agent
  - Number of TNF inhibitor used 1 or 2, n (%) (Please refer to Appendix 12 for the medication list for TNF inhibitors.)
- Nonbiologic systemic agent
- Nonbiologic nonsystemic agent

Habit:

- Tobacco use: former, current or never
  - Cigarette use: ≤10 per day versus >10 per day
- Alcohol consumption: former, current, or never

- Caffeine/xanthine ingestion: former, current, or never

Baseline NSAID (including COX-2 inhibitors) use:

- Assessment of SpondyloArthritis International Society Nonsteroidal Anti-inflammatory Drug (ASAS-NSAID) score
- Patients with NSAIDs (including COX-2 inhibitors) use: n (%)

Baseline Imaging of Spine

- MRI of spine SPARCC score
  - SPARCC spine MRI: mean (SD)
  - SPARCC spine score ≥2: n (%)
- MRI of spine Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity–Berlin Score (ASSpiMRI-Berlin) score
  - ASSpiMRI-Berlin MRI: mean (SD)
  - ASSpiMRI-Berlin score >0, n (%)

6.7.2. Historical Illness and Pre-existing Conditions

Historical illnesses and pre-existing 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 before the date of informed consent.

Pre-existing 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 before 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 (Period 3) is defined as those pre-existing conditions and AEs, which are ongoing at the treatment period baseline. Notice if a pre-existing condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on the *Adverse Events* eCRF page from the date of worsening onwards.

The following summaries will be provided for the ITT Population and/or 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 only)
- The number and percentage of patients with pre-existing conditions and AEs before first dose by treatment group and overall, by SOC and Preferred Term (PT) (ITT Population only)
- The number and percentage of patients with pre-existing conditions by treatment group and overall, by SOC and PT (Extended Treatment Period Population 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 noninsulin dependent; coronary artery disease; history of stroke and dyslipidemia) by treatment group and overall
- The number and percentage of patients with SpA features as part of ASAS criteria for classification of axSpA 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. The comparisons among treatment groups will be conducted using Fisher's exact test.

By-patient listings of historical illnesses and pre-existing conditions, respectively, for the ITT Population will be provided.

6.8. 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:

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

- For patients who complete Period 2, the number of injections prescribed (that is, expected) during Period 2 will be equal to 9 (2 injections at Week 0 and 1 injections every 2 weeks from Week 2 to Week 14).
- For patients who discontinue during Period 2, the number of injections prescribed during Period 2 can be derived from the IWRS study drug dispense dataset.
- For patients who complete Period 3, the number of injections prescribed (that is, expected) during Period 3 will be equal to 19 (2 injections at Week 16 and 1 injection every 2 weeks from Week 18 to Week 50).
- For patients who discontinue during Period 3, the number of injections prescribed during Period 3 can be derived from the IWRS study drug dispense dataset.
- 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 in 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. The comparisons between treatment groups during Period 2 will be conducted using Fisher's exact test.

A by-patient listing of study treatment administration and compliance for the Safety Population will be provided.

6.9. 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.

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

6.9.1. Previous Therapy

Previous therapy is defined as the therapy that starts and ends before 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 before 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 SpA therapy captured in the *Prior Therapy: Axial Spondyloarthritis eCRF* page to be summarized according to type (biologic agent, nonbiologic systemic agent, nonbiologic nonsystemic agent) and therapy. The previous biologic agent will be further classified as TNF-α inhibitor (includes infliximab, etanercept, adalimumab, golimumab, certolizumab pegol).
- The number and percentage of patients with each reason for discontinuation of previous SpA therapy to be summarized by type and therapy

The comparisons among treatment groups in Period 2 will be conducted using Fisher's exact test.

6.9.2. 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 that 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 the following study periods and analysis populations:

- General concomitant therapy by WHO ATC Level 4 and WHO PT for:
  - Period 2 (ITT Population)
  - Period 3 (Extended Treatment Period Population)
- Concomitant conventional DMARDs (cDMARDs), systemic corticosteroids, NSAID (including COX-2 inhibitors), and opioids use for:
  - Period 2 (ITT Population)
  - Period 3 (Extended Treatment Period Population)

The definition of above medication is provided in Appendix 12.

- The number and percentage of patients who received premedication for allergic reaction/hypersensitivity captured in the *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page will be summarized for Periods 2.

Comparisons between treatment groups will be conducted in Period 2 for the ITT Population using Fisher's exact test.

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

- For the start date:
  - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
  - If either month or month and day are missing, then use 01 January.
  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59.
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date.
  - If either month or month and day are missing, then use 31 December.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the medication will be flagged as concomitant.

6.10. Efficacy Analyses

Table RHBW.6.4 includes the description and derivation of the primary and secondary efficacy outcomes.

Sections 6.10.1, 6.10.2, 6.10.3, 6.10.4, and 6.10.5 summarize the analyses for primary and secondary efficacy measures.

Table RHBW.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for primary and secondary efficacy analyses.

Table RHBW.6.4. Description and Derivation of Primary and Secondary Efficacy Outcomes

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
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 questions 5 and 6) 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 3 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 the item score is missing
		Patient Global change from baseline and % improvement from baseline	Change from baseline calculated as: observed patient global – baseline patient global Percent improvement from baseline calculated as: $100 \times \frac{Baseline - Observed\ score}{Baseline}$	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
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): 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, 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 the item score is missing
		Spinal Pain change from baseline and % improvement from baseline	Change from baseline calculated as: observed spinal pain – baseline spinal pain Percent improvement from baseline calculated as: $100 \times \frac{Baseline\ -Observed\ score}{Baseline}$	Missing if baseline or observed value is missing
		Spinal Pain at night, NRS	Range: 0 to 10 "0" (no pain) and "10" (most severe pain)	Single item, missing if the item score is missing
		Spinal Pain at night change from baseline and % improvement from baseline	Change from baseline calculated as: observed spinal pain at night – baseline spinal pain at night Percent improvement from baseline calculated as: $100 \times \frac{Baseline\ -Observed\ score}{Baseline}$	Missing if baseline or observed value is 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 rad-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 or more hours)	Missing if both Q5 and Q6 are missing; if Q6 is missing, then use the Q5 as inflammation score.
		BASDAI score	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.
		BASDAI, 6 individual item and inflammation change from baseline and % improvement from baseline	Change from baseline calculated as: observed score – baseline score Percent improvement from baseline calculated as: $100 \times \frac{Baseline\ -Observed\ score}{Baseline}$	Missing if baseline or observed value is missing
		BASDAI50 – **major secondary outcome**	$Percent\ improvement\ from\ baseline\ = 100 \times \frac{Baseline\ BASDAI - Observed\ BASDAI}{Baseline\ BASDAI}$ 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 baseline or observed value is missing (note: baseline BASDAI is part of inclusion criteria and 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 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
		BASFI change from baseline – **major secondary outcome** Percent improvement from baseline	Change from baseline calculated as: observed BASFI – baseline BASFI Percent improvement from baseline calculated as: $100 \times \frac{Baseline\ -Observed\ score}{Baseline}$	Missing if baseline or observed value is missing
High Sensitivity C-Reactive Protein (CRP)	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.	CRP value	Lab values obtained from central lab	Missing if the value is missing
		CRP change from baseline	Change from baseline calculated as: observed CRP – baseline CRP	Missing if observed value is missing (note: if V2 CRP is missing, V1 CRP will be used as baseline).
		CRP ratio of postbaseline to baseline	Calculated as: observed CRP/baseline CRP	

<table>
<tr>
<td rowspan="3">Bath Ankylosing Spondylitis Metrology Index—Spinal Mobility (BASMI)</td>
<td rowspan="3">BASMI a combined index comprising the following 5 clinical measurements of spinal mobility in patients with rad-axSpA (Jenkinson et al. 1994).
1) Lateral Spinal Flexion
2) Tragus-to-wall distance
3) Lumbar Flexion (modified Schober)
4) Maximal intermalleolar distance
5) 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 º –A)/8.5º</td><td>Cervical rotation angle (mean right/left)</td></tr>
</table>
The average score of the 5 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 2 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 1 side (either left or right) is missing, the other nonmissing side will be used as the mean.</td>
</tr>
<tr>
<td>BASMI Linear change from baseline</td>
<td>Change from baseline calculated as: observed BASMI Linear– baseline BASMI Linear</td>
<td>Missing if baseline or observed value is missing</td>
</tr>
<tr>
<td>5 individual component change from baseline</td>
<td>Change from baseline calculated as: observed score – baseline score
Individual components will be converted to 0-10 scale for analysis.</td>
<td>Missing if baseline or observed value is missing</td>
</tr>
</table>

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 fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in centimeters (cm) will be recorded. Two tries will be recorded in the source documents. Only the better (larger) difference of 2 tries will be entered into CRF.	Chest Expansion score	One score measured in centimeter (cm) When 2 readings are taken, the better of the 2 numbers (bigger one) will be used.	Single item, missing if the item score is missing
		Chest Expansion change from baseline and % change from baseline	Change from baseline calculated as: observed Chest Expansion – baseline Chest Expansion	Missing if baseline or observed value is missing
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 2 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 the item score is missing
		Occiput to Wall Distance change from baseline and % change from baseline	Change from baseline calculated as: observed Occiput to Wall – baseline Occiput to Wall	Missing if baseline or observed value is missing

Description and Derivation of Primary and Secondary Efficacy Outcomes

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) (Sieper et al. 2009, pg 40): 1) Total back pain (BASDAI question 2) 2) Patient global 3) Peripheral pain/swelling (BASDAI question 3) 4) Duration of morning stiffness (BASDAI question 6) 5) CRP in mg/L	$ASDAS_{crp}$	$ASDAS_{crp}$ (Sieper et al. 2009, pg 41): 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). CRP is in mg/liter, the range of other variables is from 0 to 10; Ln represents the natural logarithm. Due to the constraint of CRP, $ASDAS_{crp}$ has a minimum score of 0.6361.	Missing if any of the component 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).
		$ASDAS_{crp}$ change from baseline - **major secondary outcome**	Calculated as: observed ASDAS – baseline ASDAS	Missing if baseline or observed value is missing
		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.	Missing if observed ASDAS score is missing
		ASDAS <2.1	Defined as ASDAS < 2.1	
		Clinical important improvement	Defined as at least 1.1 unit change in ASDAS from baseline	
		Major improvement	Defined as at least 2.0 unit change in ASDAS from baseline, or reached the minimum of ASDAS score (0.6361) at post-baseline visit	

Description and Derivation of Primary and Secondary Efficacy Outcomes

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), spina 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 baseline or observed ASDAS score is missing
		MASES change from baseline	Change from baseline calculated as: observed MASES – baseline MASES	Missing if baseline ASDAS score or observed ASDAS score is missing
		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 >20% (ie, 3 or more) sites are missing If ≤20% missing, then imputed sum = sum of scores from nonmissing sites x 13/ no. of nonmissing sites

Description and Derivation of Primary and Secondary Efficacy Outcomes

Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis	SPARCC enthesitis is an index used to measure the severity of enthesitis (Maksymowych et al. 2009). The SPARCC assesses 16 sites for enthesitis using a score of "0" for no activity, or "1" for activity. Sites assessed include: Medial epicondyle (left/right (L/R)), Lateral epicondyle (L/R), Supraspinatus insertion into greater tuberosity of humerus (L/R), Greater trochanter (L/R), Quadriceps insertion into superior border of patella (L/R), Patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R), c Achilles tendon insertion into calcaneum (L/R) and Plantar fascia insertion into calcaneum (L/R).	SPARCC enthesitis	The SPARCC is the sum of all site scores. Range: 0–16, higher scores indicate more severe enthesitis.	Missing if baseline or observed value is missing
		SPARCC enthesitis change from baseline	Change from baseline calculated as: observed SPARCC enthesitis – baseline SPARCC enthesitis	Missing if observed value is missing
		SPARCC enthesitis score = 0	SPARCC enthesitis score = 0 refers to complete resolution in enthesitis Analysis of SPARCC enthesitis score = 0 only applies to patients with baseline enthesitis (SPARCC enthesitis >0).	Missing if >20% (ie, 4 or more) sites are missing. If ≤20% missing, then imputed sum = sum of scores from nonmissing sites x 16/ no. of nonmissing sites.

Description and Derivation of Primary and Secondary Efficacy Outcomes

Tender Joint Count (TJC)	The number of tender and painful joints will be determined by examination of 46 joints (23 joints on each side of the patient's body). The 46 joints are assessed and classified as tender or not tender.	TJC total score	Adjusted sum of the pain/tenderness for all 46 joints: $\left(\frac{sum\ of\ all\ joints\ checked\ to\ be\ painful/tender}{number\ of\ evaluable\ joints}\right) \times 46$ See Appendix 4 for details.	Missing if baseline or observed value is missing
		Proportion of patients with TJC = 0 when baseline TJC > 0	TJC > 0 refers to incidence of TJC. Analysis of TJC = 0 only applies to patients whose baseline TJC > 0.	Missing if observed value is missing
		Proportion of patients with TJC = 0 for patients with current or historical peripheral arthritis at baseline	TJC > 0 refers to incidence of TJC. Analysis of TJC = 0 only applies to patients with current or historical peripheral arthritis at baseline.	If more than half of the joint scores are non-evaluable, the total score will be missing.
		TJC change from baseline	Calculated as: observed TJC – baseline TJC only applies to patients whose baseline TJC > 0.	Missing if observed value is missing
Swollen Joint Count (SJC)	The number of swollen joints will be determined by examination of 44 joints (22 joints on each side of the patient's body). The 44 joints are assessed and classified as swollen or not swollen.	SJC total score	Adjusted sum of the pain/tenderness for all 44 joints: $\left(\frac{sum\ of\ all\ joints\ checked\ to\ be\ swollen}{number\ of\ evaluable\ joints}\right) \times 44$ See Appendix 4 for details.	Missing if observed value is missing

Description and Derivation of Primary and Secondary Efficacy Outcomes

		Proportion of patients with SJC = 0 for patients with current or historical peripheral arthritis at baseline	SJC > 0 refers to incidence of SJC. Analysis of SJC = 0 only applies to patients with current or historical peripheral arthritis at baseline.	Missing if baseline or observed value is missing
		Proportion of patients with SJC = 0 when baseline SJC > 0	SJC > 0 refers to incidence of SJC. Analysis of SJC = 0 only applies to patients whose baseline SJC > 0.	If more than half of the joint scores are nonevaluable, the total score will be missing.
		SJC change from baseline	Calculated as: observed SJC – baseline SJC	Missing if observed value is missing

Anterior Uveitis	At each study visit, study health care providers will evaluate the patient for any symptoms of anterior uveitis.	Incidence and incidence rate of anterior uveitis	Anterior uveitis will be summarized for all patients and for patients without prior anterior uveitis, separately. Anterior uveitis is identified using the preferred term "iridocyclitis."	Missing if observed value is missing
NSAID (including COX-2 inhibitors) Intake	Information regarding NSAIDs 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	Missing if baseline or observed value is missing
		ASAS-NSAID score	See Section 6.10.4.1 and Appendix 5 for details of deriving ASAS-NSAID score ASAS-NSAID = 0 if no NSAID use	NA
		ASAS-NSAID score change from baseline	Calculated as: observed ASAS-NSAID score – baseline ASAS-NSAID score	
		ASAS-NSAID50	$100 \times \frac{Baseline\ ASAS-NSAID - Observed\ ASAS-NSAID}{Baseline\ ASAS-NSAID}$ 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 central readers.	SPARCC Spine Score	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.
		SPARCC spine score change from baseline – **major secondary outcome**	Calculated as: observed SPARCC Spine Score – baseline SPARCC Spine Score	Missing if baseline or observed value is missing
Ankylosing Spondylitis Spinal Magnetic Resonance Imaging (ASSpiMRI) Berlin Score	All 23 disco-vertebral units (DVU) of the spine (from C2 to S1) are scored for bone marrow edema. The Berlin method score range is between 0 and 3 per vertebral unit, bringing the maximum total score to 69 with higher scores reflecting worse disease (Braun et al. 2003; Lukas et al. 2007). Scoring will be performed by central readers.	ASSpiMRI-Berlin Score	The ASSpiMRI-Berlin score is a sum of 23 DVUs; the sum ranges from 0 to 69.	See 'MRI Data Programming Guidance for AxSpA Studies' for how to handle missing data
		ASSpiMRI-Berlin change from baseline	Calculated as: observed ASSpiMRI-Berlin– baseline ASSpiMRI-Berlin	Missing if baseline or observed value is missing

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASSpiMRI-Berlin = Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity–Berlin Score; CRF = case report form; CRP = C-reactive protein; eCRF = electronic case report form; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; no. = number; NRS = numeric rating scale; NSAID = Nonsteroidal Anti-inflammatory Drug; Q = question; rad-axSpA = radiographic axial spondyloarthritis; V = visit.

Table RHBW.6.5. 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	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Primary analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.1).
		Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Additional analyses of primary outcome (Section 6.10.3).
		Logistic regression analysis with NRI	Per Protocol Set	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Additional analyses of primary outcome (Section 6.10.3).
		Categorical MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Additional analysis of primary outcome (Section 6.10.3).
		Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Additional analyses of primary outcome (Section 6.10.3).
		Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W Starting Dose 160 mg and 80 mg during Period 2	Other secondary efficacy analyses for primary outcome (Section 6.10.4).
		pMI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Sensitivity analyses (Section 6.10.5.1)
		Tipping point analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Sensitivity analyses (Section 6.10.5.2)
		Descriptive statistics of ASAS40 response rate	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (including efficacy data post treatment discontinuation)	Sensitivity analyses (Section 6.10.5.3)
		Subgroup analyses	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Subgroup Analysis (Section 6.13.1)

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	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses for primary outcome (Section 6.10.4) This summary includes Extended Treatment Period Population overall and by ASAS20 or ASAS40 response status (responder vs non-responder) at Week 16 (Visit 8) (NRI).
		Descriptive statistics of ASAS40 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses for primary outcome (Section 6.10.4)
ASAS20	ASAS20 – **Major Secondary**	Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Logistic regression analysis with NRI	Per Protocol Set	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.10.4)
		Categorical MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of ASAS20 response rate	ITT Population	IXE80Q2W & IXE80Q4W Starting Dose 160 mg and 80 mg during Period 2	Other secondary efficacy analyses (Section 6.10.4)
		pMI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Sensitivity analyses (Section 6.10.5.1)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Tipping point analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Sensitivity analyses (Section 6.10.5.2)
		Subgroup analyses	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Subgroup Analysis (Section 6.13.1)
		Descriptive statistics of ASAS20 response rate	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4). This summary includes Extended Treatment Period Population overall and by ASAS20 response status (responder vs non-responder) at Week 16 (Visit 8). (NRI)
		Descriptive statistics of ASAS20 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
ASDAS	$ASDAS_{crp}$ change (**Major Secondary**)	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is MMRM analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF/LOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		pMI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Sensitivity analyses (Section 6.10.5.1)
		Tipping point analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Sensitivity analyses (Section 6.10.5.2)

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 treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4).
ASDAS	ASDAS <2.1 **Major Secondary**	Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Categorical MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of ASDAS <2.1 response rate	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4). This summary includes Extended Treatment Period Population overall and by ASAS20 or 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 ASDAS <2.1 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
ASDAS	ASDAS Inactive Disease	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of response rate	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of response rate	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
	ASDAS Disease Activity States	Repeated measures proportional odds model analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses for primary outcome (Section 6.10.4)
		Descriptive statistics of ASDAS disease activity states	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
	ASDAS clinical important improvement;	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
	major improvement	Descriptive statistics of response rate	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of response rate	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4).
BASDAI	BASDAI50	Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Categorical MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of BASDAI50 response rate	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of BASDAI50 response rate	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
	BASDAI change from baseline (**Major Secondary**)	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is MMRM mean change analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
	and % improvement from baseline (incl. 6 individual items and inflammation)	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF/LOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
BASFI	BASFI change from baseline (**Major Secondary**) and % improvement from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is MMRM mean change analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF/LOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)

