I1F-MC-RHBX Statistical Analysis Plan Version 2

A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic Axial Spondyloarthritis

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1. Statistical Analysis Plan: I1F-MC-RHBX: A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic Axial Spondyloarthritis

Ixekizumab (LY2439821) Axial Spondyloarthritis

Study I1F-MC-RHBX is a Phase 3, multicenter, randomized, double-blind, and placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of subcutaneous (SC) ixekizumab (LY2439821) treatment regimens (80 mg every 2 weeks [Q2W] and 80 mg every 4 weeks [Q4W] with an 80-mg or 160-mg starting dose) as compared to SC placebo in patients with active nonradiographic axial spondyloarthritis (axSpA) who are biological disease-modifying antirheumatic drug (bDMARD)-naive, during a 52-week treatment period.

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Protocol I1F-MC-RHBX
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 09 November 2016
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

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2. Table of Contents

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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to first permanent data transfer, on 09 November 2016.

Revisions since Version 1

Section	Revision
Entire document	Editorial changes on minor grammatical or formatting changes as needed
Section 4 Objectives	Updated primary objective per protocol amendment (b); In addition, made the following changes to major secondary objectives: 1. Replaced BASFI with SF-36 PCS 2. Changed ASDAS inactive disease to ASDAS low disease activity; 3. Removed objective for Changed clinically meaningful changes in background therapy due to sparse data 4. Added BASDAI change from baseline Added starting dose analyses for additional endpoints for secondary objective
Section 5.2 Determination of Sample Size	Updated per protocol amendment (b)
Section 5.3 Method of Assignment to Treatment	Clarified stratification factor
Section 6.1.1 Analysis Populations	Clarified the PPS population Table 6.1 – add additional continuous efficacy and health outcome analyses for IR population besides the categorical efficacy analyses
Section 6.1.2 General Considerations for Analyses during the Blinded Treatment Dosing Period (Period 2)	Removed the time-to response analysis
Section 6.1.2.2.	Clarified the treatment period for the biologic IXE rescue
Section 6.3.2 Modified Baseline Observation Carried Forward	Clarified the mBOCF analysis for ITT population and IR population.
Section 6.3.3 Last Observation Carried Forward	Removed the LOCF analysis
Section 6.3.4 and Section 6.3.5	Clarified pMI and tipping point analysis
Section 6.5 Multiple Comparisons /Multiplicity	Updated multiplicity scheme per protocol amendment and update to major secondary objectives
Section 6.7 Patient Characteristics	Updated/clarified some baseline variables
Section 6.7.2 Historical Illness and Preexisting Conditions	Updated analyses for pre-existing conditions for Period 2
Section 6.9.1 Previous Therapy	Removed Previous therapy due to redundancy to previous AxSpA therapy
Section 6.9.2 Concomitant therapy	Removed analysis for premedication for allergic reaction
Section 6.10 Efficacy analyses Table 6.4 and Table 6.5	Updated the analyses for TJC/SJC, ethesitis and anterior uveitis and MRI scores
Section 6.10.4.1 Analyses on NSAID Intake	Added NSAID equivalent scoring system from reference and from medical input

Section	Revision
Section 6.10.6 Exploratory Analyses	Removed the analyses on patients who took other biologics after IXE rescue due to too few patients in this population
Section 6.11 Health Outcomes/Quality-of-Life Analyses Table 6.6 and 6.7	Updated the missing imputation for ASAS HI; Added additional analyses for ASASHI; Clarified both transformed and norm-based SF-36 domain score are analyzed
Section 6.12 Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods	Updated text for PK analyses
Section 6.13.2 Adverse Events and Section 6.13.1 Deaths, Other Serious Adverse Events, and Other Notable Adverse Events	Added additional safety analyses for Period between Week 0 and Week 16 for AEs and selected AESIs Removed the TEAE possibly related table and TEAE by SOC and PT table; Added exposure-adjusted incidence rate analyses for the Safety population in Period 2 prior to initiation of biologic rescue and IR population in Period 2 post initiation of biologic rescue for AEs and selected AESIs
Section 6.13.3.1 Special Safety Topics including Adverse Events of Special Interest, and Table 6.8	Removed the analyses on the FU population during period 3 for cytopenia. Text updates for definition/derivation of AESIs to be consistent with PSAP; Changed Covance to performing lab reference range
6.13.4 Clinical Laboratory Evaluation	Added analyses for Period between Week 0 and Week 16 for the categorical lab analyses for the Safety population; Removed the analyses for Period 3; Clarified the reference ranges for WBC parameters and hepatic parameters
6.13.5 Vital Signs and Other Physical Findings	Removed the listing and analyses for Period 3
6.13.8 Immunogenicity	revised the analysis population and baseline definitions; Removed the follow-up ADA analyses
6.14. Analysis for Submission to Japan – Regulatory Body	Updated analyses for Japan
6.15 Subgroup analyses	Replaced ASDAS inactive disease with ASDAS<2.1; Removed the allergic reaction safety subgroup analysis; Updated list of subgroups
6.16 Protocol Deviations	Removed statistical programming guidance to an external document; Updated condition for exclusion from PPS for INC27, 28, 29, 35, 38, EX-CM; Added a new important PD as Category = Investigational Product and Subcategory = Unblinding per medical's request. Updated the source to identify INC02 and "Informed Consent not obtained…" deviations from "Monitor and Stat" to "Stat" as agreed by medical.
Section 6.17 Interim Analyses and Data Monitoring	Removed the data review committee and data monitoring committee meeting as they were not happened prior to W52 lock.