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	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
SPARCC Spine Score	SPARCC-Spine change from baseline **Major Secondary**	ANCOVA with observed case analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analysis is ANCOVA with observed case analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		ANCOVA with mBOCF/LOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.10.4)
ASSpiMRI-Berlin Score	ASSpiMRI Berlin change from baseline	ANCOVA with observed case analysis	ITT Population who participate in MRI addendum	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.10.2)
		ANCOVA with mBOCF	ITT Population who participate in MRI addendum	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Other secondary efficacy analyses (Section 6.10.4)
ASAS	ASAS5/6 and ASAS partial remission	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of ASAS5/6 response rate and ASAS partial remission	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4) This summary includes Extended Treatment Period Population overall and by ASAS20 or 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
Patient Global	Patient Global change and % improvement from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
Spinal Pain	Spinal Pain and Spinal Pain at night change and % improvement from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
CRP	CRP change from baseline; ratio of postbaseline to baseline CRP	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		MMRM	ITT Population	IXE80Q2W & IXE80Q4W Starting Dose 160 mg and 80 mg during Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
Mobility-Related Measures	BASMI linear (incl. 5 components); chest expansion, occiput to wall distance change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
Enthesitis Scores	MASES and SPARCC change from baseline	MMRM	ITT Population with Baseline MASES >0(or SPARCC >0)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF	ITT Population with Baseline MASES >0(or SPARCC >0)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population with Baseline MASES >0(or SPARCC >0)	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
	MASES score = 0 (similarly SPARCC = 0)	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population with Baseline MASES >0(or SPARCC >0)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics of MASES = 0 (or SPARCC=0)	Extended Treatment Period Population with Baseline MASES >0 (or SPARCC >0)	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
Peripheral Arthritis	TJC and SJC change from baseline	MMRM	ITT Population with Baseline TJC>0 (or SJC>0)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		ANCOVA with mBOCF	ITT Population with Baseline TJC>0 (or SJC>0)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of change from baseline	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
	TJC = 0, SJC=0, respectively, when patients had current or historical peripheral arthritis at baseline	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population with current or historical peripheral arthritis at baseline	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of TJC = 0 (or SJC =0)	Extended Treatment Period Population with current or	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)

Measure	Variable	Analysis Method (Sections 6.1, 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
			historical peripheral arthritis at baseline		
	TJC = 0 when baseline TJC >0 (similarly SJC = 0 when baseline SJC >0)	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population with Baseline TJC>0 (or SJC>0)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics of TJC = 0 (or SJC =0)	Extended Treatment Period Population with Baseline TJC>0 (or SJC>0)	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
Anterior Uveitis	Crude and exposure-adjusted incidence rates for patients with anterior uveitis	Fisher's exact test and Poisson regression	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo during Period 2	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Other secondary efficacy analyses (Section 6.10.4)
		Descriptive statistics	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Other secondary efficacy analyses (Section 6.10.4)
NSAID (including COX-2 inhibitors) Intake	Proportion of patients taking NSAID	Descriptive statistics	Extended Treatment Period Population	At baseline (Week 0), Weeks 16, 24, 32, 44, 52	Analyses on NSAID intake (Section 6.10.4.1)

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, 24, 32, 44, 52	Analyses on NSAID intake (Section 6.10.4.1)
	ASAS-NSAID50; ASAS-NSAID10; ASAS-NSAID0	Descriptive statistics	Extended Treatment Period Population who have NSAID (including COX-2 inhibitors) intake at baseline	At Weeks 16, 24, 32, 44, 52	Analyses on NSAID intake (Section 6.10.4.1)

Abbreviations: ANCOVA = analysis of covariance; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS = Assessment of Spondyloarthritis International Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = C-reactive protein; IXE = ixekizumab; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; ITT = intent-to-treat; LOCF = last observation carried forward; MASES = ; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NSAID = nonsteroidal anti-inflammatory drug; NRI = nonresponder imputation; pMI = placebo multiple imputation; SJC = swollen joint count; TJC = tender joint count.

6.10.1. Primary Outcome and Methodology

The primary outcome is the proportion of patients achieving treatment success, defined as achieving ASAS40 at Week 16 (Visit 8) and remaining on the initially randomized treatment. This is a de-facto effectiveness estimand (that is, the relative effect attributable to the originally randomized treatment, ixekizumab and placebo, at the primary time point of Week 16 in all treated patients). With this estimand, any patient who discontinues treatment before Week 16 is considered a treatment failure through the use of the NRI. The numeric result for treatment success/failure is identical to NRI but interpreted differently and has different consequences for missing data. With NRI, as the acronym implies, there is explicit imputation of missing ASAS40 outcomes. With treatment success/failure, discontinuation of study medication is considered a treatment failure because if patients cannot adhere to the medication, they will not have sustained benefit from it. Therefore, every patient will have an observation for treatment success/failure, and there will be no missing data for this estimand and hence inferences will not depend on missing data assumptions. These attributes also apply to other endpoints involving use of NRI.

The primary outcomes related to improvement in symptomatic features of axSpA are assessed at Week 16 (Visit 8) before placebo patients being rerandomized to ixekizumab during Period 3 (Extended Treatment Period).

The primary analysis will be based on the ITT Population for the Blinded Treatment Dosing Period (Period 2) comparing each ixekizumab treatment group and placebo at Week 16 (Visit 8). The primary analysis is a logistic regression analysis with treatment, geographic region, number of prior TNF inhibitors used, and baseline CRP status in the model (Section 6.1.1).

In the primary analysis, treatment groups of ixekizumab 80 mg Q2W and Q4W will be analyzed without regard to starting dose. The primary comparison will be tested based on the graphical multiple testing procedures detailed in Section 6.5.

Table RHBW.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for the primary outcome.

6.10.2. Major Secondary Efficacy Analyses

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

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

* Detailed descriptions and analyses on SF-36 PCS and ASAS HI are described in Table RHBW.6.6 and Table RHBW.6.7.

The major secondary analysis will be based on the ITT Population for the Blinded Treatment Dosing Period (Period 2) comparing each ixekizumab treatment group and placebo at Week 16 (Visit 8). In the major secondary analyses, treatment groups of ixekizumab 80 mg Q2W and Q4W will be analyzed without regard to starting dose.

The primary analysis for categorical major secondary outcomes is a logistic regression analysis with treatment, geographic region, number of prior TNF inhibitors used, and baseline CRP status in the model (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 a MMRM analysis with treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, 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 score is an observed case analysis using ANCOVA with treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, and baseline value in the model (Section 6.1.1). Only patients with both baseline and Week 16 MRI 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 6.5.

Table RHBW.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for major secondary outcomes.

6.10.3. Additional Analyses of the Primary Outcome

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

In the additional analyses of ASAS40, treatment groups of ixekizumab 80 mg Q2W and Q4W will be analyzed without regard to starting dose, unless indicated otherwise.

To support the primary outcome analysis ASAS40 will be analyzed based on the PPS Population for Period 2 at Week 16 (Visit 8) using a logistic regression analysis with treatment, geographic region, number of prior TNF inhibitors used, and baseline CRP status in the model (Section 6.1.1) [de-facto estimand]. Missing data will be imputed using the NRI method (Section 6.3.1).

Additional analyses based on the ITT Population for Period 2 for ASAS40, include:

- Comparisons of each ixekizumab treatment group and placebo at postbaseline visits other than Week 16 (Visit 8) using logistic regression analysis with treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, in the model (Section 6.1.1) [de-facto estimand]. Missing data will be imputed using the NRI method (Section 6.3.1).

- Comparisons of each ixekizumab treatment group and placebo at Week 16 (Visit 8) and all other postbaseline visits using Categorical MMRM analysis with treatment, geographic region, number of prior TNF inhibitors used, baseline CRP status, visit, treatment-by-visit as fixed factors (Section 6.1.1) [de-jure estimand]
- Comparisons of each ixekizumab treatment group and placebo at Week 16 (Visit 8) and all other postbaseline visits using Fisher's exact test with NRI (Sections 6.1.1 and 6.3.1) [de-facto estimand]

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.

Table RHBW.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for the additional analyses on primary outcome.

6.10.4. 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 include:

- ASAS40: analyses other than primary analysis (Section 6.10.1) and additional analysis of the primary outcome (Section 6.10.3)
- ASAS20: analyses other than major secondary efficacy analysis (Section 6.10.2)
- ASAS5/6 and partial remission
- Change from baseline in individual components of the ASAS criteria (patient global, spinal pain, function [see BASFI below], inflammation [see BASDAI below], CRP [see CRP below], and spinal mobility [lateral spinal flexion] [see BASMI below])
- Change from baseline in BASDAI: analyses other than major secondary efficacy analysis, 6 individual items and inflammation (mean of Q5 and Q6 on BASDAI)
- BASDAI 50: analyses for other major secondary efficacy analysis (Section 6.10.2)
- Change from baseline in ASDAS: analyses other than major secondary efficacy analysis (Section 6.10.2)
- ASDAS <2.1: analyses other than major secondary efficacy analysis (Section 6.10.2)
- ASDAS inactive disease
- ASDAS disease activity states: inactive disease, low disease activity, high disease activity, very high disease activity, clinically important improvement and major improvement
- Change from baseline in CRP
- Change from baseline in BASFI: analyses other than major secondary efficacy analysis (Section 6.10.2)
- Change from baseline in SPARCC spine score: analyses other than major secondary efficacy analysis (Section 6.10.2)

- Change from baseline in mobility (BASMI linear and individual components, chest expansion, occiput to wall distance)
- Change from baseline in MRI ASSpiMRI –Berlin score
- Change from baseline in enthesitis score (MASES and SPARCC)
- Change from baseline in TJC and SJC
- Incidence of peripheral arthritis by TJC and SJC scores of 46/44 joints
- Incidence rate of anterior uveitis or uveitis flares
- Change from baseline in ASAS-NSAID score (apply to Period 3 analysis only), Section 6.10.4.1.

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

The impact of ixekizumab starting doses will be evaluated for the categorical responses (including ASAS40 and ASAS20) and mean change in continuous efficacy measure of CRP at Week 16 and earlier time point as described in Section 6.1.1.

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

Table RHBW.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for other secondary outcomes.

6.10.4.1. Analyses on NSAID Intake

ASAS-NSAID score is used to present the NSAID (including COX-2 inhibitors) 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 5 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 (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: 6 days/week
- 4/7: 4 - 5 days/week
- 2/7: 2 - 3 days/week
- 0.5/7: ≤1 day/week
- 0: no intake

Using an example in Dougados and colleagues (2011), if during a period of interest (between 2 visits) of 6 months, the patient has taken piroxicam 20 mg during 4 months and if during this 4-month period he has taken piroxicam 3 to 5 days per week, the calculation of ASAS-NSAID is as follows:

100 (20 mg piroxicam score) × 120 (4 months) × 4/7 (3–5 days/ week)/180 (6 months) = 38.1

If the patient has used 10 mg piroxicam during the remaining 2 months on 2 days a week, the NSAID score for this period is:

50 (10 mg piroxicam score) ×60 (2 months) × 2/7 (1 to 3 days/week)/180 (6 months) = 4.8

In this example, 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

- Proportion of patients with 50% decrease in ASAS-NSAID scores compared with baseline
- Proportion of patients with ASAS-NSAID score <10
- Proportion of patients with ASAS-NSAID score = 0

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

6.10.5. Sensitivity Analyses

6.10.5.1. pMI

ASAS40, ASAS20, and mean change in ASDAS at Week 16 (Visit 8) will be analyzed based on the ITT Population using the pMI method, as described in Section 6.3.4. Analyses for ASAS40 and ASAS20 will be based on the logistic regression analysis with treatment, geographic region, number of prior TNF inhibitors used, and baseline CRP status in the model (Section 6.1.1). Analysis for mean change in ASDAS will be based on MMRM analysis. The model will include treatment, geographic region, and number of prior TNF inhibitors used, baseline CRP status,

baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors (Section 6.1.1).

6.10.5.2. Tipping Point Analysis

ASAS40, ASAS20, as well as mean change in ASDAS at Week 16 (Visit 8) will be analyzed based on the ITT Population using the tipping point method (Section 6.3.5).

6.10.5.3. Analysis Including Efficacy Data Post Treatment Discontinuation

Per recommendation in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, additional efficacy data for patients who prematurely discontinued Period 2 are collected during the Post-Treatment Follow-Up Period (Period 4). Patients who discontinue treatment before Week 16 are instructed to schedule a Post-Treatment Follow-Up visit such that the post-treatment data will be collected 16 weeks after initial randomization. The efficacy data of ASAS40 at Week 16 will be summarized by treatment group, but no formal statistical comparison will be performed.

6.10.6. Health Outcomes/Quality-of-Life Analyses

The health outcomes and quality of life (QOL) measures are ASAS HI, SF-36, Fatigue NRS, JSEQ, WPAI-SpA, and QIDS-SR16.

The analyses of health outcomes and QOL measures for Period 2 will be based on the ITT Population. There will be no adjustment for multiple comparisons.

Descriptive statistics will be provided for Period 3 based on the Extended Treatment Period Population.

Table RHBW.6.6 includes the description and derivation of the health outcomes and QOL measures.

Table RHBW.6.7 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for health outcomes and QOL analyses.

Table RHBW.6.6. 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]
		ASAS HI change from baseline-Major Secondary	Calculated as: observed ASAS HI – baseline ASAS HI	Missing if baseline or observed value is missing
		Proportion of patients with ≥3 improvement from baseline	The smallest detected change of ASAS HI is 3. This variable will only be derived for patients with baseline score ≥3.	Missing if baseline or observed value is missing
		Proportion of patients reaching Good ASAS HI (defined as ASAS HI≤5)	This variable will only be derived for patient with baseline score >5.	Missing if baseline or observed value is missing
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	8 associated domain scores: • Physical Functioning, • Role Physical, • Bodily Pain, • General Health,	Per copyright owner, the QualityMetric Health Outcomes™ Scoring Software 4.5 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	Missing data handling offered by SF-36 software will not be used.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	physical well-being are captured by the Mental Component Summary and Physical Component 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]).	• Vitality • Social Functioning • Role Emotional • Mental Health 2 component Scores: • MCS Score • PCS Score	transformed into the domain scores (t-scores) using the 1-week recall period. The procedure to derive the SF-36 scores is described in Appendix 6. It entails exporting the patient data in a CSV or tab-delimited file for import, generation of the SF-36 scores and reports, and export of the calculated scores in a CSV or tab-delimited file for integration into SDTM/ADaM datasets. The summary scores range from 0 to 100.	
		PCS change from baseline-Major Secondary	Calculated as: observed score – baseline score	Missing if baseline or observed value is missing
		MCS and domain scores change from baseline	Calculated as: observed score – baseline score	Missing if baseline or observed value is missing
Fatigue Severity Numeric Rating Scale	The fatigue severity NRS is a patient-administered single-item 11-point horizontal scale anchored at 0 and 10, with 0 representing “no fatigue” and 10 representing “as bad as you can imagine” (Naegeli et al. 2013). Patients rate their fatigue (feeling tired or worn out) by circling the 1 number that describes their worst level of fatigue during the previous 24 hours.	Fatigue Severity NRS	Range: 0 to 10. 0 (no fatigue) and 10 (as bad as you can imagine).	Single item, missing if missing
		Fatigue Severity change from baseline	Calculated as: observed Fatigue Severity NRS – baseline Fatigue Severity NRS	Missing if baseline or observed value is missing
Work Productivity and Activity Impairment Questionnaire —Spondylo-	The Work Productivity 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,	Percentage of absenteeism	Percent work time missed due to problem: (Q2/(Q2 + Q4))*100	If Q2 or Q4 is missing, then missing
		Percentage of absenteeism - change from baseline	Calculated as: observed value – baseline value	if baseline or observed value is missing, then the value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
arthritis	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 rad-axSpA 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 presenteeism	Percent impairment while working due to problem: (Q5/10)*100	If Q5 is missing, then missing
		Percentage of presenteeism - change from baseline	Calculated as: observed value – baseline value	If baseline or observed value is missing, then missing
		Overall work impairment score	Percent 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
		Overall work impairment score - change from baseline	Calculated as: observed value – baseline value	If baseline or observed value is missing, then missing
		Percentage of activity impairment	Percent activity impairment due to problem: (Q6/10)*100	If Q6 is missing, then the value is missing
		Percentage of activity impairment - change from baseline	Change from baseline is calculated as: observed value – baseline value	If baseline or observed value is missing, then missing
Jenkins Sleep Questionnaire	The Jenkins Sleep Evaluation Questionnaire (JSEQ) is a 4-item scale designed to estimate sleep problems in clinical research. The JSEQ assesses the frequency of sleep disturbance in 4 categories: 1) trouble falling asleep, 2)	JSEQ score	Sum of 4-item score (each on a 6-point Likert scale, 0 = no days and 5 = 22-30 days) Range: 0 to 20, higher scores indicating greater sleep disturbance (Deodhar et al. 2010)	Missing if >20% items (ie, any of the 4) are missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	waking up several times during the night, 3) having trouble staying asleep (including waking up far too early), and 4) waking up after the usual amount of sleep feeling tired and worn out. Patients report the numbers of days they experience each of these problems in the past month on a 6 point Likert Scale ranging from 0 = "no days" to 5 = "22-30 days."	JSEQ score change from baseline	Change from baseline calculated as: observed JSEQ – baseline JSEQ	Missing if baseline or observed value is missing
Quick Inventory of Depressive Symptoma-tology-self report 16 items	See Section 6.12.6 for description of QIDS-SR16	9 Domains	See Section 6.12.6 for description of each domain	See Section 6.12.6
		Change from baseline in each domain	Calculated as: observed domain score – baseline domain score	Missing if baseline or observed value is missing
		16 Individual items	Range: 0 to 3	Missing if item is missing.
		Change from baseline in each individual item	Calculated as: observed individual item score – baseline individual item score	Missing if baseline or item is missing
		QIDS-SR16 total score	See Section 6.12.6 for description of QIDS-SR16 total score	See Section 6.12.6
		Change from baseline in QIDS-SR16 total score	Calculated as: observed total score – baseline total score	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		Proportion of patients with at least a 50% decrease in QIDS-SR16 total score	% reduction from baseline calculated as: $100 \times \frac{\text{Baseline} - \text{Observed score}}{\text{Baseline}}$ If the value of % reduction from baseline is ≥50, patients had at least a 50% decrease in QIDS-SR16 total score.	Missing if baseline or observed score is missing

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; JSEQ = Jenkins Sleep Evaluation Questionnaire; MCS = mental component summary; NRS = numeric rating scale; PCS = physical component summary; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; Q2W = every 2 weeks; Q4W = every 4 weeks; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report 16 items; SpA = spondyloarthritis; rad-axSpA = radiographic axial spondyloarthritis.

Table RHBW.6.7. 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	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary analysis is MMRM analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		ANCOVA with mBOCF/LOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Health Outcomes/QOL analyses (Section 6.10.6)
	MCS, domain scores, change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
ASAS Health Index (ASAS HI)	ASAS HI change from baseline **-Major Secondary**	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary analysis is MMRM analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 16 (Section 6.10.2).
		MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		ANCOVA with mBOCF/LOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	ITT Population Who are Initially Randomized to Ixekizumab	No treatment group comparisons during Combined Periods 2 and 3	Health Outcomes/QOL analyses (Section 6.10.6)
	Proportion of patients with ASAS HI ≥3 points improvement from baseline	Logistic regression with NRI; Fisher's exact test with NRI	ITT population With Baseline Score ≥3	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population With Baseline Score ≥3	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)
	Proportion of patients reaching Good ASAS HI (defined as ASAS HI ≤5)	Logistic regression with NRI; Fisher's exact test with NRI	ITT population With Baseline Score >5	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
		Descriptive statistics	Extended Treatment Period Population With Baseline Score>5	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)
Fatigue Severity Numeric Rating Scale	Fatigue Severity change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
Work Productivity and Activity Impairment Questionnaire—Spondylo-arthritis	Change from baseline in: • percentage of absenteeism • percentage of presenteeism • overall work impairment score • percentage of activity impairment	ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)
JSEQ	JSEQ score change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16 and all other postbaseline visits in Period 2	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)
Quick Inventory of Depressive Symptomatology-self report 16 items (QIDS-SR16)	Change from baseline in QIDS-SR16 total score, the 9 QIDS-SR16 domains and 16 individual item	ANCOVA with mBOCF	ITT Population ITT Population with moderate depression at baseline (QIDS-SR 16 total score ≥11)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics	Extended Treatment Period Population Extension Period	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.5)	Comparison/Time Point	Analysis Type
			Population with moderate depression at baseline (QIDS-SR 16 total score ≥11)		
	Proportion of patients with at least a 50% decrease in QIDS-SR16 total score	Logistic regression with NRI; Fisher's exact test with NRI	ITT Population for patients with moderate depression at baseline (QIDS-SR16 total score)	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Health Outcomes/QOL analyses (Section 6.10.6)
		Descriptive statistics with NRI	Extension Period Population with moderate depression at baseline (QIDS-SR 16 total score ≥11)	No treatment group comparisons during Period 3	Health Outcomes/QOL analyses (Section 6.10.6)

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; ITT = intent-to-treat; JSEQ = Jenkins Sleep Evaluation Questionnaire; mBOCF = modified baseline observation carried forward; LOCF = last 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; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report 16 items.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Observed ixekizumab serum concentrations will be summarized by treatment group, visits, and corresponding time when sampling occurred.

As appropriate, the pharmacokinetic (PK) and the exposure-response relationship between ixekizumab exposure and clinically important efficacy measures (for example, ASAS40 or ASAS20 at Week 16) may be explored using graphical methods and/or a modeling approach. Pharmacokinetic and/or exposure-response data from this study may be combined with existing PK and/or exposure-response data from other studies, if considered appropriate.

If a trend or statistically significant difference between the ixekizumab dose cohorts and/or the placebo cohort is noted in any safety endpoint, the exposure relationship for this endpoint may be explored graphically.

In addition, the potential impact of immunogenicity on ixekizumab exposure and/or efficacy responses may be evaluated by graphical assessments, as appropriate, to compare drug exposure or efficacy responses between ADA negative and ADA positive patients at corresponding visits, or before and after ADA development for patients who developed ADA. Both treatment-emergent only and all ADA positive/negative patients may be explored. A similar approach may be taken if patients become NAb positive. The effect of immunogenicity may be evaluated as a covariate in the population PK and exposure-response analyses, if applicable.

For further details, refer to the PK/PD analysis plan.

6.12. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, QIDS-SR16, and Columbia-Suicide Severity Rating Scale (C-SSRS). The duration of treatment exposure will also be summarized.

For Period 2, safety data will be summarized for the safety population. Treatment group comparisons will be performed on categorical safety data using Fisher's exact test as described in Section 6.1.1, continuous safety data will be analyzed by an ANCOVA model as described in Section 6.1.1.

For Period 3, safety data will be summarized for the Extended Treatment Period Population, and no treatment group comparisons will be performed.

For Combined Periods 2 and 3, safety data will be summarized for the Safety Population which is initially randomized to ixekizumab, and no treatment group comparisons will be performed. In addition, safety data on ixekizumab will be summarized for the All Ixekizumab Exposures Safety Population.

For Period 4, safety data will be summarized according to the treatment patients were on or before entering Post-Treatment Follow-up Period.

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 nonmissing 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).

6.12.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group for the Safety Population during the Period 2 and Extension Period Population for Period 3 using descriptive statistics. Exposure for Safety Population who are randomized to ixekizumab at Week 0 and All Ixekizumab Exposures Safety Population during Combined Periods 2 and 3 will be provided.

A by-patient listing of exposure duration with number of active injections and total dose will be provided.

The duration of exposure will be calculated as:

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

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 day and ≥273 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)

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 (Q2W or Q4W), the total dose (in mg) taken during Period 2 or 3 will be calculated as follows:

$Total\ Period\ 2 \text{ or } 3\ dose\ for\ patients\ on$ ixekizumab 80 $mg\ Q2W$
$= Total\ number\ of$ active $injections\ (including\ loading\ doses, if\ any)\ received\ in\ Period\ 2 \text{ or } 3$
$\times 80$

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

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.

6.12.2. Adverse Events

Adverse events 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 pre-existing 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 TEAE is defined as an event that first occurred or worsened in severity after baseline and on or before 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 adverse events will be assigned to the study period to which it is 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 before the first dose date/time in the treatment period will be used as the pretreatment 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.
- Adverse events 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 (that is, a patient has no pre-existing conditions with that LLT), or if the severity is greater than the pretreatment severity for that LLT. 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 15 (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 15 or ETV, the maximum severity recorded for each LLT on or before the date of Visit 15 or ETV will be used as the follow-up baseline severity for that LLT.

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

- For the start date:
  - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
  - If either month or month and day are missing, then use January 1.
  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date in the follow-up period.
  - If either month or month and day are missing, then use December 31.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date in the follow-up period.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the event will be flagged as treatment-emergent or follow-up emergent according the corresponding study period. If a FEAE was already counted as treatment-emergent during the prior treatment period, it will not be counted as a FEAE.

Adverse events and TEAEs will be summarized for the following study periods and analysis populations, treatment comparisons between treatment groups in Period 2 will be conducted using a Fisher's exact test.

- Period 2 (Safety Population)
- Period 3 (Extended Treatment Period Population)
- Combined Periods 2 and 3 (Safety Population which is randomized to ixekizumab at Week 0)
- Combined Periods 2 and 3 (All Ixekizumab Exposures Safety Population)

Otherwise specified, the following summaries/analyses will be performed for all of 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
- TEAE by SOC and PT (Safety Population only)
- TEAE by PT
- TEAE by maximum severity, SOC, and PT

Follow-up emergent adverse events will be summarized for the Follow-Up Population for 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 total ixekizumab group, followed in the order of ixekizumab Q2W, ixekizumab Q4W, and 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 will be provided.

6.12.2.1. Common Adverse Events

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

The following tables will be provided for common TEAEs by treatment group and study period. When SOC is presented, then events will be ordered by decreasing frequency in the total ixekizumab group, within SOC. When SOC is not presented, then events will be ordered by decreasing frequency in the total ixekizumab group.

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

- Common TEAEs by PT nested within SOC
- Common TEAEs by PT
- Common TEAEs by maximum severity by PT nested within SOC

6.12.3. 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 (including treatment group comparison for Period 2) 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 Safety Population who are initially randomized to ixekizumab at Week 0 and 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 15 (that is, Week 52) or the ETV. The following summary tables will be provided for the Follow-Up Population for the Period 4:

- FESAE by PT
- FEAEs that lead to treatment discontinuation (including death) by PT

6.12.3.1. 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 RHBW.6.8 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.

Fisher's exact tests will be used to compare the treatment group for the safety population during Period 2.

For Period 3, summaries will be provided for the Extended Treatment Period Population.

For Combined Periods 2 and 3, selective summaries will be provided for the Safety Population which is initially randomized to ixekizumab at Week 0.

In addition, for Combined Periods 2 and 3, 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 for hepatic laboratory tests.

Table RHBW.6.8. 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) and Combined Periods 2 and 3 (Summary)**: TEAE by PT within SMQ or sub-SMQ **Listing (in Spotfire):** 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 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 nonmissing 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 nonmissing 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 nonmissing 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 nonmissing 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 nonmissing maximum	**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
	baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN, or missing. o The analysis of 2× ULN will contain 5 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN to <2× ULN, ≥2× ULN, or missing. • 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 nonmissing maximum baseline value is ≤1× ULN, >1× ULN to ≤1.5× ULN, >1.5× ULN, or missing.	
	Shift for ALT, AST, 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 nonmissing value in the baseline period. • Use the maximum nonmissing postbaseline value within each study period. • Categories are: o ALT: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10 to <20× ULN, and ≥20× ULN o AST: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10× to <20× ULN and ≥20× ULN o Total bilirubin: ≤1× ULN, >1 to <1.5× ULN, ≥1.5 to <2× ULN, ≥2× ULN o ALP; ≤1× ULN, >1 to ≤1.5× ULN, >1.5× ULN • With additional categories: o Decreased: postbaseline category < baseline category o Increased: postbaseline category > baseline category o Same: postbaseline category = baseline category	**Period 2, Period 3 (Summary) and Combined Periods 2 and 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 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 (to be prepared in Spotfire)

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 1 postbaseline ALT and total bilirubin, which contributes 1 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), Period 3 (Summary) and Combined Periods 2 and 3 (Summary)**: TEAE by PT within sub-SMQ, **Listing** (to be prepared in Spotfire)**:** 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 OSC), serious infections, potential opportunistic infections, and infections resulting in anti-infective medication administration (ie, antibacterial, antivirals, antifungals, antiparasitic treatments).	**Period 2 (Fisher's exact test), Period 3 (Summary) and Combined Periods 2 and 3 (Summary)**: SAE by PT, AE leading to treatment discontinuation by PT (Period 2 only) .
	Anti-infective medications are defined in Appendix 7. 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** (to be prepared in Spotfire)**:** TEAE with anti-infective medications
	The list of MedDRA terms used to identify infections that are predefined as potential OIs are found in Appendix 11. 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	**Period 2, Period 3 (Summary) and Combined Periods 2 and 3 (Summary)**:

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	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: source of identification (CRF or Lilly specified list), primary/secondary site of infection, primary/secondary infection type, primary/secondary identified by a laboratory diagnostic test (Yes/No), acquired in a Health care setting (Yes/No).	TEAE of OIs by PT (Period 2 only) TEAE of OIs by maximum severity by PT **Listing** (to be prepared in Spotfire)**:** TEAE of OIs
	The duration of each common (≥1% of total ixekizumab) TEAE PT of Infections and narrow terms for Opportunistic infections is 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 Period 2 or 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**: 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 2 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	**Period 2 (Fisher's exact test), Period 3 (Summary) and Combined Periods 2 and 3 (Summary)** : TEAE by maximum severity by PT within Category, SAE by PT within Category, AE leading to treatment discontinuation by PT within Category (Period 2 only)

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• Anaphylactoid shock • Kounis Syndrome • Type I hypersensitivity 2) to identify possible cases, following Criterion 2 as defined by Sampson et al (2006). Criterion 2 for anaphylaxis requires having TEAEs from 2 or more of 4 categories of AEs as described by Sampson et al (2006). Occurrence of these events should be nearly coincident; based on recording of events on CRFs. All qualifying events must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: • Category A: Involvement of the skin-mucosal tissue • Category B: Respiratory compromise • Category C: Reduced blood pressure or associated symptoms • Category D: Persistent gastrointestinal symptoms The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in Appendix 8. Summaries of Criterion 2 anaphylactic TEAEs will be provided by the specific combination of categories as follows: • AB: events based on meeting Category A and Category B (but no other category) • AC: events based on meeting Category A and Category C (but no other category) • AD: events based on meeting Category A and Category D (but no other category) • BC: events based on meeting Category B and Category C (but no other category) • BD: events based on meeting Category B and Category D (but no other category) • CD: events based on meeting Category C and Category D (but no other category) • ABC: events based on meeting Category A, Category B, and Category C (but no other category) • ABD: events based on meeting Category A, Category B, and Category D (but no other category) • ACD: events based on meeting Category A, Category C, and Category D (but no other category) • BCD: events based on meeting Category B, Category C, and Category D (but no other category) • ABCD: events based on meeting each of the 4 Criterion 2 categories Summaries of treatment-emergent anaphylactic AEs will be provided for patients meeting each of the 2 criteria and for patients who meet either criteria overall. 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.	

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	Allergic Reactions/Hypersensitivity Events, Non-Anaphylaxis: TEAEs of allergic reaction/hypersensitivity categorized as nonanaphylaxis events are defined by the narrow terms within Hypersensitivity SMQ (20000214) excluding the PTs noted in Appendix 9 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 nonanaphylaxis, and the associated information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page if identified by the investigator.	**Listing** (to be prepared in Spotfire)**:** TEAE including information collected on *Allergic / Hypersensitivity Reaction Follow-Up* 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 1 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 • [3] Bright red	**Period 2 (Fisher's exact test) and Period 3 (Summary)**: TEAE by maximum severity by PT within HLT SAE by PT within HLT AE leading to treatment discontinuation by PT within HLT (Period 2 only) 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

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• [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	**Listing** (to be prepared in Spotfire)**:** 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 nonevent (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)
	• Peripheral Vascular Events
		Period 2 (Fisher's exact test), Period 3 (Summary) and Combined Periods 2 and 3 (Summary):
		TEAE by PT within Subcategory,
		Listing (to be prepared in Spotfire)**:**
		TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	○ Peripheral arterial event ○ 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) • Nonfatal myocardial infarction • Nonfatal 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'. • Nonfatal 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. • Nonfatal 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 nonfatal stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed nested within nonfatal stroke category.	**Period 2 (Fisher's exact test), Period 3 (Summary) and Combined Periods 2 and 3 (Summary)**: TEAE by maximum severity by PT within category **Listing** (to be prepared in Spotfire)**:** 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 [Nonhaematological tumours of unspecified malignancy]	**Period 2 (Fisher's exact test), Period 3 (Summary) and Combined Periods 2 and 3 (Summary)**: TEAE by PT within category, **Listing** (to be prepared in Spotfire)**:** 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 (excluding suicide and self-injury)]).	**Period 2 (Fisher's exact test) and Period 3 (Summary)**: TEAE by PT within SMQ and sub-SMQ, **Listing** (to be prepared in Spotfire)**:** 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	**Period 2 (Fisher's exact test), Period 3 (Summary) and Combined Periods 2 and 3 (Summary)**: TEAE by PT within subcategory, **Listing** (to be prepared in Spotfire)**:** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	listed in Appendix 10.	
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** (to be prepared in Spotfire): TEAE (included in the same listing with hepatic, depression and interstitial lung disease AESIs)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; CRF = case report form; eCRF = electronic case report form; HLT = high-level term; OI =opportunistic infection; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment emergent adverse event; ULN = upper limit of normal.

6.12.4. Clinical Laboratory Evaluation

Clinical laboratory assessments include hematology, serum chemistry, urinalysis, and safety-related immune markers such as neutrophil counts.

Continuous laboratory tests will be summarized as changes from baseline to last observation for patients who have both baseline and at least 1 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.
- Both international system of unit (SI) and conventional unit will be summarized when different.
- For the Safety Population Period 2, the comparisons between and among treatment group 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 1 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 displays with both SI and conventional units will be provided when different.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least 1 postbaseline result, mean, SD, 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, 3, and 4, respectively). The comparisons between and among treatment groups will be conducted using Fisher's exact test for the Safety Population for the 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 LLN 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 6.12.3.1 and a separate analysis addressing leukocytes (WBC) and platelets is described in Section 6.12.4.1. 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 laboratory test values will be provided. Listing of laboratory tests reference ranges (Lilly defined LLN for leukocyte, neutrophil, lymphocyte and platelet counts, and Performing Lab reference ranges for other lab tests) will be provided. 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.

6.12.4.1. Leukocytes (WBC) and Platelets

Further analyses will be conducted for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils. Neutrophils will include both segmented neutrophils and absolute neutrophils (derived by adding segmented neutrophils and band neutrophil). The segmented neutrophils and absolute neutrophils will be summarized using the same categories.

Shift table will be produced showing the number and percentage of patients shifting from baseline to a minimum postbaseline result in each relevant category by treatment groups for study Period 2, Period 3, and Combined 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 nonmissing 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.

6.12.4.2. Neutrophil Follow-Up

Neutrophil counts will be followed throughout the study. Patients will continue in Period 4 until their neutrophil counts have recovered.

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 before entering Period 4 and less than the patient's baseline absolute neutrophil count (that is, before first injection at Week 0). These patients are monitored during Period 4 until neutrophil recovery.

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/µL (SI units: ≥1.5× 10^9/L) or greater than or equal to a patient's minimum absolute neutrophil count before 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 patient will return for Visit 803 (12 weeks after Visit 802). Additional

visits may be required for appropriate patient management depending upon the degree of neutropenia. If at Visit 802, a patient has met the criteria for neutrophil recovery, the patient's participation in the study will be considered complete unless the investigator deems additional follow-up may be necessary.

The number and percentage of patients achieving neutrophil clinical recovery will be presented by 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, before first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

6.12.5. Vital Signs and Other Physical Findings

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 1 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 and among 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 1 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 1 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 predose and postdose vital signs at Weeks 0 and 16 by treatment groups for the safety population.

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, 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 RHBW.6.9 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 RHBW.6.9. 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.

6.12.6. 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 [WWW] 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 4 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 2 weeks), and #9 (increased weight within the last 2 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 2 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 follows:

- None (no depression): 0 – 5
- Mild: 6 – 10
- Moderate: 11 – 15
- Severe: 16 – 20
- Very severe: 21 – 27

The following summaries will be produced for QIDS-SR16 total score category by treatment groups for Safety Population during Periods 2 and 3:

- 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 by treatment groups for the Safety Population during the Period 2 and Extended Treatment Period Population for Period 3:

- Improved: maximum postbaseline QIDS-SR16 item 12 score < maximum baseline item 12 score
- Worsened; maximum postbaseline QIDS-SR16 item 12 score > maximum baseline item 12 score

- Same; maximum postbaseline QIDS-SR16 item 12 score = maximum baseline item 12 score

6.12.7. 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 (Columbia University Medical Center (WWW).

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

Category 1 – Wish to be Dead
Category 2 – Nonspecific 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 (nonfatal)
Category 10 – Completed Suicide
Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

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

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

The Self-Harm Supplement Form is a 1-question form that is completed, at any visit, including baseline visit, that asks for the number of suicidal behavior, possible suicide 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.*'

6.12.8. Immunogenicity

6.12.8.1. Definitions and Terms

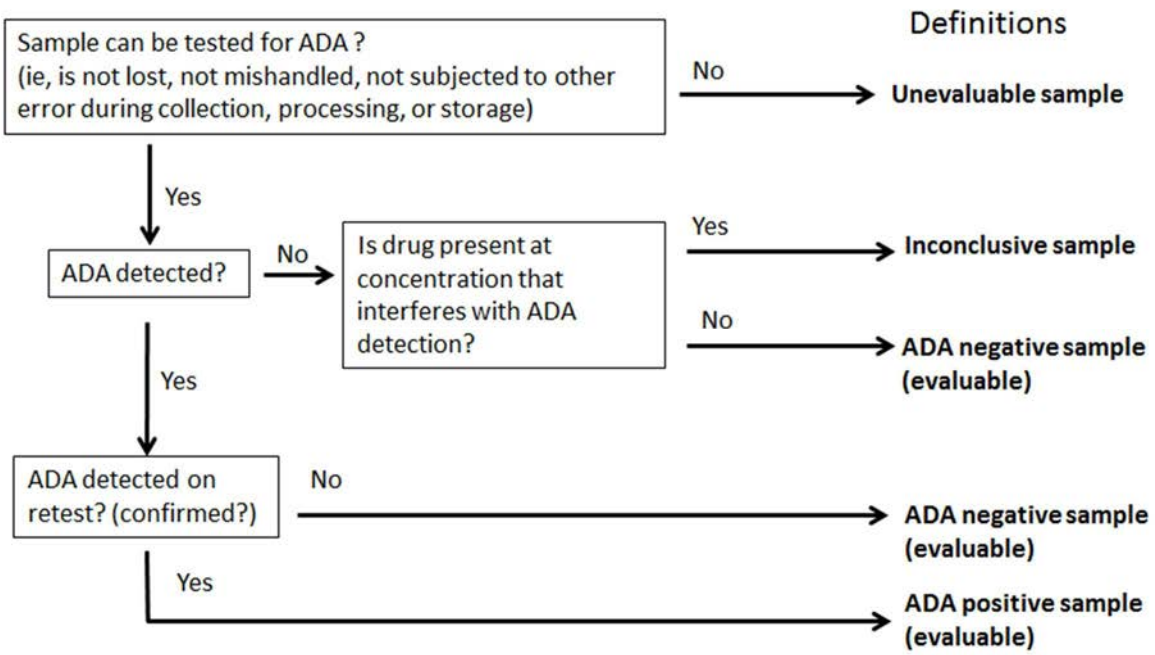
The following sample- and patient-related definitions and parameters will be used to describe the immunogenicity data.