Section	Revision
Section 6. 18	Fatigue NRS psychometric analyses were removed
Section 6.18.1	The empirical cumulative distribution function (eCDF) and probability density function (PDF) plots for change in ASAS HI from baseline to Week 16 (mBOCF) by the selected anchors and treatment group (including placebo) were added ROC analysis was removed
Section 6.18.2	The empirical cumulative distribution function (eCDF) and probability density function (PDF) plots for change in SF-36 from baseline to Week 16 (mBOCF) by the selected anchors and treatment group (including placebo) was added.
Appendix 4	Removed the non-evaluable joint imputation
Appendix 6	Updated to use version of '2009 general US population'; Added to include norm-based score for SF-36 domain; Updated to include incomplete records into the CSV file and allow software to handle the item=level missing within the software.
Appendices 7-11	Updated relevant AE terms per most recent PSAP
Appendix 12, 13	Added ATC codes/terms for drug of special interest; medical guidance on clinically meaningful change

4. Study Objectives

Objectives	Endpoints
Primary The primary objective is to compare both ixekizumab regimens (80 mg every 2 weeks [Q2W] or 80 mg every 4 weeks [Q4W]) versus placebo in patients with active nonradiographic axial spondyloarthritis (nonrad-axSpA).	• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 16 (for regulatory agencies that accept Week 16 as primary endpoint) • Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 52 (for regulatory agencies that require Week 52 as primary endpoint)
Secondary **The major secondary objectives are:** • To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W versus placebo in patients with active nonrad-axSpA at Week 16 and Week 52	• Proportion of patients achieving ASAS40 response at Week 16 (for regulatory agencies that require Week 52 as primary endpoint) • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 16 • Change from baseline in ASDAS at Week 52 • Change from baseline in 36-item Short Form Health Survey (SF-36) physical component [PCS] at Week 16 • Change from baseline in SF-36 physical component [PCS] at Week 52 • Proportion of patients achieving ASDAS low disease activity (<2.1) at Week 16 • Proportion of patients achieving ASDAS low disease activity (<2.1) at Week 52 • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 16 • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 52 • Change from baseline in magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] score) at Week 16
Other secondary objectives are: • To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo during the 52-week period	• 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 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Proportion of patients reaching BASDAI50

Objectives	Endpoints
	• Change from baseline in ASDAS • Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline ≥1.1), major improvement (change of ASDAS from baseline ≥2.0), or inactive disease (ASDAS <1.3), or ASDAS <2.1 • Change from baseline in the measure of C-reactive protein (CRP) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (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 MRI of the SIJ (SPARCC score) • Change from baseline in SPARCC SIJ Structural Score (SSS) • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) • Change from baseline in SPARCC Enthesitis Score • The incidence and severity of peripheral arthritis by tender and swollen joint count 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 Health Index (HI) score, Jenkins Sleep Evaluation Questionnaire (JSEQ), Work Productivity Activity Impairment—Spondyloarthritis (WPAI-SpA) scores, SF-36 (both physical component [PCS] and mental component scores [MCS]), and Quick Inventory of Depressive Symptomatology–Self-Report (16 Items) (QIDS-SR16) score. • Nonsteroidal anti-inflammatory drug (NSAID) intake (ASAS-NSAID score and % of patients taking NSAIDs)
• To explore the effect of starting dose (160 mg compared to 80 mg)	• Onset of action and treatment response (ASAS, ASDAS, CRP, BASFI, BASDAI, spinal pain and SF-36 PCS)
• To evaluate the incidence of anti-ixekizumab antibodies and its relationship to efficacy of ixekizumab	• Efficacy response rates listed below at Weeks 16 and 52 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status o Proportion of patients achieving ASAS40

Objectives	Endpoints
	○ Proportion of patients achieving ASAS20 ○ 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 Week 16 and/or Week 52 • Ixekizumab serum trough concentrations associated with anti-drug antibody (ADA) titer
Exploratory Objective	
• CCI [redacted]	• CCI [redacted]

5. Study Design

5.1. Summary of Study Design

Study I1F-MC-RHBX (RHBX) 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 nonradiographic axial spondyloarthritis (nonrad-axSpA) who are biological disease-modifying antirheumatic drug (bDMARD) naive, during a double-blind, 52-week treatment period (Period 2).

Figure RHBX.5.1 illustrates the study design. Within the active treatment groups, half the patients will be given a 160-mg starting dose and the other half will be given an 80-mg starting dose.

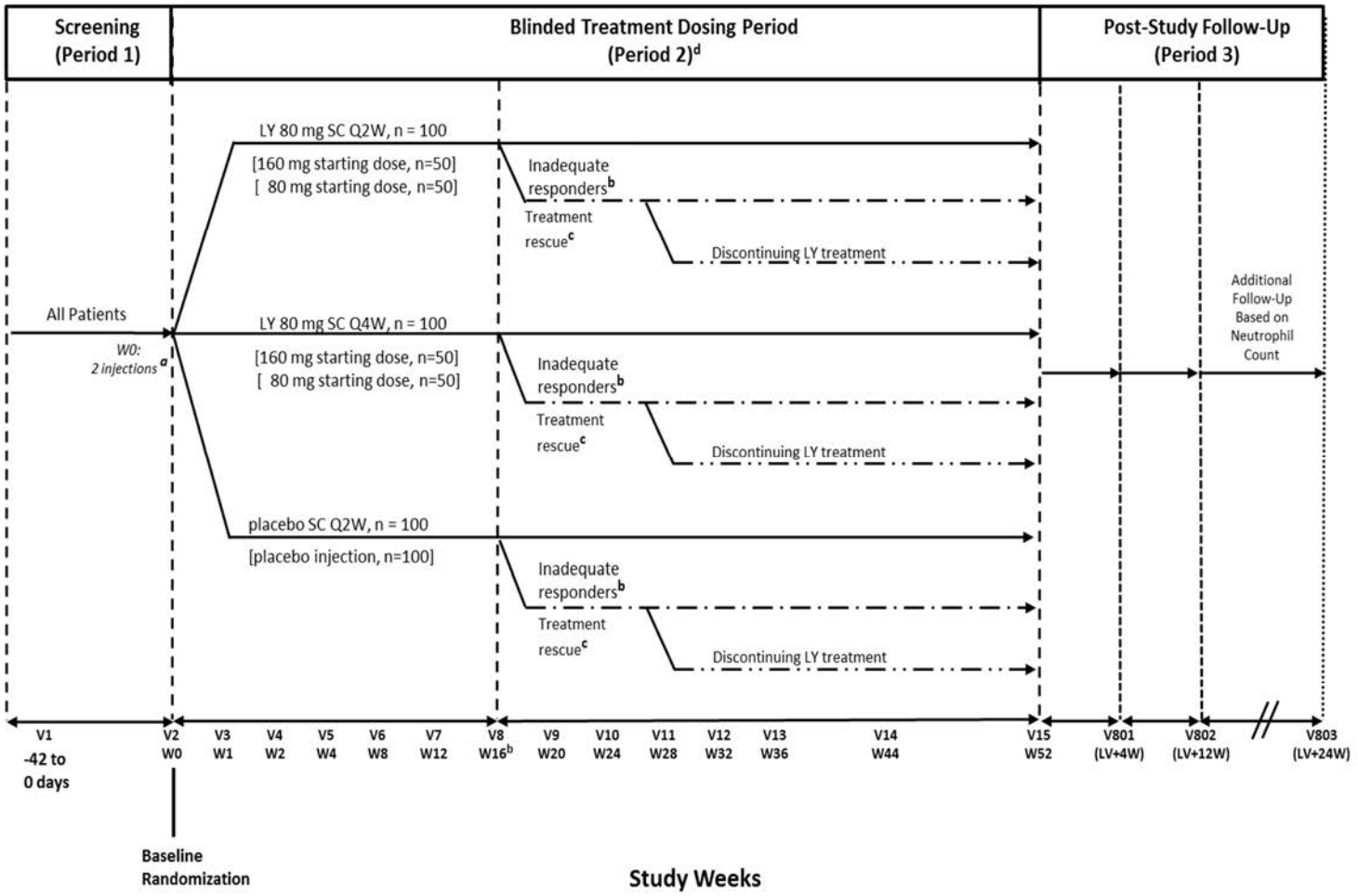

Figure RHBX.5.1. Illustration of study design for Clinical Protocol I1F-MC-RHBX.

Abbreviations: DMARD = disease-modifying antirheumatic drug; ETV = early termination visit; LV = last visit; LY = ixekizumab; n = number; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TNF = tumor necrosis factor; V = study visit; W = study week.

Illustration of study design for Clinical Protocol I1F-MC-RHBX (footnotes)

[a] All patients will receive 2 injections at baseline at Week 0 to maintain the blind with a 80-mg or 160-mg starting dose of ixekizumab or placebo.

[b] Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, may be identified by an investigator based on clinical judgment as an inadequate responder and receive rescue treatment. At such time changes in background therapy (including, but not limited to NSAIDs, nonbiologic DMARDs or the use of rescue biologic treatment) can be made at the discretion of the investigator, while remaining blinded to the original randomization treatment assignment. Changes in ongoing medications at that time can include changes in dose of NSAIDS or nonbiologic DMARDs, including the introduction of new medications. Investigator may also decide to use biologic rescue of ixekizumab 80 mg Q2W with an 80-mg starting dose.

[c] Following any treatment modifications, investigators are to reevaluate the clinical status of the patient as appropriate to assess effect of treatment modification. Treatment guidelines recommend a minimum period of 12 weeks to evaluate effect of biologic treatment modifications; however, if in the opinion of the investigator, a patient does not show any clinical improvement after at least 8 weeks of the ixekizumab 80 mg Q2W treatment modification, then the investigator may consider discontinuation of the patient from ixekizumab treatment. Such patients may then receive other medical therapies (potentially including a TNF inhibitor) that are prescribed by their physician and are to remain in the study until Week 52 per study schedule.

[d] Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 or study participation (regardless of timing) are to complete an ETV and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period. V801 and V802 are required for patients in the Post-Study Follow-Up Period; V803 may be needed depending on neutrophil counts.

5.2. 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, this study will have approximately 98% power to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 16. The following assumptions were used for the power calculations for ASAS40 response rates at Week 16 regardless of starting dose: 46% for ixekizumab 80 mg Q2W treatment group and 18% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed. These assumptions are based on the data from historical clinical studies in nonrad-axSpA patients with objective signs of inflammation (etanercept, adalimumab, certolizumab, and golimumab [Sieper et al. 2013; Dougados et al. 2014; Landewé et al. 2014; Sieper et al. 2015]).