6.12.8.1.1. Sample Category Definitions

Samples are classified into the following categories:

- **Unevaluable sample:** Sample could not be tested for antidrug antibody (ADA) due to sample loss, mishandling, or errors in collection, processing, storage, and so on.
- **Antidrug 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 antidrug antibody (NAb) Positive sample:** NAb are reported as detected.
- **Antidrug antibody (ADA) Negative sample:** The presence of ADA is not detected and the assay drug tolerance level is not exceeded.
- **NAb Negative sample:** The presence of NAb is not detected and the assay drug tolerance level is not exceeded.
- **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.

Figure RHBW.6.4 illustrates the relationship of some of the above terms.



Abbreviation: ADA = antidrug antibody.

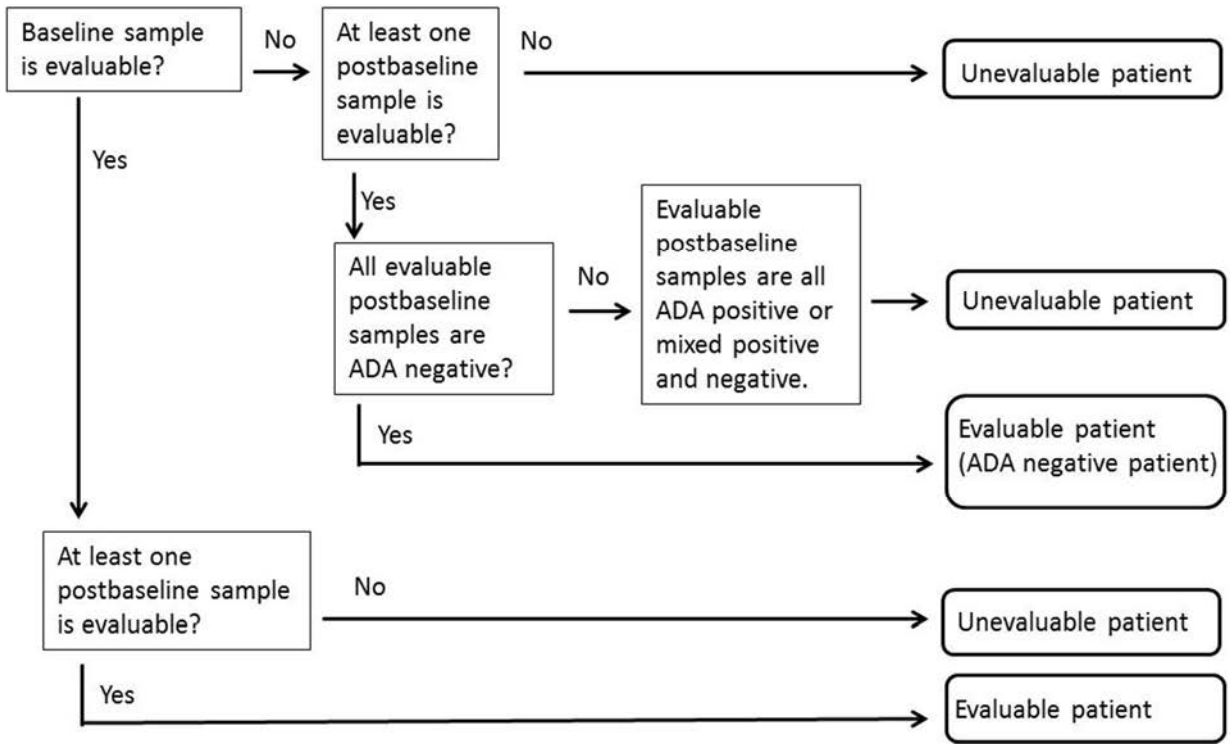
Figure RHBW.6.4. Sample definitions.

6.12.8.1.2. 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

Figure RHBW.6.5 illustrates the relationship of the above terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHBW.6.5. Patient categories (evaluable/unevaluable) based on sample status at baseline and postbaseline.

6.12.8.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses during Period 2, baseline is the last nonmissing observation on, or before, the date of the first injection of study treatment (Week 0). Unless otherwise specified, the baseline for subsequent treatment periods is defined as the last nonmissing observation on, or before, the date of first injection of ixekizumab. For patients originally randomized to ixekizumab during Period 2, baseline is the last nonmissing observation on, or before, 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 nonmissing observation on, or before, the date of the first injection of ixekizumab. See Table RHBW.6.10 for further details.

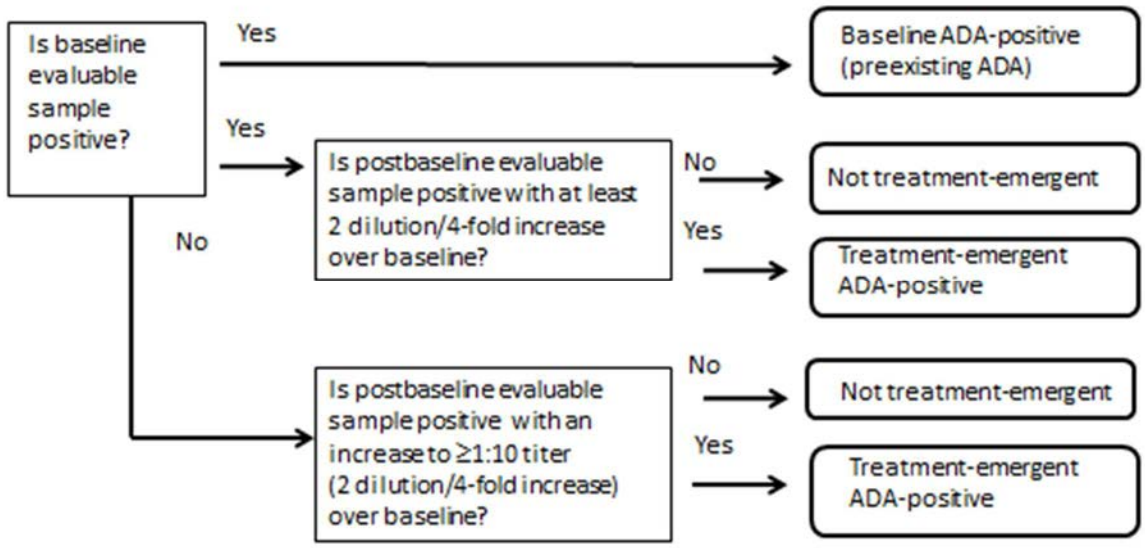
Table RHBW.6.10. Baseline Definition for Immunogenicity Analyses for Extended Treatment Period

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

[a] Last nonmissing observation on, or before, the date of the first injection of study treatment at the defined week.

- **Baseline ADA positive (pre-existing antibody):** ADA detected in a sample collected at baseline
- **Treatment-emergent antidrug antibody (TE-ADA) positive:** 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
- **Baseline ADA-negative:** ADA is not detected in a sample collected at baseline.
- **TE-ADA inconclusive patient:** A patient without a TE-ADA positive sample and with at least 1 sample for which drug levels may interfere with the ADA assay
- **TE-ADA negative patient:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive

Figure RHBW.6.6 illustrates the relationship of some of these terms.



Abbreviation: ADA = anti-drug antibody.

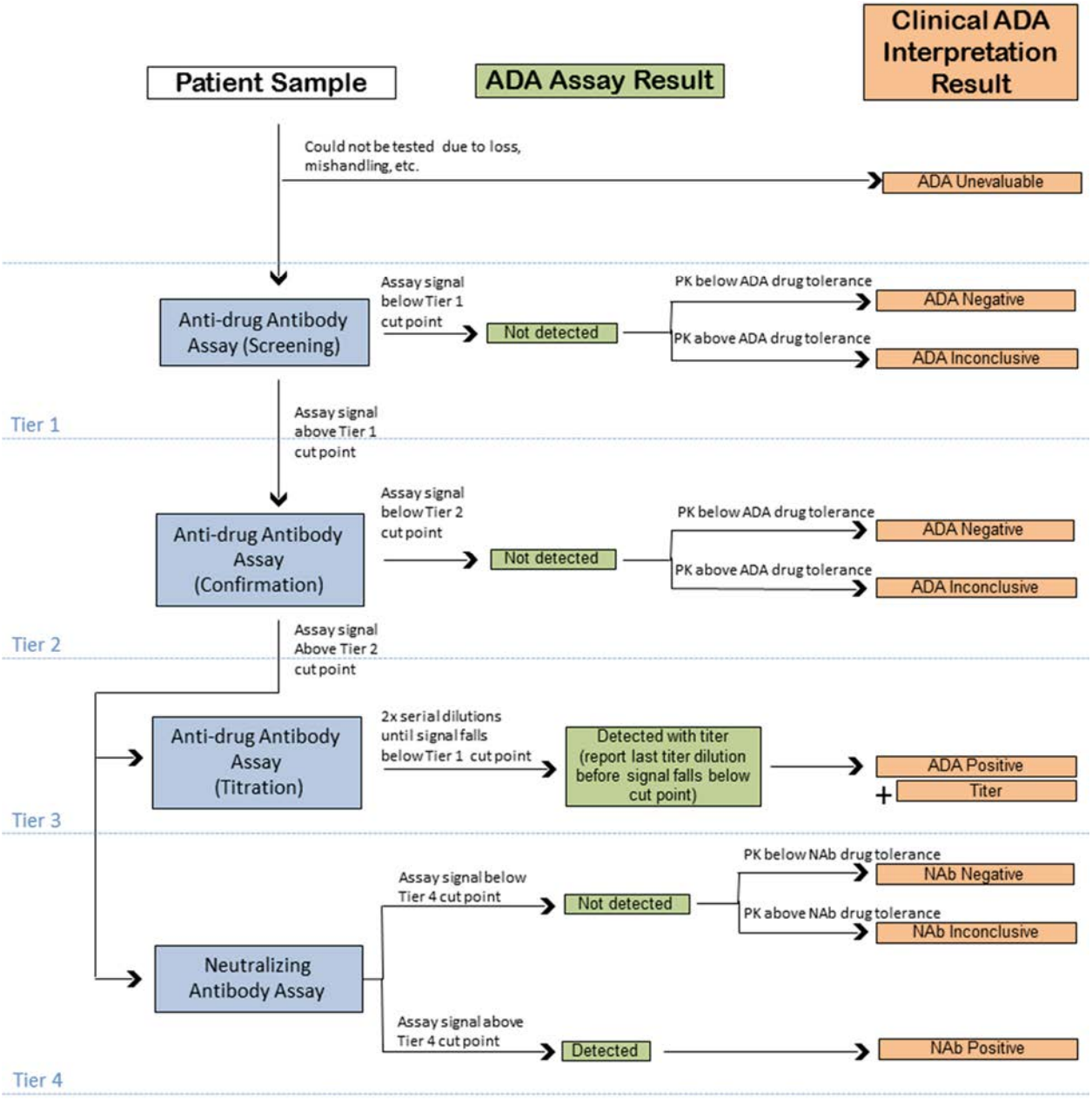
Figure RHBW.6.6. Relationship of terms for clinical interpretation of assay results for evaluable patients.

- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment period. This excludes unevaluable patients.
- **Follow-up emergent ADA:** ADA is first detected during the follow-up period, after study drug administration is discontinued. This category includes patients negative at baseline who increased to ≥1:10 titer after baseline in the follow-up period or patients ADA positive at baseline and increased at least 4-fold (2 dilutions) over baseline for the first time in the follow-up period.

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 1 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

A flow chart that reflects the connection between the analytical test results and the clinical interpretation based on the definitions is shown in Figure RHBW.6.7.



Abbreviation: ADA = antidrug antibody; NAb = Neutralizing antidrug antibody; PK = pharmacokinetics.

Figure RHBW.6.7. Flow chart of ADA assessment with clinical interpretation of the various result possibilities.

6.12.8.2. 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 6.12.8.1.2 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
  - 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 RHBW.6.11. 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 RHBW.6.11. TE-ADA Status Dichotomous Variables for AE Analysis

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

Abbreviations: AE = adverse event; TE-ADA = treatment-emergent antidrug 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 before *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 RHBW.6.11. 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.

6.12.8.2.1. 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 the 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 RHBW.6.10.

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 RHBW.6.11), 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 the individual studies, for patients with any 1 sample of ADA (or NAb) positive or inconclusive.

6.12.8.2.2. Analyses of ADA Effects on Efficacy

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

The ASAS40, ASAS20, and ASDAS <2.1 at Week 16 with NRI will be summarized by the TE-ADA status groups as described in Section 6.12.8.2.1.

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. 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 groups 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, 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.

6.12.8.2.3. Analyses of Treatment-Emergent ADA Effects 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 RHBW.6.10.

Adverse events of special interest (AESI) of allergic reaction/hypersensitivity (anaphylaxis and nonanaphylaxis) 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 RHBW.6.11), patients will be categorized according to whether they were (i) always in lesser-TE-ADA status postbaseline or (ii) at some point postbaseline, were in greater-TE-ADA status. For each AESI, within the time-varying TE-ADA status groups, a summary will be provided of the number of patients who had no event, events only while in lesser-TE-ADA status for group (i), or for group (ii) – at least 1 event while in greater-TE-ADA status.

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

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

6.13. Subgroup Analyses

6.13.1. Efficacy Subgroup Analyses

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

For categorical response variables (ASAS20 and ASAS40), a logistic regression analysis with treatment, subgroup, and of treatment-by-subgroup interaction included 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.

The following subgroups will be analyzed:

- Patient Demographics Subgroups:
  - Sex
  - Age category: <40 years, ≥40 years
  - Age category: <50 years, ≥50 years
  - Age category: <65 years, ≥65 years
  - Weight: <70 kg, ≥70 kg
  - BMI: 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); or extreme obese (≥40 kg/m^2)
  - Ethnicity: Hispanic/Latino, Non-Hispanic/Non-Latino
  - Race: American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple
- Geographic Region Subgroups:
  - Geographic region: US (including Puerto Rico sites) or ROW
  - Geographic region: Europe or Non Europe
  - Geographic region: North America (US including Puerto Rico, Canada), ROW
  - Geographic region: America, Asia, Europe, and ROW
- Baseline Severity of Disease Subgroups:
  - Baseline (CRP categories):
    - ≤3.00 mg/L or >3.00 mg/L
    - ≤5.00 mg/L or >5.00 mg/L
    - ≤10.00 mg/L or >10.00 mg/L

        - ≤15.00 mg/L or >15.00 mg/L
    - Baseline MRI status:
        - ASSpiMRI-Berlin score >0 or = 0
        - SPARCC Spine score ≥2 or <2
    - Number of prior TNFi used: 1 or 2
    - Baseline BASDAI:
        - 4 ≤ BASDAI <6 or BASDAI ≥6
    - Baseline ASDAS:
        - ASDAS ≤3.5 or ASDAS >3.5
- Other Patient Characteristics Subgroups:
    - Duration of symptom since axSpA onset category: <10 years or ≥10 years
    - Duration of symptom since axSpA onset category: <5 years or ≥5 years
    - Duration of symptom since axSpA of onset category: <3 years or ≥3 years
    - HLA-B27 status: positive or negative
    - Smoking status: current or former/never
    - Concomitant cDMARDs (methotrexate, sulfasalazine, hydroxychloroquine) at baseline: yes or no
    - History of arthritis: yes or no
    - History of uveitis: yes or no
    - History of dactylitis: yes or no
    - History of psoriasis: yes or no
    - History of enthesitis: yes or no
    - History of inflammatory bowel disease: yes or no
    - History of extra-axial involvement: yes or no

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

6.13.2. Safety Subgroup Analyses

Safety subgroup analysis for common TEAEs and AESI of allergy reaction/hypersensitivity and infections will be summarized by treatment group and overall, using the safety population for Period 2. The common TEAEs will be presented by MedDRA PT within SOC. The AESI of allergy reaction/hypersensitivity will be presented by anaphylaxis and nonanaphylaxis events, by PT within category. The AESI of infection will be presented by PT.

A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. The response variable will be each AE. Treatment groups' differences will be evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only the descriptive statistics will be provided for that subgroup (that is, no inferential testing).

The subgroups include baseline demographics and geographic region, which are defined as in Section 6.13.1.

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

6.14. 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.

Table RHBW.6.12 includes 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 for the CSR.

The number and percentage of patients having important protocol deviation(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.