There is little data from similarly designed 52-week placebo-controlled trials regarding the ASAS40 response rate for active and placebo treated patients to guide power estimation at Week 52. Table RHBX.5.1 provides power estimates to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 52, assuming various ASAS40 response rates for ixekizumab Q2W and placebo at Week 52. A 2-sided Fisher's exact test at the 0.05 level is assumed.

Table RHBX.5.1. Power Estimates for Week 52

ASAS40 Response Rates (%) at Week 52		
Ixekizumab Q2W (N = 100)	Placebo (N = 100)	Power (%)
50	10	99
40	10	99
30	10	93
50	15	99
40	15	97
30	15	66

Abbreviations: ASAS40 = Assessment of Spondyloarthritis International Society 40; N = number of subjects; Q2W = every 2 weeks.

5.3. 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 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 and screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP;

negative MRI and elevated CRP). Elevated CRP is defined as >5.00 mg/L. Due to operational feasibility, stratification by CRP is based on the CRP value at Screening.

Target enrollment will be a minimum of approximately 20% for each of the MRI/CRP strata. Once a specific stratum is fully enrolled, the sponsor may stop further enrollment of patients fitting the criteria of that stratum.

6. A Priori Statistical Methods

6.1. General Considerations

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

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 greater than or equal to 0.001, and less than or equal to 0.999, will be presented to 3 decimal places. All other p-values which are less than 0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals will be presented to 1 more decimal place than the raw data.

Age, sex, and race will be reported on all by-patient listings unless otherwise specified. Sex will be abbreviated as follows: female (F) and male (M). Race will be abbreviated as follows: 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. 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 at Week 0. For patients who were deemed as inadequate responders by their investigators and were treated with biologic rescue of ixekizumab 80 mg Q2W, only data up to the time of initiation of biologic rescue of ixekizumab 80 mg Q2W will be included in the primary analyses for Period 2.

Per-Protocol Set (PPS): 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 6.16). For example, patients who are not compliant with therapy during Period 2 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 at an injection week are counted as 1 dose), and not have any occurrence of over-dosing (that is, took more injections at the same time point than specified in the protocol). For sensitivity analyses for primary endpoint of ASAS40 at Weeks 16 and 52, two PPS's will be defined: PPS-16 requires that important protocol deviations not be occurring during Weeks 0 to 16; while PPS-52 requires important protocol deviations not be occurring during Weeks 0 to 52 when patients were on originally assigned treatment.

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. For patients who were deemed as inadequate responders by their investigators and were treated with biologic rescue of ixekizumab 80 mg Q2W, only data up to the time of initiation of biologic rescue of ixekizumab 80 mg Q2W will be included in the Period 2 analyses. Patients will be analyzed according to the treatment to which they were assigned at Week 0.

Inadequate Responder (IR) Population: Selected safety and efficacy summaries will be provided for the IR Population, defined as inadequate responders (identified by investigators based on clinical judgment) who had initiated biologic rescue of ixekizumab 80 mg Q2W.

Follow-Up Population: Safety analyses for Period 3 will be conducted on the Follow-Up Population, defined as all randomized patients who received at least 1 dose of study treatment and have entered the Period 3. Patients will be analyzed according to the treatment they received before entering the Follow-up Period.

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

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

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

	Intent-to-Treat (ITT) Population	Per-Protocol Set (PPS)	Inadequate Responder (IR) Population	Safety Population	Follow-Up Population
Disposition	x		x		x
Baseline Characteristics [a]	x		x		
Treatment Compliance			x	x	
Concomitant Medication	x		x [b]		
Protocol Deviation	x		x [b]		
Exposure			x [b]	x	
Efficacy and Health Outcomes Analyses	x	For ASAS40	Selected efficacy [b]		
Safety Analyses			Categorical safety [b]	x	x
Subgroup Analyses on Efficacy	x				
Subgroup Analyses on Safety Outcome				x	

Abbreviation: ASAS40 = Assessment of Spondyloarthritis International Society 40.

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

[b] These summaries will focus on the time period during biologic rescue of ixekizumab 80 mg every 2 weeks (Q2W).

Table RHBX.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 (ITT) Population; Per-Protocol Set (PPS); Safety Population	Placebo	PBO	IXE80Q4W vs. PBO
		Ixekizumab 80 mg Q4W	IXE80Q4W	IXE80Q2W vs. PBO
		Ixekizumab 80 mg Q2W	IXE80Q2W	Overall[a]
		Total Ixekizumab	Total IXE	
		Total	Total	
		Add the following treatment groups for analyses evaluating the impact of ixekizumab starting dose:		
		Ixekizumab 80 mg Q4W / 80 mg Starting Dose	IXE80Q4W/80S[b]	IXE80Q4W/80S[b] vs. IXE80Q4W/160S[b]
		Ixekizumab 80 mg Q4W / 160 mg Starting Dose	IXE80Q4W/160S[b]	IXE80Q2W/80S[b] vs. IXE80Q2W/160S[b]
		Ixekizumab 80 mg Q2W / 80 mg Starting Dose	IXE80Q2W/80S[b]	Total IXE/80S[b] vs. Total IXE/160S[b]
		Ixekizumab 80 mg Q2W / 160 mg Starting Dose	IXE80Q2W/160S[b]	
		Total Ixekizumab / 80 mg Starting Dose	Total IXE/80S[b]	
		Total Ixekizumab / 160 mg Starting Dose	Total IXE/160S[b]	
Blinded Treatment Dosing Period (Period 2)	Inadequate Responder (IR) Population	Placebo IR / Ixekizumab 80 mg Q2W	PBO IR/IXE80Q2W	No Between-Group or Overall Comparisons
		Ixekizumab 80 mg Q4W IR / Ixekizumab 80 mg Q2W	IXE80Q4W IR/IXE80Q2W	
		Ixekizumab 80 mg Q2W IR / Ixekizumab 80 mg Q2W	IXE80Q2W IR/IXE80Q2W	
		Total Ixekizumab IR / Ixekizumab 80 mg Q2W	Total IXE IR/IXE80Q2W	
		Total IR / Ixekizumab 80 mg Q2W	Total IR/IXE80Q2W	
Post-Treatment Follow-Up Period (Period 3)[c]	Follow-Up Population	Placebo	PBO	No Between-Group or Overall Comparisons
		Ixekizumab 80 mg Q4W	IXE80Q4W	
		Ixekizumab 80 mg Q2W[d]	IXE80Q2W	
		Total Ixekizumab	Total IXE	
		Other Biologic[e]	Other[e]	
		Total	Total	

Abbreviations: IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Overall comparison will be conducted for demographics, historical illness, medical history, preexisting 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 dose, differences between starting dose groups and 95% confidence interval (CI) will be provided.

[c] Treatment group refers to the treatment regimen that the patient received prior to entering Period 3.

[d] Including patients who were on biologic rescue ixekizumab 80 mg Q2W before entering Period 3.

[e] Including patients who have discontinued study treatment and were on other biologic therapy prior to entering Period 3.

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

6.1.2.1. Intent-to-Treat Population and Safety Population

Period 2 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 early termination visit (ETV; between Weeks 0 and 52). For patients who were deemed as inadequate responders by their investigators and were treated with biologic rescue of ixekizumab 80 mg Q2W, only data up to the time of initiation of biologic rescue of ixekizumab 80 mg Q2W will be included in the Period 2 analyses using the ITT and Safety Populations. These patients will be considered nonresponders to categorical assessment per the nonresponder imputation (NRI) method after initiation of biologic rescue with ixekizumab 80 mg Q2W. Data collected after biologic rescue therapy has started will be summarized separately for the IR Population (Section 6.1.2.2).

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

Comparisons between each initially randomized ixekizumab treatment group (80 mg Q2W or 80 mg Q4W) and initially randomized placebo will be performed for all analyses in Period 2.

The randomization to treatment groups is stratified by country and screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP) as described in Protocol Section 6.2. The countries will be categorized into geographic regions for analysis. Geographic regions are defined in Table RHBX.6.3. Unless otherwise specified, the statistical analysis models will adjust for geographic region and screening MRI/CRP status.

Screening MRI and CRP status included in all the analysis models for Period 2 is determined based on the MRI readings and central lab CRP values obtained at screening visit (Visit 1).

Unless otherwise specified, treatment groups of ixekizumab 80 mg Q2W and Q4W 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), and screening MRI/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 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, screening MRI/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), Week 52 (Visit 15), 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. The primary analyses for MRI endpoints 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, screening MRI/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), Week 52 (Visit 15) 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 mean change from baseline and ratio of postbaseline to baseline in CRP, MMRM model will include treatment, geographic region, screening MRI/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, screening MRI/CRP status, and baseline value (except for the analysis of CRP, see paragraph below).

Type III sums of squares for the Least Squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported.

For the analysis of mean change from baseline and ratio of postbaseline to baseline in CRP, ANCOVA model will include treatment, geographic region and screening MRI/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 ASDAS disease activity states (ie, inactive, low, high, and very high disease states), the repeated measures proportional odds model will include treatment, geographic region, screening MRI/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 will be summarized and evaluated. Response rates in selected categorical variables (ASAS40/20, ASDAS<2.1, BASDAI50, ASDAS clinical important improvement, ASDAS major improvement) and LS mean change in selected continuous efficacy and health outcome measures (CRP, BASFI, BASDAI, spinal pain and SF-36 PCS) at Weeks 16 and 52 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 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 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 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 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.

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 modified baseline observation carried forward (mBOCF) endpoint analyses, and other categorical analyses.

For selective efficacy measures, percent improvement will be calculated. For measures with higher scores indicating more severe, percent improvement will be calculated as 100 x (baseline score – observed scores)/baseline score; for measures with lower scores indicating more severe,

percentage improvement will be calculated as 100 x (observed scores – baseline score)/baseline score. 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.

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

6.1.2.2. Inadequate Responder Population

The treatment period for biologic rescue of ixekizumab 80 mg Q2W starts at the time of first injection of biologic rescue of ixekizumab 80 mg Q2W on or after Week 16 (Visit 8) and ends at the date of study treatment discontinuation for patients who did not initiate other biologic therapy, or at the start of other biologic treatment for patients who initiated other biologic therapy.

The treatment period for other biologic rescue (excluding ixekizumab 80 mg Q2W) starts at the time of first injection of other biologic rescue and ends on the date of Week 52 (Visit 15) or the ETV/last regularly scheduled visit.