Table RHBW.6.12. Identification and Action of Important Protocol Deviations

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
Category: Eligibility		
Sub-Category: Inclusion/Exclusion		
[1] No established diagnosis of rad-axSpA at screening	Exclude from PPS	Monitor and Stats
[2] History of back pain <3 months or age at onset ≥45 years	Exclude from PPS	Monitor and Stats
[3] No active rad-axSpA defined as BASDAI ≥4 and total back pain ≥4 on an NRS at screening and baseline	Exclude from PPS	Monitor and Stats
[4] No prior TNF inhibitor OR more than 2 TNF inhibitors OR the patients have not discontinued at least 1 TNF inhibitor due to either intolerance or an inadequate response	Exclude from PPS	Monitor and Stats
[5] Not have had an inadequate response to 2 or more NSAIDs at therapeutic dose range for a total duration of at least 4 weeks AND not have history of intolerance to NSAID	Exclude from PPS	Monitor
[6] Not have a history of prior therapy for axSpA of at least 12 weeks before screening	Exclude from PPS	Monitor and Stats
[7] Not have stable dose for NSAID or COX-2 for at least 2 weeks before baseline randomization, if taking NSAID or Cox-2 inhibitors	Only Exclude from PPS if 1. Stopped or decreased dose for a current one <3 days before randomization; 2. Start or increased dose for a current one or started a new one <2 weeks before randomization.	Monitor and Stats
[8] Not ≥18 years of age at time of screening	Exclude from PPS	Monitor and Stats
[9] Female patient of childbearing potential with positive pregnancy test; or did not use a reliable method of birth control, if applicable	Do not exclude from PPS	Monitor and Stats
[11] Have total ankylosis of the spine at screening	Exclude from PPS	Monitor
[12] Have a history of other systemic inflammatory diseases or other chronic pain conditions that might confound the evaluations of benefit from ixekizumab therapy	Exclude from PPS	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
[13] Have active Crohn's disease (CD) or active ulcerative colitis (UC) at screening	Do not exclude from PPS	Monitor and Stats
[14] Have evidence of active anterior uveitis (an acute episode) within the last 4 weeks before baseline randomization	Do not exclude from PPS	Monitor and Stats
[15] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease; or have active or history of malignant disease within 5 years before V2	Do not exclude from PPS	Monitor
[16] Have had fluid overload, MI or new onset ischemic heart disease, uncompensated heart failure, or other serious cardiac disease within 12 weeks before V2	Do not exclude from PPS	Monitor
[17] Presence of significant, uncontrolled cerebro-cardiovascular events at screening	Do not exclude from PPS	Monitor
[18] Presence of respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorder at screening that pose unacceptable risk to patient or interfering with interpretation of data	Do not exclude from PPS	Monitor
[19] Presence of neurologic or neuropsychiatric disorders at screening that pose unacceptable risk to patient or interfering with interpretation of data	Do not exclude from PPS	Monitor
[20] Presence of significant uncontrolled neuropsychiatric disorder, recent history (30 days before V1 and anytime between V1 and V2) of a suicide attempt, have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the QIDS-SR16 at V1 or V2, or at risk for suicide	Do not exclude from PPS	Monitor and Stats
[21] Deleted in protocol.		
[22] In the past 12 weeks before V2, had a serious infection, hospitalization or IV antibiotics for an infection; in the past 24 weeks before V2, had a serious bone or joint infection, ever had an infection of an artificial joint, or infection that occurs with increased incidence in an immunocompromised host	Do not exclude from PPS	Monitor
[23] Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient	Do not exclude from PPS	Monitor
[24] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of V2	Do not exclude from PPS	Monitor
[25] Have any other active or recent infection within 4 weeks of V2 that would pose an unacceptable risk to the patient	Do not exclude from PPS	Monitor
[26] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study	Exclude from PPS	Monitor
[27] Have had surgical treatment of a joint to be assessed in the study within 8 weeks before	Exclude from PPS depending on the clinical	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
baseline randomization or will require such during the first 16 weeks of the trial	significance	
[28] Had any major surgery within 8 weeks before V2, or will require such during the study that would pose an unacceptable risk to the patient	Do not exclude from PPS	Monitor
[29] Have received cDMARDs, and/or other therapies such as but not limited to: gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents within 4 weeks before baseline randomization.	Exclude from PPS 1. Stopped or decreased dose for a current one ≤3 days before randomization; or 2. Start new treatment or increased dose for current one or started a new one <4 weeks before randomization.	Monitor and Stats
[30] Current use of oral corticosteroids >10 mg/day prednisone or its equivalent	Exclude from PPS 1. If dose >10mg/day any time within 4 weeks; or 2. Stopped or decreased dose for a current one <10 days before randomization; or 3. Start new treatment or increased dose for current one or started a new one <4 weeks before randomization;	Monitor and Stats
[31] Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents, including investigational therapies (such as but not limited to Janus kinase (JAK) inhibitors, IL-1, IL-6 , IL-23 , IL-17 (including ixekizumab), IL-17R, T cell, or B cell targeted therapies)	Exclude from PPS	Monitor and Stats
[32] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product (IP) or nonapproved use of a drug or device within the last 30 days before screening or a period of at least 5 half-lives of the last administration of the drug, whichever is longer; for Brazil patients, patients completed a clinical trial involving an IP or nonapproved use of drug or device unless there is direct benefit to patient	Exclude from PPS	Monitor
[33] Are currently (for all sites except Brazil sites) or concurrently (for Brazil sites, unless	Exclude from PPS	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
there is direct benefit to patient) enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study		
[34] Are currently receiving or have received treatment with denosumab within 6 months before baseline randomization	Do not exclude from PPS	Monitor and Stats
[35] Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks before baseline randomization, or a parenteral injection of glucocorticosteroids is anticipated during the Period 2	Exclude from PPS	Monitor and Stats
[36] Use of any opiate analgesic at average daily doses >30 mg/day of morphine or its equivalent or use of variable doses of any opiate analgesic within 6 weeks before baseline randomization.	Exclude from PPS 1. If doses >30 mg/day any time within 6 weeks before randomization; or 2. Stopped or decreased dose for a current one <7 days before randomization; 3. Start new treatment or increased dose for current one or started a new one <6 weeks before randomization.	Monitor and Stats
[37] Had a live vaccination or participated in a vaccine clinical study within 12 weeks before V2, or intend to have a live vaccination during the study or within 12 weeks of completing study treatment	Do not exclude from PPS	Monitor
[38] Had a vaccination with BCG within 12 months before V2, or intend to have this vaccination with BCG during the study or within 12 months of completing study treatment	Do not exclude from PPS	Monitor and Stats
[39] Have a body temperature ≥38°C (100.5°F) at V2	Do not exclude from PPS	Monitor and Stats
[40] Have evidence or suspicion of active or latent TB	Do not exclude from PPS	Monitor
[41] Are positive for human immunodeficiency virus serology (HIV)	Do not exclude from PPS	Monitor and Stats
[42] Have evidence of or test positive for hepatitis B virus (HBV) and are HBV DNA	Do not exclude from PPS	Monitor and

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
positive		Stats
[43] Have evidence of or test positive for hepatitis C virus (HCV)	Do not exclude from PPS	Monitor and Stats
[44] Have ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study	Do not exclude from PPS	Monitor
[45] At V1, have a neutrophil count <1.50 GI/L	Do not exclude from PPS	Monitor and Stats
[46] At V1, have a lymphocyte count <0.80 GI/L;	Do not exclude from PPS	Monitor and Stats
[47] At V1, have a platelet count <100 GI/L	Do not exclude from PPS	Monitor and Stats
[48] At V1, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)	Do not exclude from PPS	Monitor and Stats
[49] At V1, have a total white blood cell (WBC) count <3.00 GI/L	Do not exclude from PPS	Monitor and Stats
[50] At V1, have hemoglobin <8.5 g/dL for male patients and <8.0 g/dL for female patients	Do not exclude from PPS	Monitor and Stats
[51] Have other clinical laboratory test results at V1 that are outside the normal reference range for the population and are considered clinically significant	Do not exclude from PPS	Monitor
[52] Have donated >450 mL of blood within the last 4 weeks before V1, or intend to donate blood during the course of the study	Do not exclude from PPS	Monitor
[53] Are women who are lactating or breastfeeding	Do not exclude from PPS	Monitor
[54] Are investigator-site personnel directly affiliated with this study and/or their immediate families	Exclude from PPS	Monitor
[55] Are Lilly employees or its designee or are employees of third-party organizations (TPOs) involved in the study	Exclude from PPS	Monitor
[56] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient,	Exclude from PPS when occurred in Period 2	Monitor
[57] Have any other condition that precludes the patient from following and completing the protocol	Exclude from PPS	Monitor
[58] Patients having contraindications to MRI (This is only for MRI addendum countries)	Do not exclude from PPS	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
Sub-Category: Other		
Rescreened patients were enrolled but did not meet rescreening criteria per protocol.	Do not exclude from PPS	Monitor
Category: Study Procedures		
Sub-Category: Violation of Discontinuation Criteria		
[D1] Lilly medical not consulted when patient met hepatic lab criteria for consideration of discontinuation	Do not exclude from PPS	Monitor
[D2-N] Neutrophil counts <0.50 GI/L, or ≥0.50 GI/L and <1.00 GI/L based on 2 test results within 1 week of knowing 1st result, or ≥1.00 GI/L and <1.50 GI/L based on 3 test results and a concurrent infection	Do not exclude from PPS	Monitor and Stats
[D2-W] Total WBC count <2.00 GI/L	Do not exclude from PPS	Monitor and Stats
[D2-L] Lymphocyte count <0.50 GI/L	Do not exclude from PPS	Monitor and Stats
[D2-P] Platelet count <50 GI/L	Do not exclude from PPS	Monitor and Stats
[D3] Patient experiences a severe AE, an SAE, or a clinically significant change in a laboratory value that merits the discontinuation of the investigational product and appropriate measures being taken	Do not exclude from PPS	Monitor
[D4] Clinically significant systemic hypersensitivity reaction does not respond to treatment	Do not exclude from PPS	Monitor
[D5] Patient became pregnant	Do not exclude from PPS	Monitor
[D6] Patient developed a malignancy (Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers during the study)	Do not exclude from PPS	Monitor
[D7] Enrolled in prohibited medical research	Exclude from PPS when occurred in Period 2	Monitor
[D11] Lilly stopped the patient participation	Do not exclude from PPS	Monitor
[D12] Patient became HBV DNA positive	Do not exclude from PPS	Monitor
[D13] Patient developed a clinically significant infection during study participation for patients from UK sites	Do not exclude from PPS	Monitor
[D14] Patient received a live vaccination during the course of the study for patients from UK	Do not exclude from PPS	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
sites		
Category: Study Procedures		
Sub-Category: Excluded Con-meds	Exclude from PPS (Excluded Con-meds refers to clinically meaningful change in con-meds [Appendix 13] when occurred during Period 2 and prescribed for primary study condition) Excluded Con-meds in Period 3 refer to the lists in Appendix 13.	Monitor and Stats
Sub-Category: Lab/Imaging Criteria		
Missing imaging as per protocol schedule of events	Do not exclude from PPS	Monitor
Missing lab chemistry and hematology: missing baseline or not having at least 1 postbaseline	Do not exclude from PPS	Stats
Sub-Category: Other		
Missing QIDS total score: missing baseline or any scheduled visit before discontinuation visit	Do not exclude from PPS	Stats
Missing Columbia scale at any visit except V1	Do not exclude from PPS	Monitor and Stats
Missing ASAS components for ASAS40 derivation: not having Week 16 measurement for patients who have completed Week 16	Do not exclude from PPS. Note: if missing ASAS components lead to missing ASAS40, such patient will be treated as nonresponder for the Week 16 ITT analyses	Stats
Had unqualified site personnel perform clinical safety and/or efficacy assessments	Do not exclude from PPS	Monitor
Category: Investigational Product		
Sub-Category: Treatment Assignment/Randomization Error		
Took incorrect study medication	Do not exclude from PPS. Analyze 'As randomized' or 'As assigned'.	Monitor and Stats
Sub-Category: Compliance	Exclude from PPS when occurred during Period 2	Stats

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
Sub-Category: Patient took medication not fit for use	Do not exclude from PPS	Monitor
Sub-Category: Unblinding	Exclude from PPS	Monitor
Sub-Category: Other		
Randomized but did not take any study medication	Exclude from PPS	Stats
Category: Safety		
Sub-Category: SAEs	Do not exclude from PPS	Monitor
Category: Informed Consent		
Sub-Category: Informed Consent not Obtained/Missing/Late	Exclude from PPS	Monitor and Stats
Subcategory: Improper Informed Consent	Do not exclude from PPS	Monitor
Category: Administrative/Oversight		
Sub-Category: Reg/Ethic Approvals	Exclude from PPS	Monitor
Sub-Category: Other		
Enrolled in a site with significant GCP non-compliance issue	Exclude from PPS	Monitor

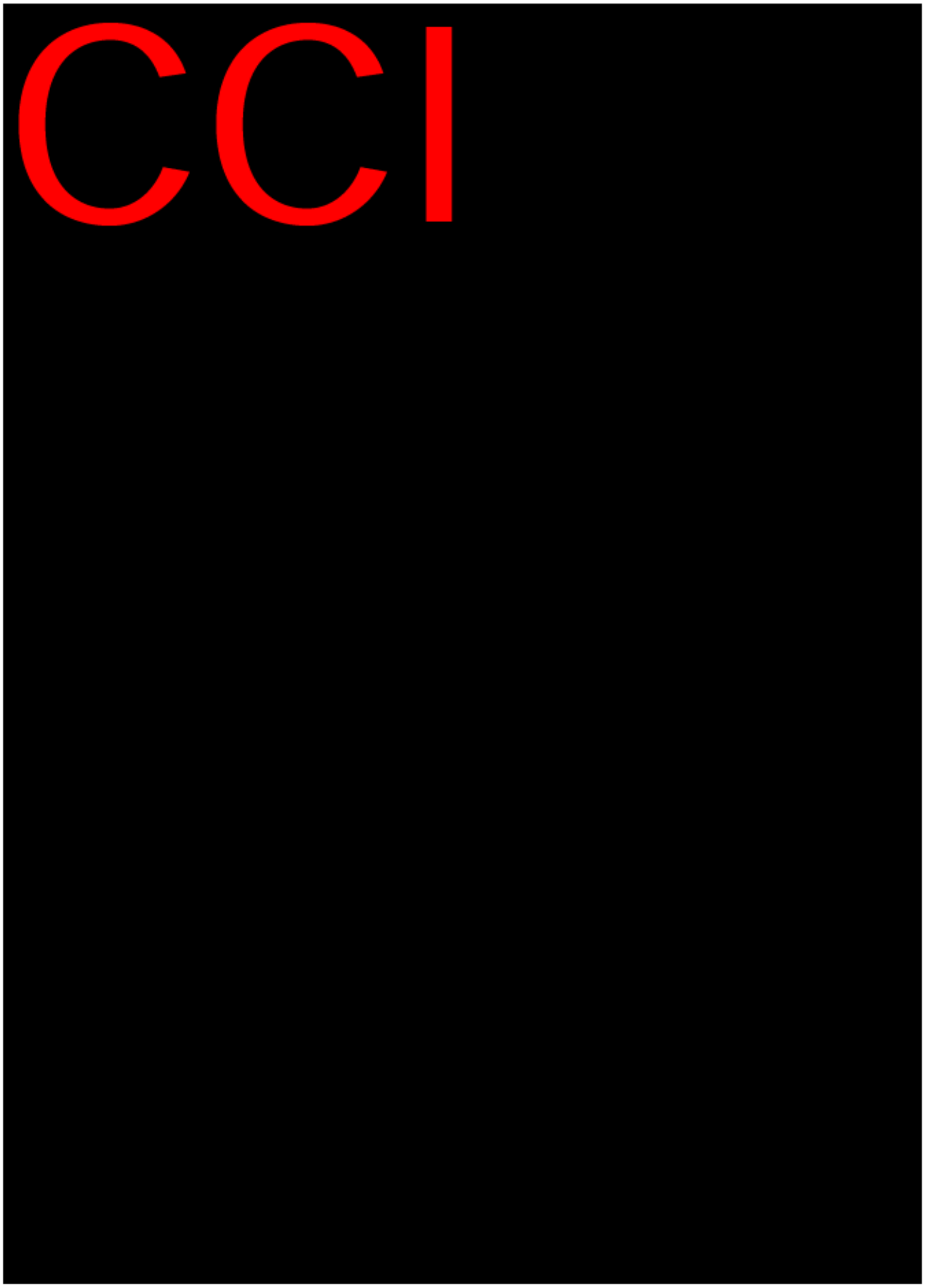
Abbreviations: AE = adverse event; axSpA = axial spondyloarthritis; ASAS = Assessment of Spondyloarthritis International Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BCG = Bacille de Calmette et Guérin; BSA = body surface area; cDMARD = conventional disease-modifying antirheumatic drug; ECG = electrocardiogram; eCRF = electronic case report form; GCP = good clinical practice; IL = interleukin; ITT = intent-to-treat; IV = intravenous; IWRS = interactive web-response system; NSAID = nonsteroidal anti-inflammatory drug; MI = myocardial infarction; NRS = numerical rating scale; PCP = pneumocystis pneumonia; PPS = per protocol set; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self-Report 16 items; rad = radiographic; TB = tuberculosis; V = visit; WBC = white blood cell.

[a] The term "Monitor" indicates the protocol deviation will be identified by site monitors and entered into monitor's list using a spreadsheet. The spreadsheet will be exported as Study Data Tabulation Model (SDTM) DV domain.
The term "Stats" indicates the protocol deviation will be programmed based on data in clinical database by statistical programmers with the statistical programming guidance provided. The detailed programming specification will be documented in Analysis Data Model (ADaM) specification.
The terms "Monitor and Stats" indicates the protocol deviation will be a combination of monitor's list (SDTM.DV domain) and statistical programming from clinical database, the deviation will show if either source identifies.

6.15. 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 who 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 Period 3 or after completion of Period 4 to fulfill the need for regulatory interactions or publication purposes.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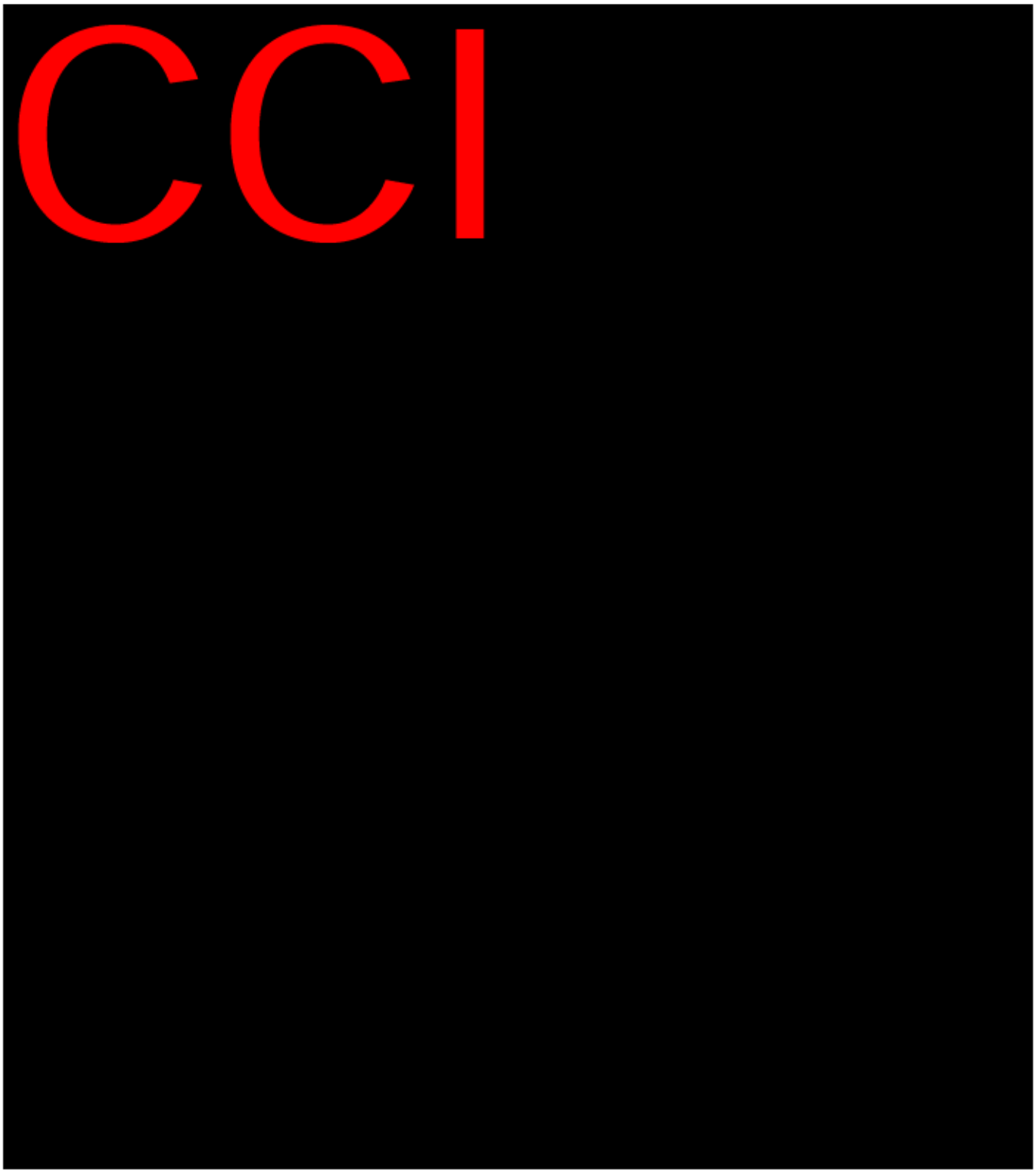
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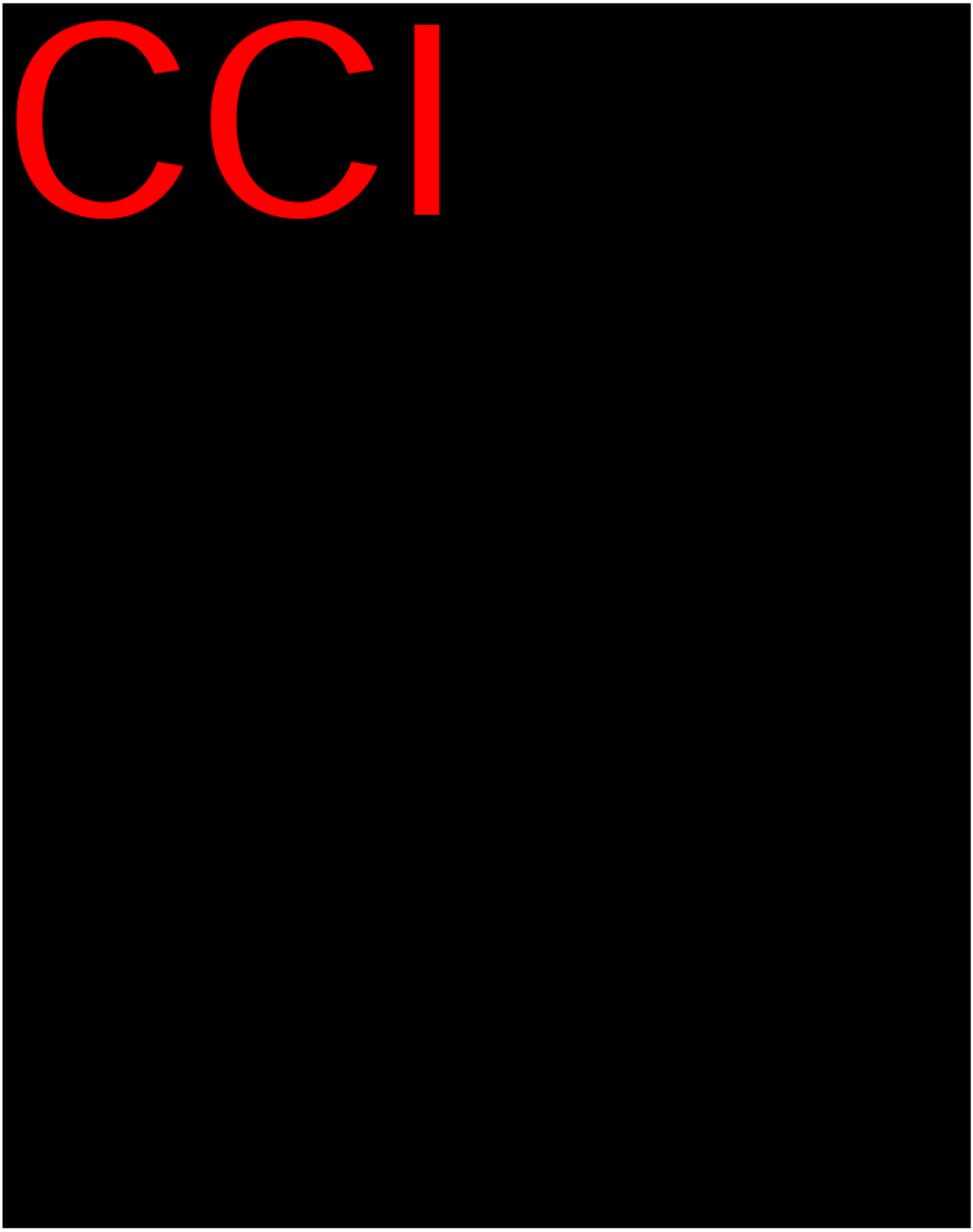
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6.17. Annual Report Analyses