For efficacy analyses on the IR Population, baseline is defined as the last nonmissing assessment recorded on or prior to the date of first study drug injection at Week 0 (Visit 2). For safety analyses, baseline and baseline period are defined as the last nonmissing assessment prior to the first injection of biologic rescue of ixekizumab 80 mg Q2W. For treatment-emergent adverse events (TEAEs) during biologic rescue with ixekizumab 80 mg Q2W, baseline is the event ongoing just prior to the first injection of biologic rescue of ixekizumab 80 mg Q2W; for TEAEs during other biologic rescue, baseline is the event ongoing just prior to the first injection of other biologic rescue (excluding ixekizumab 80 mg Q2W).

For IR Population, efficacy measures after initiation of biologic rescue of ixekizumab 80 mg Q2W will be summarized by originally assigned treatment group without inferential statistics. If sufficient patients took other biologic rescue after taking biologic rescue of ixekizumab 80 mg Q2W, additional efficacy summary may be provided.

The categorical safety measures will be summarized with incidence rates only.

6.1.3. General Considerations for Analyses during the Post-Treatment Follow-Up Period (Period 3)

For the safety analyses during Period 3, baseline is defined as the last nonmissing assessment on or prior to entering Period 3, that is, on or prior to Week 52 (Visit 15), or ETV.

Safety data collected will be summarized using descriptive statistics.

6.2. Adjustments for Covariates

The randomization to treatment groups in Period 2 is stratified by country and screening MRI/CRP status (that is, positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP; elevated CRP is defined as >5.00 mg/L) as described in Protocol Section 6.2. The countries will be categorized into geographic regions for statistical analysis (Table RHBX.6.3). Unless otherwise specified, the statistical analysis models will adjust for geographic region and screening MRI/CRP status (that is, positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP; positive MRI is defined as presence of sacroiliitis on MRI based on central reading; elevated CRP is defined as >5.00 mg/L at screening visit (Visit 1).

Table RHBX.6.3 outlines the country allocations and classifications for geographic regions.

Table RHBX.6.3. Geographic Regions for Statistical Analysis

Geographic Region	Countries
Europe	Austria, Russia[a], Czech Republic, Finland, Poland, Germany, Romania, The Netherlands
non-Europe	United States, Canada, Argentina, Brazil, Mexico, Japan, Korea

[a] Russia is combined with European countries due to the preponderance of investigative sites in the western part of Russia.

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

6.3. Handling of Dropouts or Missing Data

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

6.3.1. Nonresponder Imputation

Analysis of categorical efficacy and health outcome variables will be assessed using a nonresponder imputation (NRI) method. Patients will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the primary analysis time points. All nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as nonresponders for the NRI analysis at Week 16. Similarly, all nonresponders at Week 52 (Visit 15), as well as patients who discontinue study treatment at any time prior to Week 52 for any reason, will be defined as nonresponders for the NRI analysis at Week 52. Patients who are deemed as inadequate responders by the investigator on or after Week 16 but remain on initially assigned blinded study treatment and only have modifications in concomitant medications will not influence whether or not a patient would be considered a nonresponder. Patients who stopped originally assigned blinded study treatment and use rescue ixekizumab 80 mg Q2W will be analyzed as nonresponders for the Week 52 analysis. They will be considered as nonresponders after the time of initiation of biologic rescue of ixekizumab 80 mg Q2W.

Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

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

6.3.2. Modified Baseline Observation Carried Forward

An mBOCF analysis will be performed on continuous efficacy and health outcomes variables in the major and other secondary objectives. For ITT population, if patients did not initiate the rescue ixekizumab 80 mg Q2W and discontinue study drug due to an AE, the baseline observation will be carried forward to the corresponding time point for evaluation; if they discontinue study drug for any other reason, the last nonmissing observation before study drug discontinuation will be carried forward to the corresponding time point for evaluation. For ITT patients who discontinue originally assigned blinded study treatment and initiate biologic rescue of ixekizumab 80 mg Q2W (inadequate responders), the last nonmissing observations prior to the initiation of rescue ixekizumab 80 mg Q2W will be carried forward to subsequent time points. 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.

For IR population during the biologic rescue of ixekizumab period, if patients discontinue study drug due to an AE, the baseline observation at Week 0 will be carried forward to subsequent time points; if they discontinue study drug for any other reason, the last nonmissing observation will be carried forward to the corresponding time point for evaluation.

6.3.3. Last Observation Carried Forward

No last observation carried forward (LOCF) analysis will be performed.

6.3.4. Placebo Multiple Imputation

For the primary endpoint ASAS40 and major secondary endpoint change from baseline in ASDAS, if randomized patients were treated with biologic rescue of ixekizumab 80 mg Q2W (inadequate responders), all observations after the time of initiation of biologic rescue of ixekizumab will be set as missing. The placebo multiple imputation (pMI) method will be used for the analyses of ASAS40, and ASDAS change from baseline at Week 16 (Visit 8) and Week 52 (Visit 15) for missing data due to rescue and due to discontinuations. 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 or rescue by ixekizumab 80 mg Q2W becomes that of placebo-treated patients. Multiple imputations (MIs) are used to replace missing outcomes for drug- and placebo-treated patients, 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 the outcome. For 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 and NRI because, unlike mBOCF and NRI, 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

For the primary endpoint ASAS40 and major secondary endpoint change from baseline in ASDAS, if randomized patients were treated with biologic rescue of ixekizumab 80mg Q2W (inadequate responders), all observations after the time of initiation of biologic rescue of ixekizumab will be set as missing.

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 as well as mean change from baseline in ASDAS at Weeks 16 and 52 due to rescue and due to discontinuations. Appendix 2 presents the detailed scientific justification of the tipping point method.

For continuous variables (mean change in ASDAS at Weeks 16 and 52), 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 on and prior to the time of rescue are utilized from each patient. A delta score is added to all imputed scores (at the primary time point) for patients in any ixekizumab treatment group in order to evaluate a scenario in which patients treated with ixekizumab would have worse outcomes than patients from the placebo group. An independent delta score will be added to 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 in order 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 at Weeks 16 and 52) 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 (each probability is imputed based on 20 data sets). NRI will be used as the most extreme case.
- For the placebo group, different response probability (for example, probability = 0, 0.2,… 1, respectively) will be used to impute the missing values for ASAS40 (each probability is imputed based on 20 data sets).
- Analyses using the principal analysis model are aggregated across the 20 imputed data sets using SAS® PROC MI ANALYZE in order 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 outcomes of ASAS40 at Week 16 (for regulatory agencies that accept Week 16 as primary endpoint) and ASAS40 at Week 52 (for regulatory agencies that require Week 52 as primary endpoint) will be tested. These tests will use the primary analysis method, logistic regression analysis with treatment, geographic region, and screening MRI/CRP status in the model, with NRI missing data imputation approach. Because this study has different primary endpoints for different regulatory agencies, the significances of both primary endpoints will not be required in order for the study to be considered successful. No further multiplicity adjustment will be made for the 2 primary endpoints.

Since Study RHBX is conducted to meet registration requirements from various regulatory agencies, 2 separate lists of primary and major secondary outcomes are created and multiplicity adjustment is conducted within each of the lists [each list will be tested at a total alpha of 0.05], using the graphical multiple testing procedure (Bretz et al. 2011). This graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate (Alosh et al. 2014).

6.5.1. For regulatory agencies that accept Week 16 endpoints for approval purposes

For regulatory agencies that accept Week 16 endpoints for approval purposes, the following is the list of primary and major secondary outcomes to be tested for both ixekizumab 80 mg Q2W and Q4W regimens at Week 16:

- Primary - proportion of patients achieving an ASAS40 response [ASAS40] at Week 16
- Secondary 1 - change from baseline in ASDAS score [ASDAS CFB] at Week 16
- Secondary 2 - change from baseline in BASDAI [BASDAI CFB] at Week 16
- Secondary 3 - change from baseline in SF-36 PCS [SF-36 PCS CFB] at Week 16
- Secondary 4 - proportion of patients achieving ASDAS low disease activity [ASDAS <2.1] at Week 16
- Secondary 5 - change from baseline in MRI of the SI joint SPARCC score [MRI SPARCC SIJ CFB] at Week 16

The 5 major secondary outcomes are grouped into 2 tiers for testing (Figure RHBX.6.2).

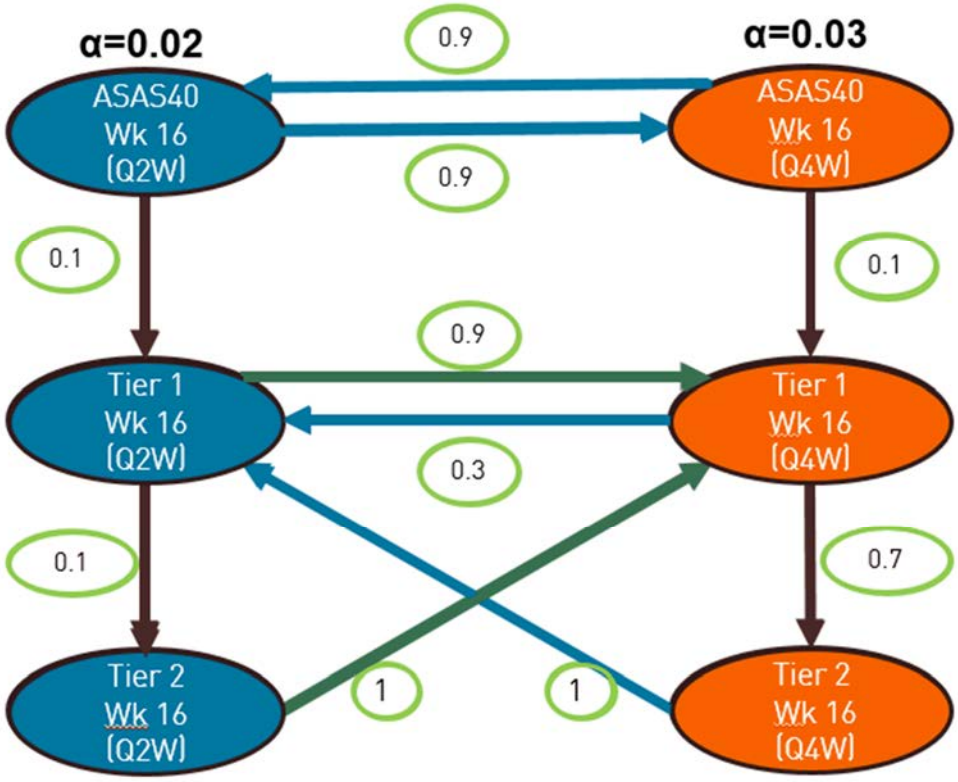
Figure RHBX.6.1 shows the graphical testing scheme with initial α allocation and weights, and Figure RHBX.6.2 shows the graphical testing schemes used within the Tier 1 and Tier 2 groups of endpoints. All comparisons are at Week 16. The testing steps are outlined below:

The primary outcome of ASAS40 at Week 16 will be initially tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided α=0.02, and for ixekizumab 80 mg Q4W versus placebo at a 2-sided α=0.03. If neither null hypothesis can be rejected, no further testing is conducted as the α for the test of ixekizumab 80 mg Q2W versus placebo and the α for the test of ixekizumab 80 mg Q4W versus placebo are considered 'spent' and cannot be passed to other endpoints.