Annual report analyses will be documented in a separate document.

6.18. 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 SAE and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures such as the CSR.

7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

8. References

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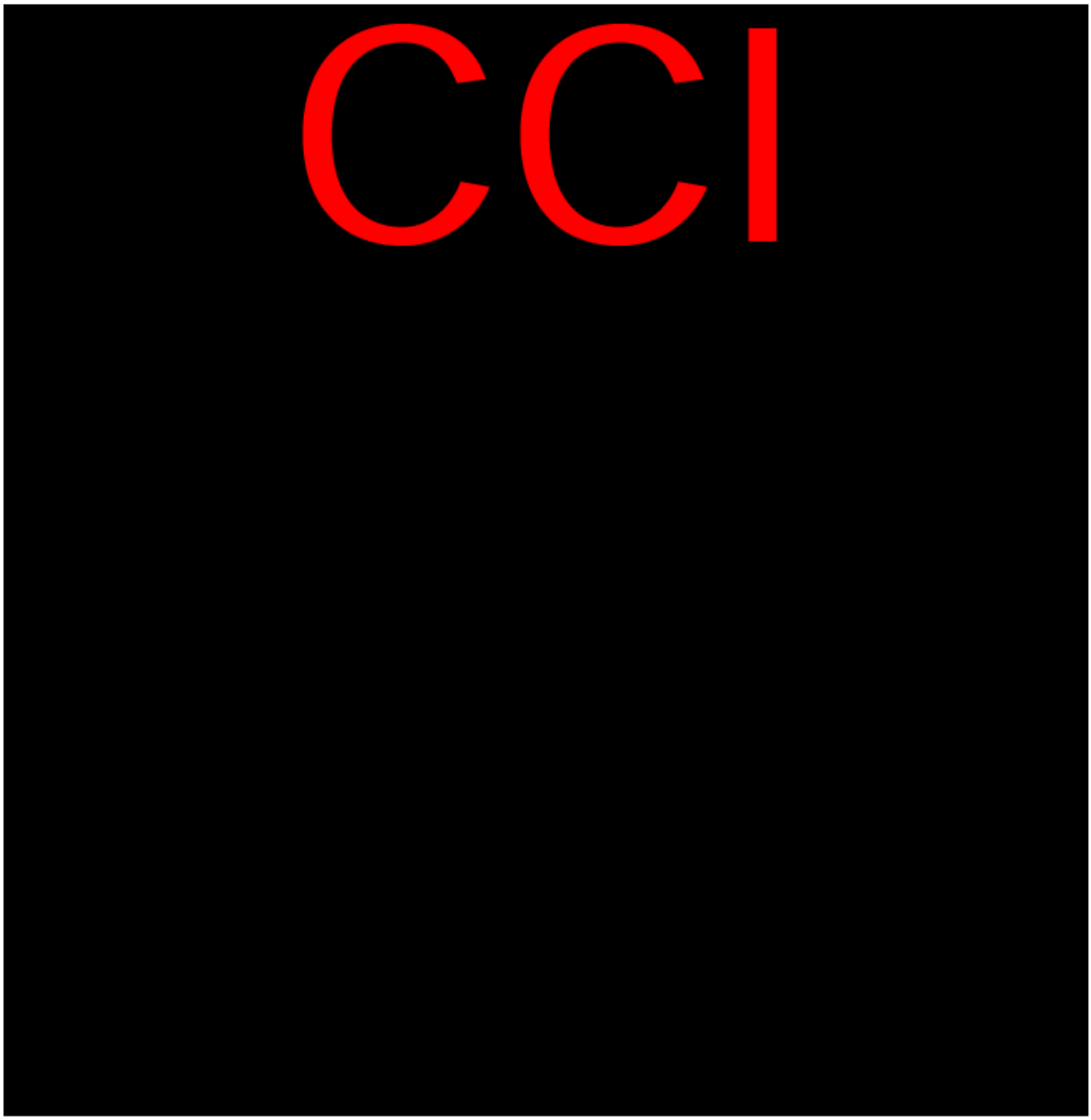
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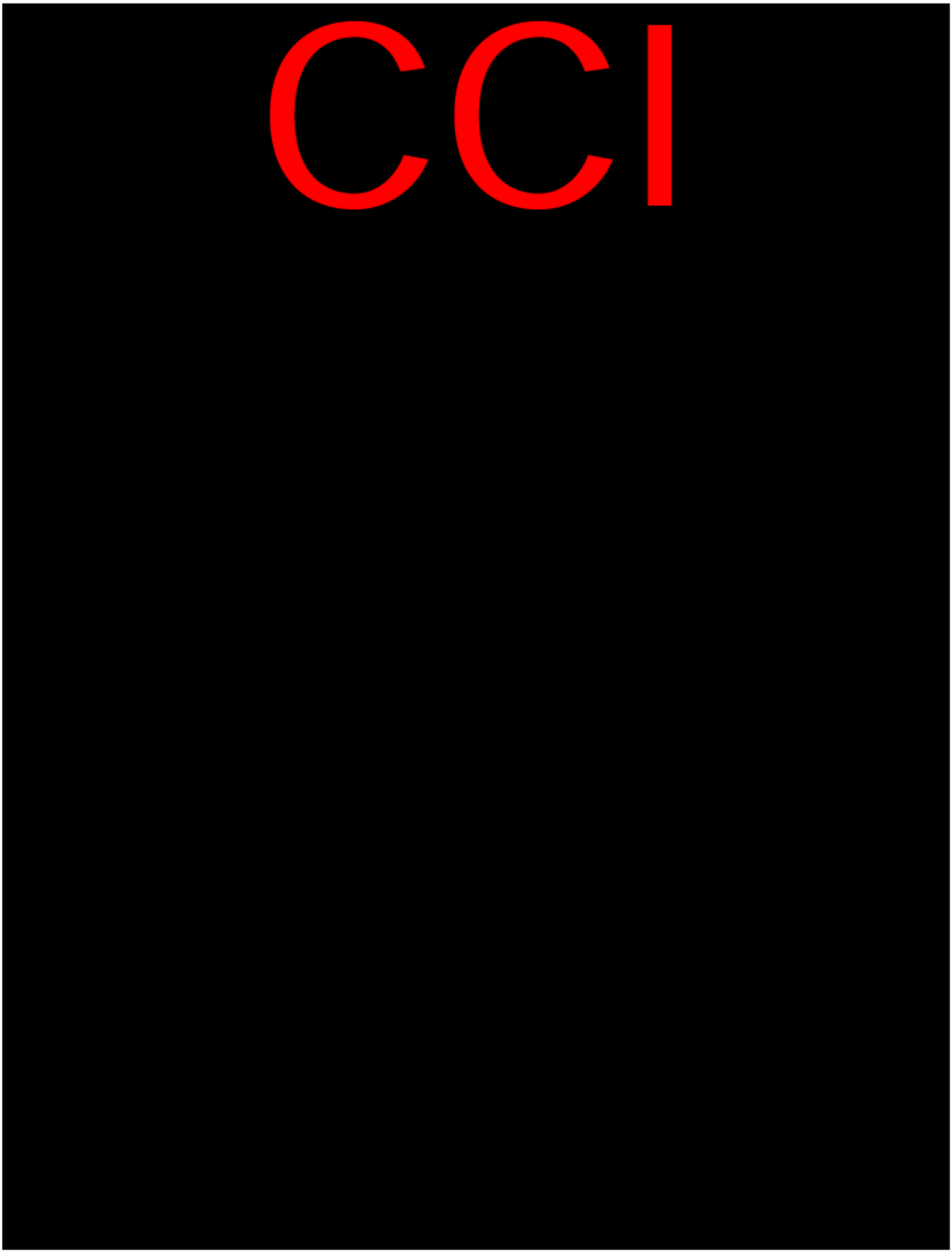
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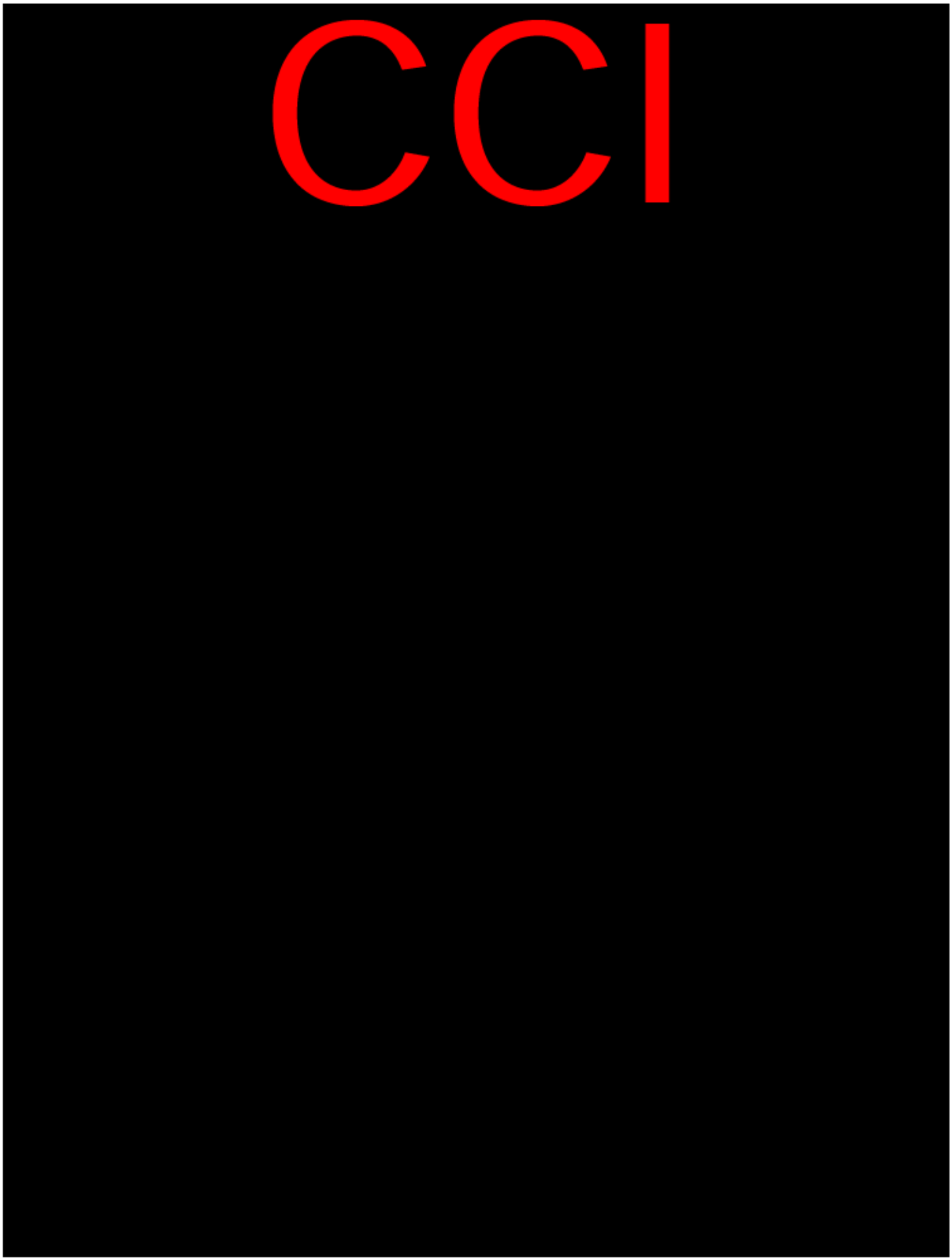
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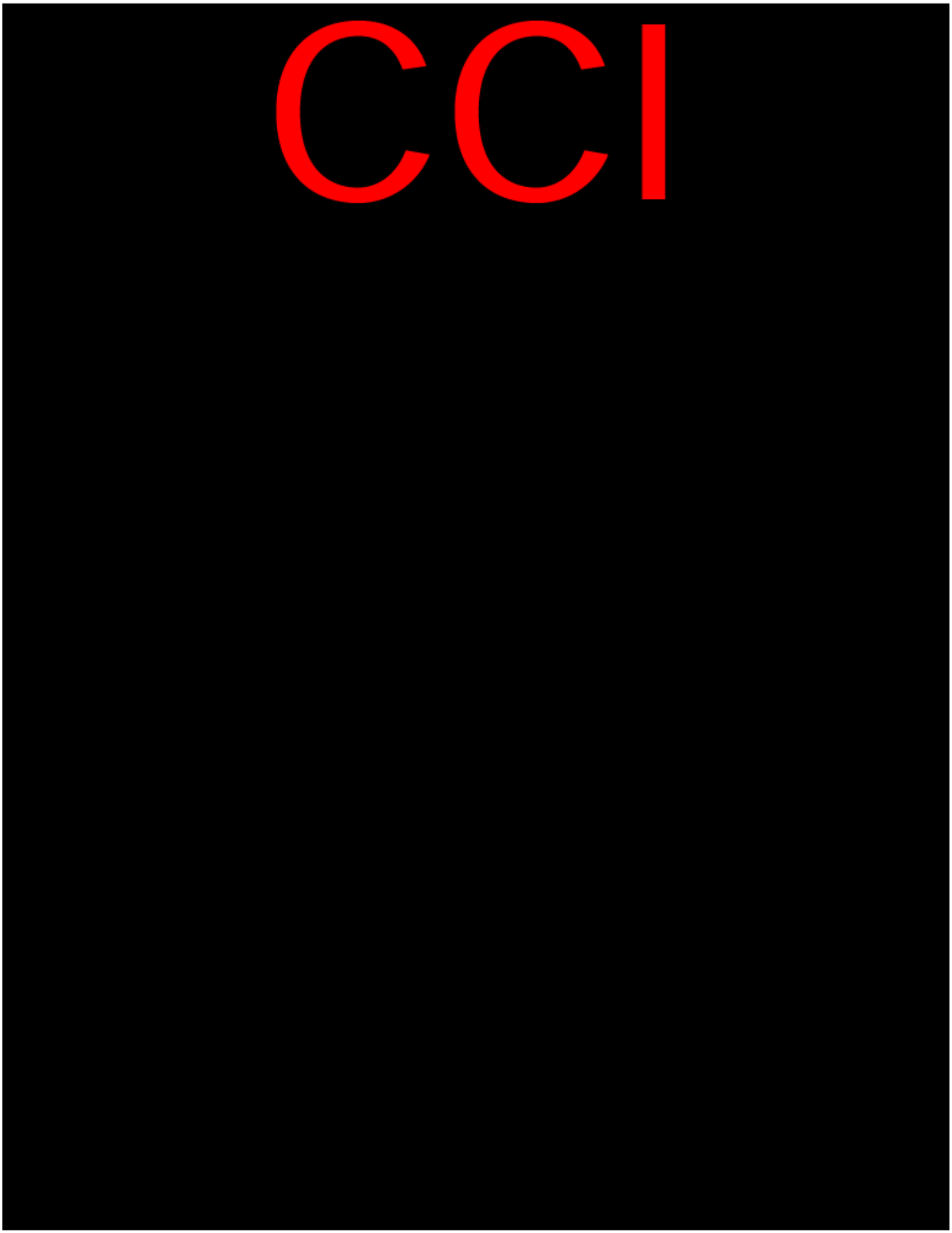
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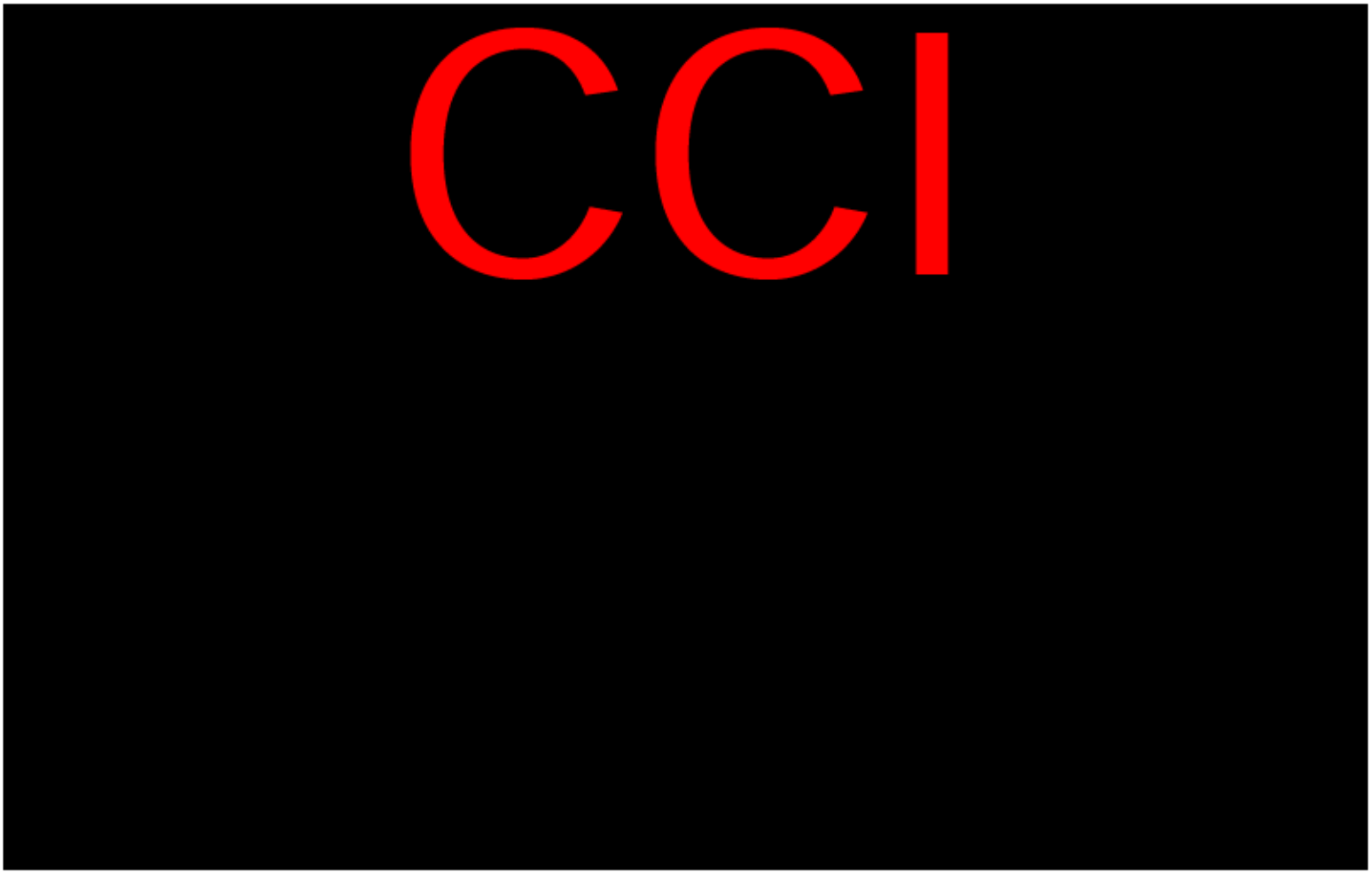
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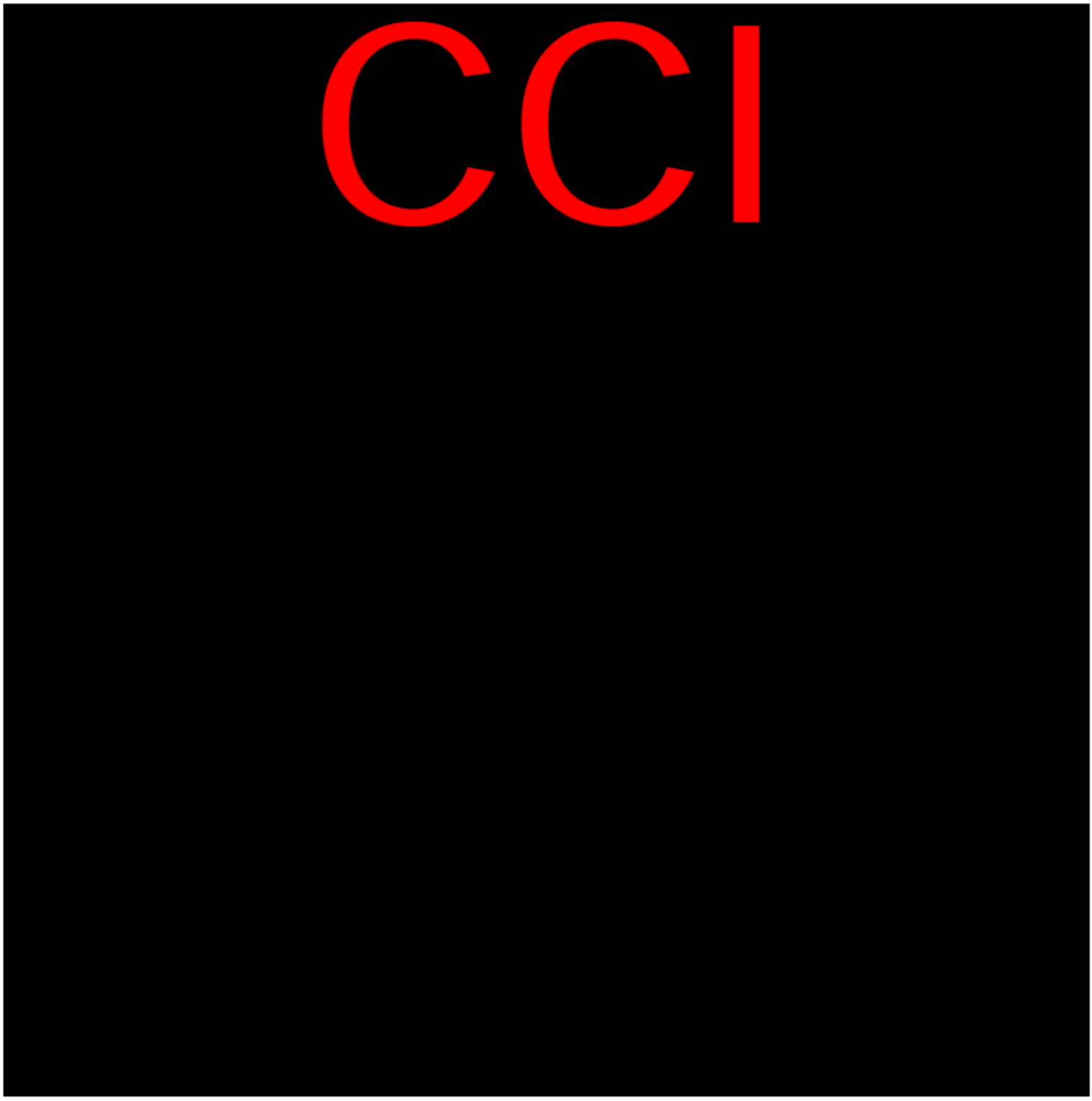
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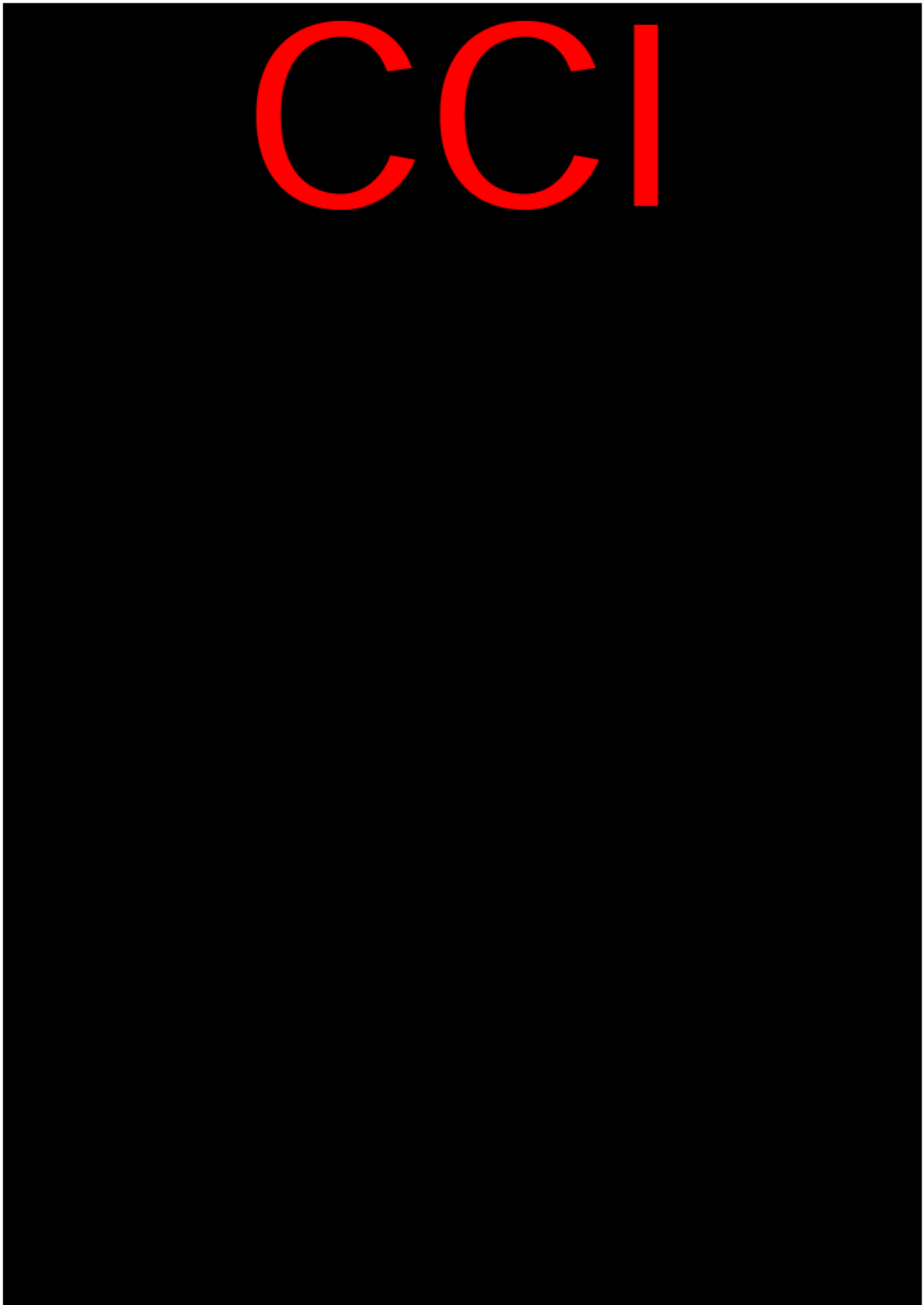
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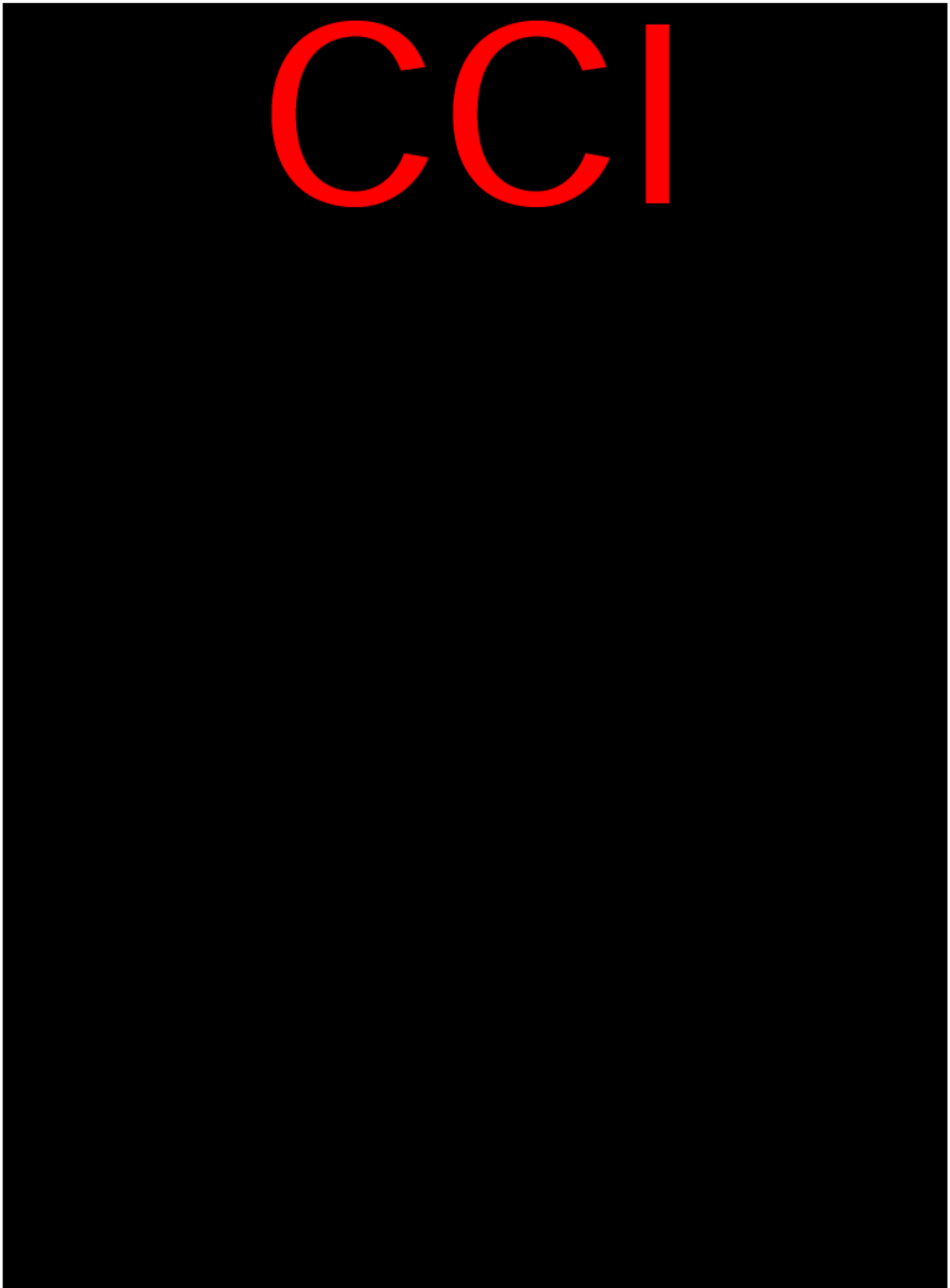
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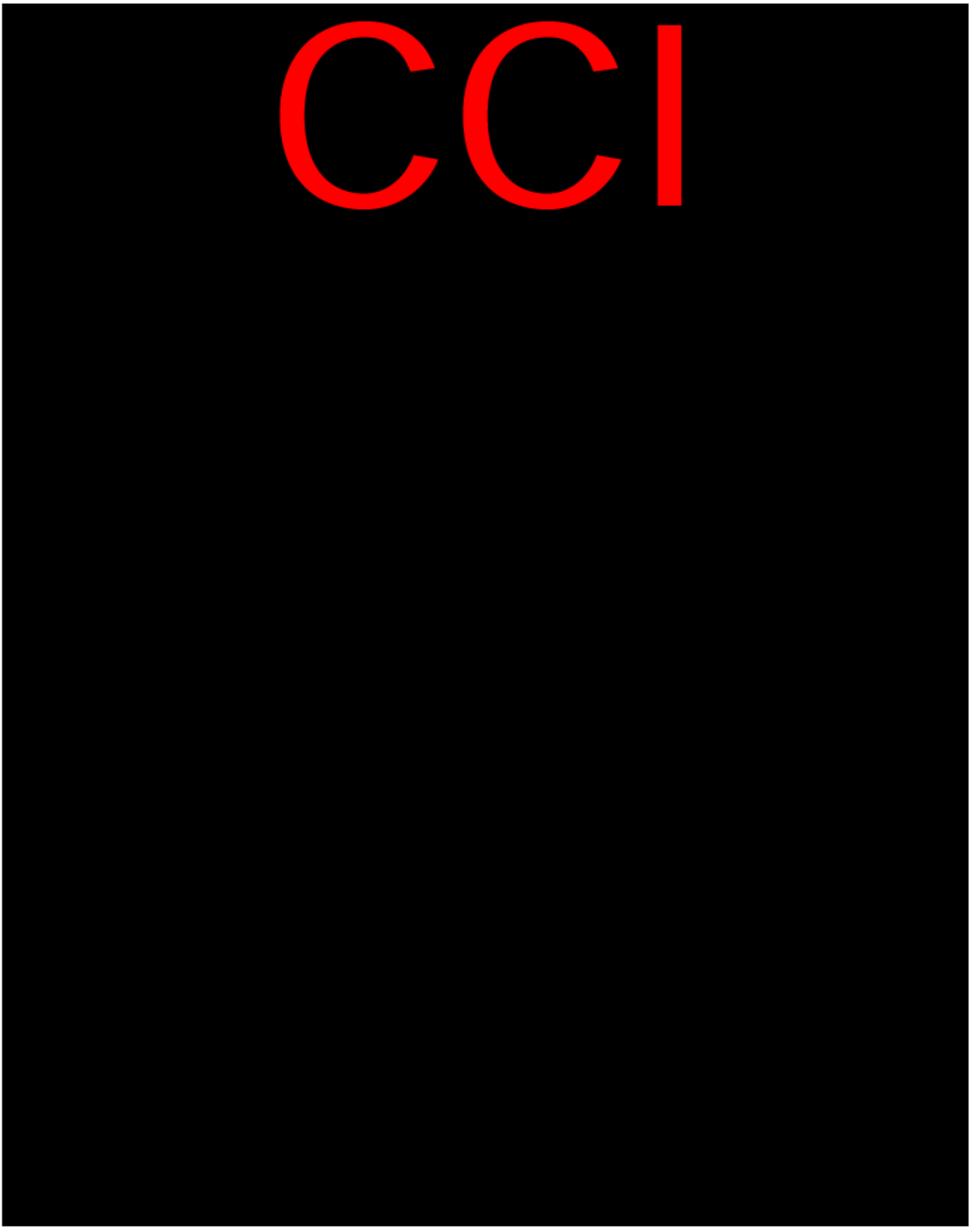
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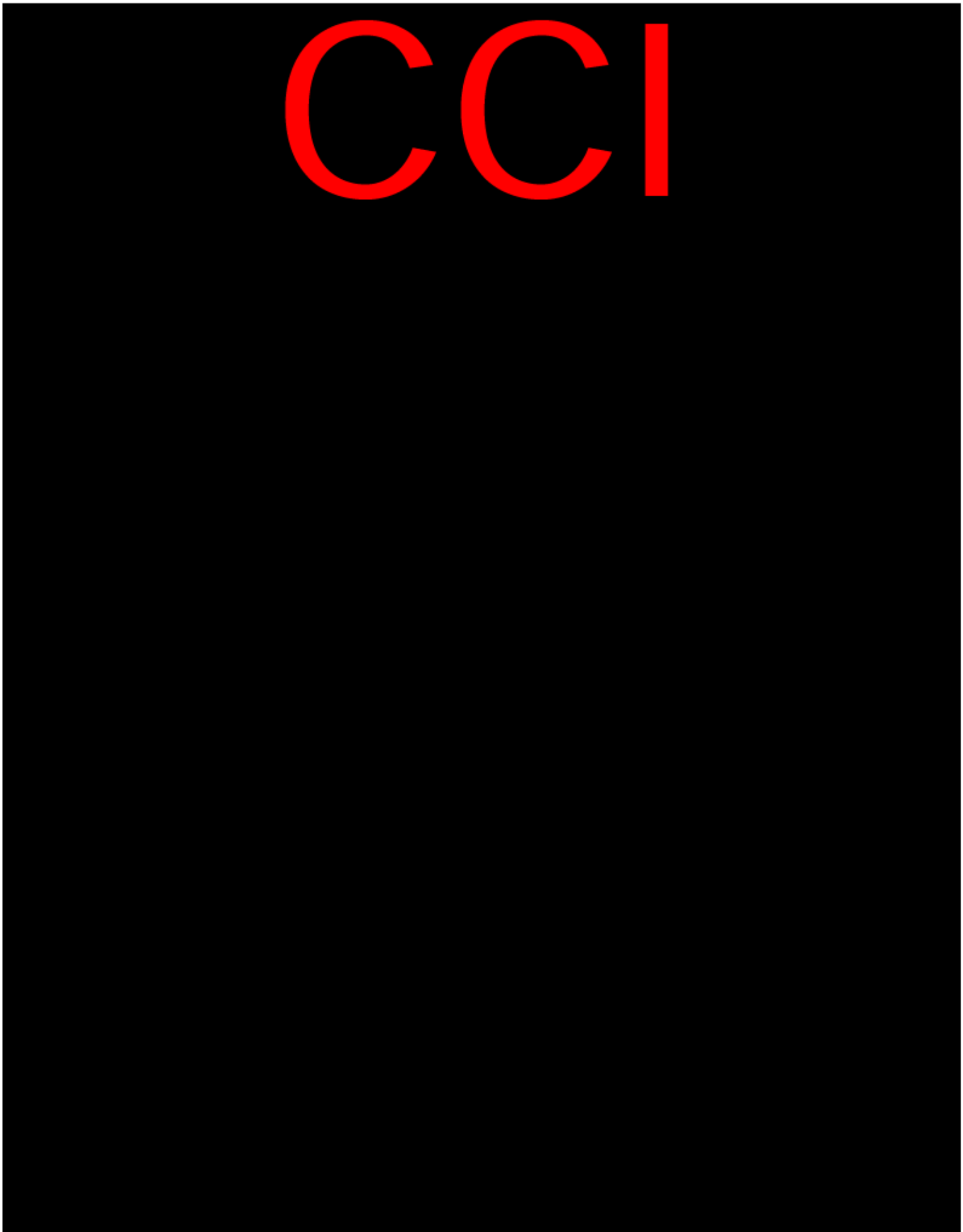
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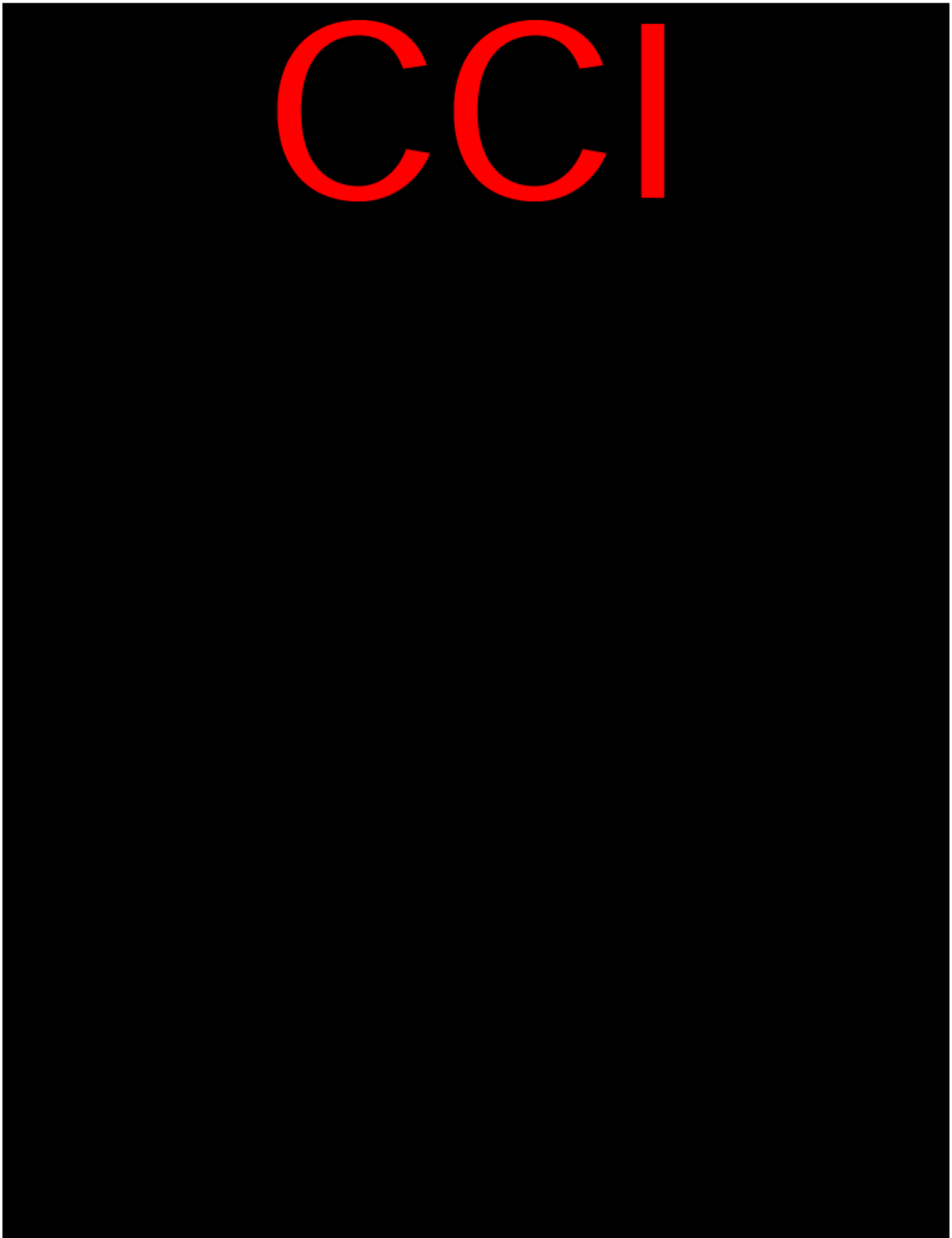
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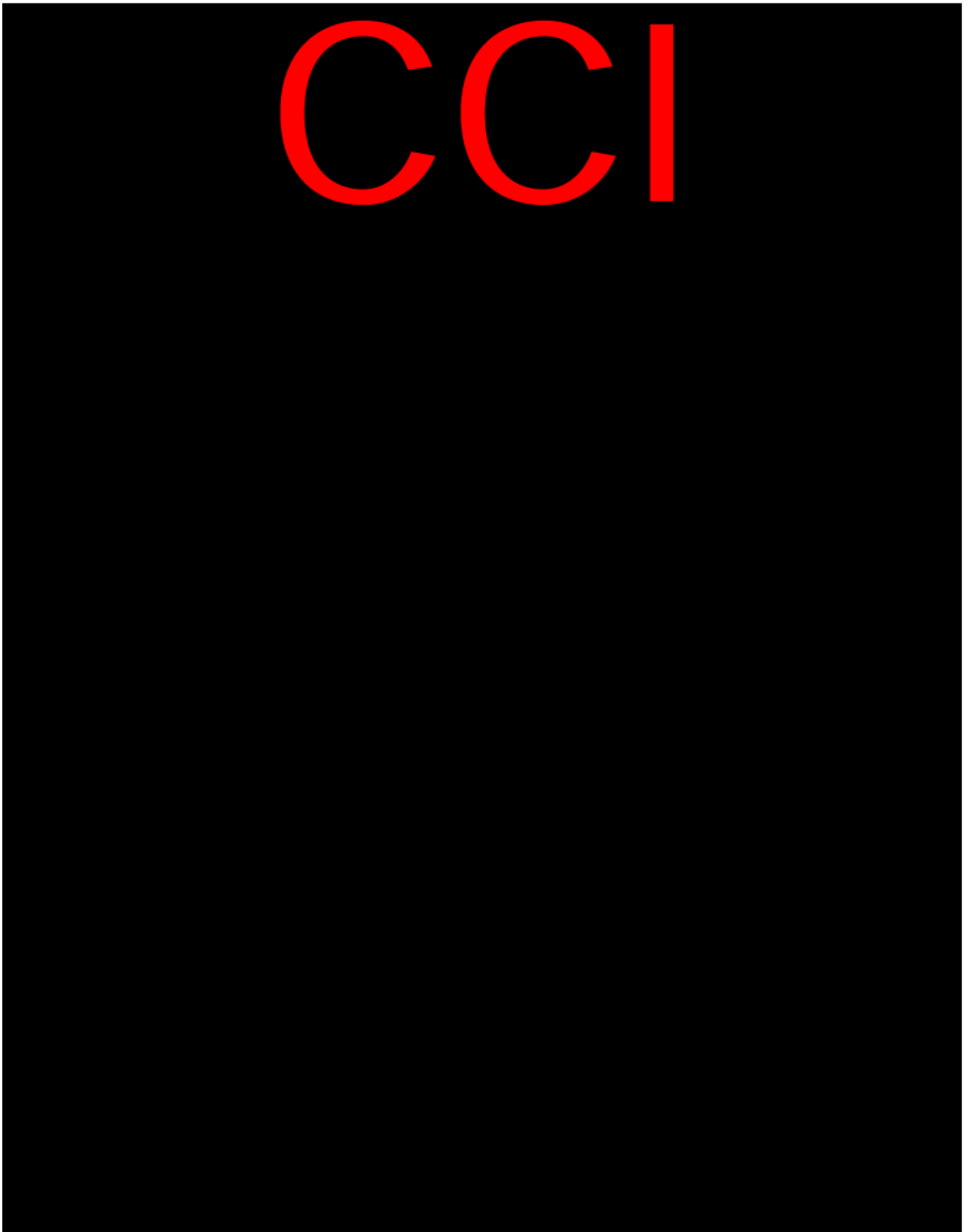
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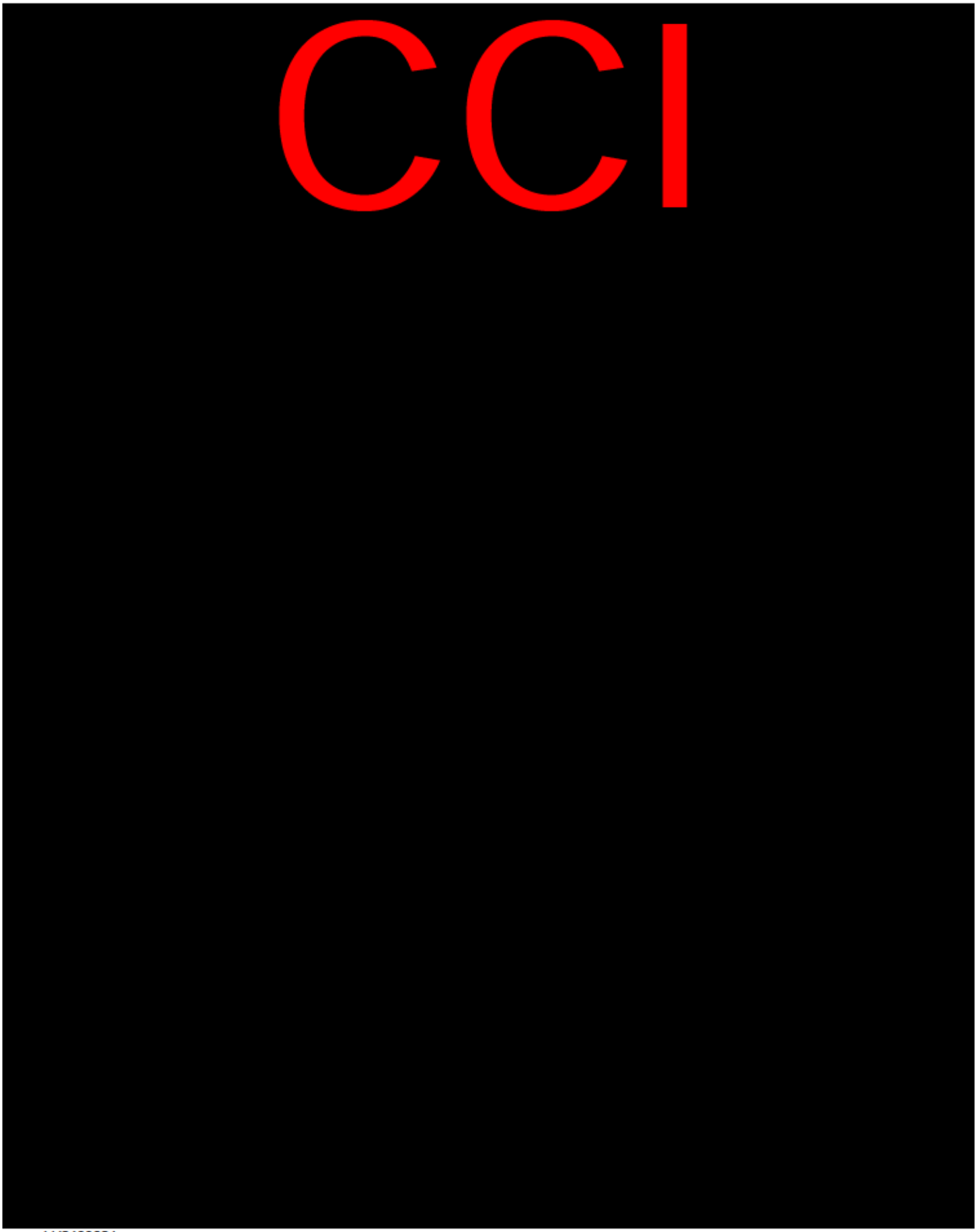
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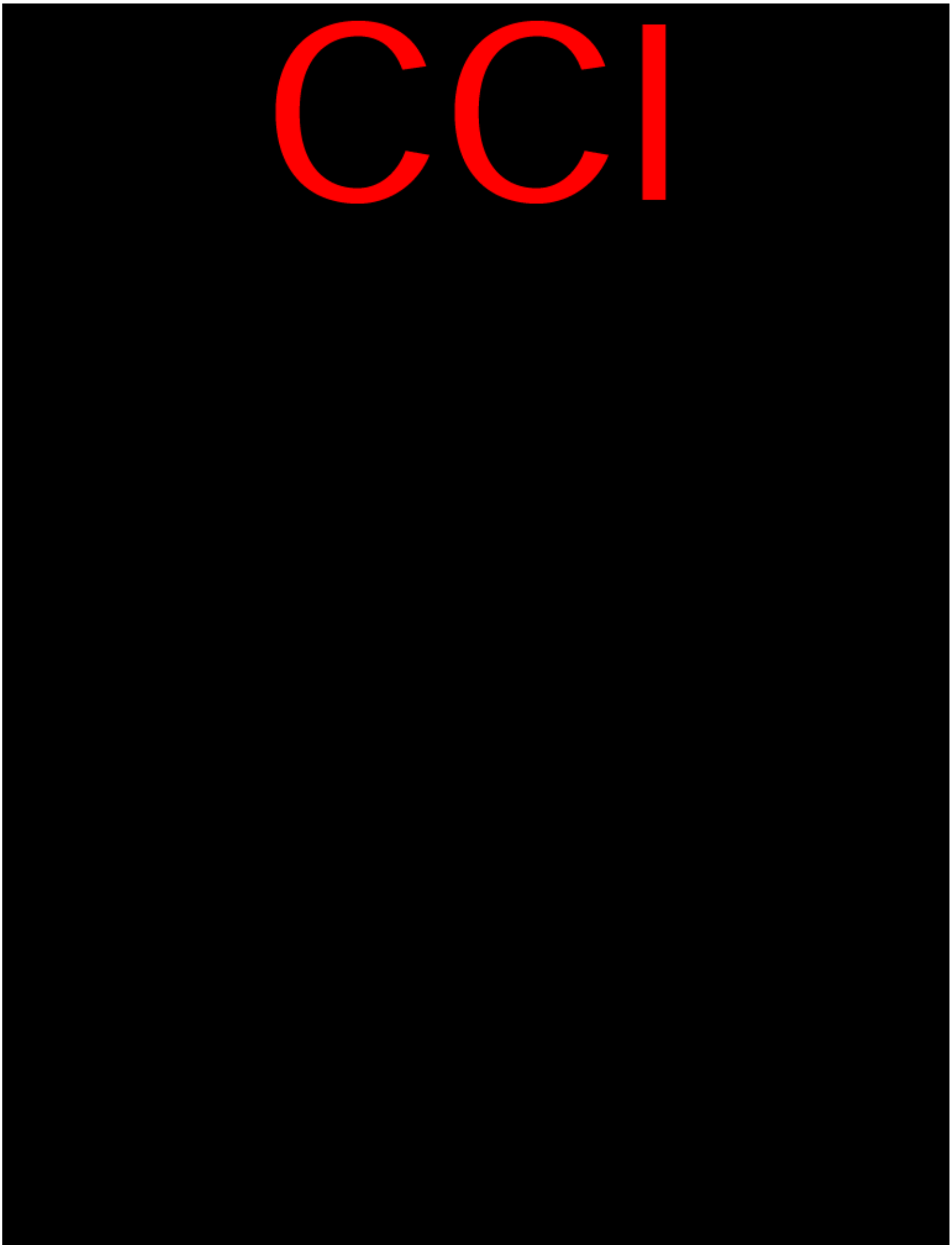
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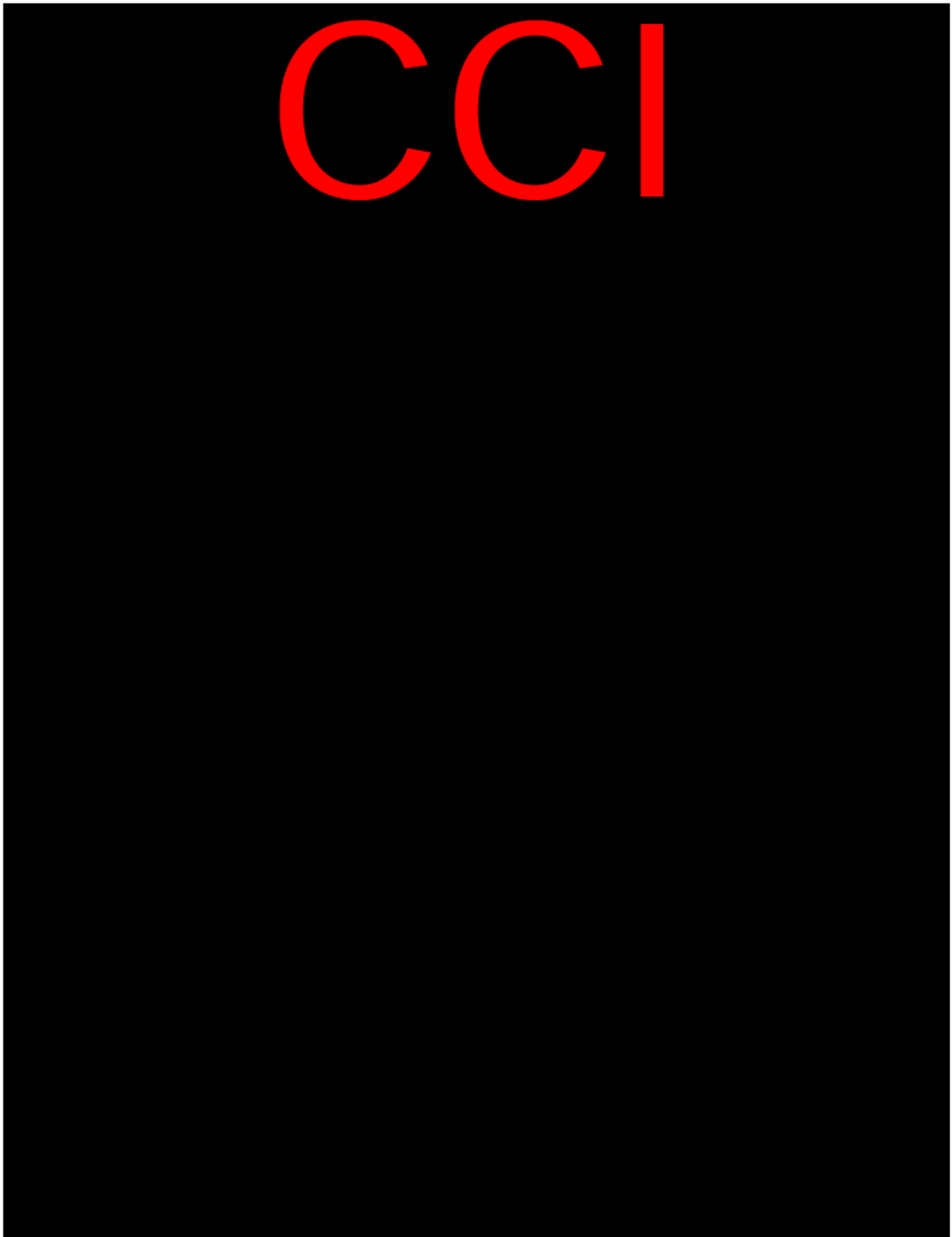
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