If at least one of these null hypotheses can be rejected at the corresponding α levels, the testing continues for the remaining outcomes according to the procedure specified by the graphs, by allocating the remaining α to the next set of outcomes as long as at least one 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 RHBX.6.1 and Figure RHBX.6.2.

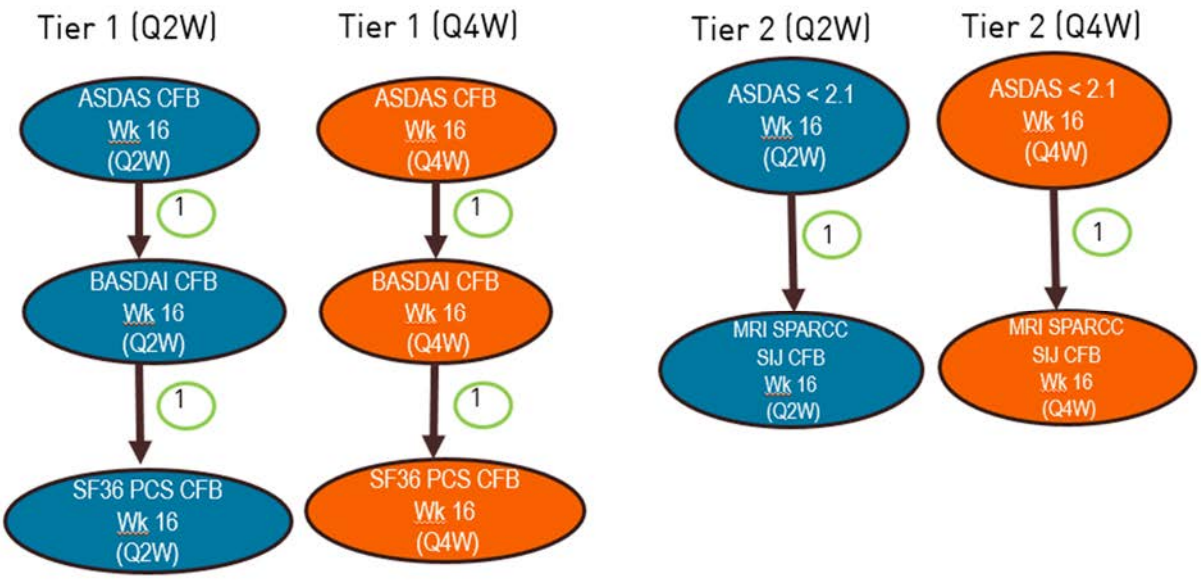
Multiple testing scheme for regulatory agencies that accept Week 16 endpoints for approval purposes:

All outcomes are assessed at Week 16:



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; Q2W = every 2 weeks; Q4W = every 4 weeks; wk = week.

Figure RHBX.6.1. Graphical multiple testing scheme for regulatory agencies that accept Week 16 endpoints for approval purposes.



Abbreviations: ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CFB = change from baseline; MRI = magnetic resonance imaging; SIJ = sacroiliac joints; Q2W = every 2 weeks; Q4W = every 4 weeks; SPARCC = Spondyloarthritis Research Consortium of Canada; SF-36 PCS = Short Form 36 physical component score; Wk = Week.

Figure RHBX.6.2. Graphical multiple testing scheme used within the Tier 1 and Tier 2 group of endpoints.

6.5.2. For regulatory agencies that require Week 52 endpoints for approval purposes

For regulatory agencies that require Week 52 endpoints for approval purposes, the following is the list of primary and major secondary outcomes to be tested for both ixekizumab 80 mg Q2W and Q4W regimens at Week 52. Note that ASAS40 will also be tested at Week 16 as a major secondary endpoint in addition to be tested at Week 52 as a primary endpoint. In addition, MRI SPARCC of SIJ will be tested at W16:

- Primary - proportion of patients achieving an ASAS40 response [ASAS40] at Week 52
- Secondary 1 - proportion of patients achieving an ASAS40 response at Week 16
- Secondary 2 - change from baseline in ASDAS score [ASDAS CFB] at Week 52
- Secondary 3 - change from baseline in BASDAI [BASDAI CFB] at Week 52
- Secondary 4 - change from baseline in SF-36 PCS [SF-36 PCS CFB] at Week 52

- Secondary 5 - proportion of patients achieving ASDAS low disease activity [ASDAS <2.1] at Week 52
- Secondary 6 - change from baseline in MRI of the SI joint SPARCC score [SPARCC CFB] at Week 16

The 6 major secondary outcomes are grouped into 2 tiers for testing (Figure RHBX.6.4).

Figure RHBX.6.3 shows the graphical testing scheme with initial α allocation and weights, and Figure RHBX.6.4 shows the graphical testing schemes used within the Tier 1 and Tier 2 groups of endpoints. All comparisons are at Week 52 unless otherwise noted on the graphs. The testing steps are outlined below:

Step 1: The primary outcome of ASAS40 at Week 52 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 at Week 52 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.

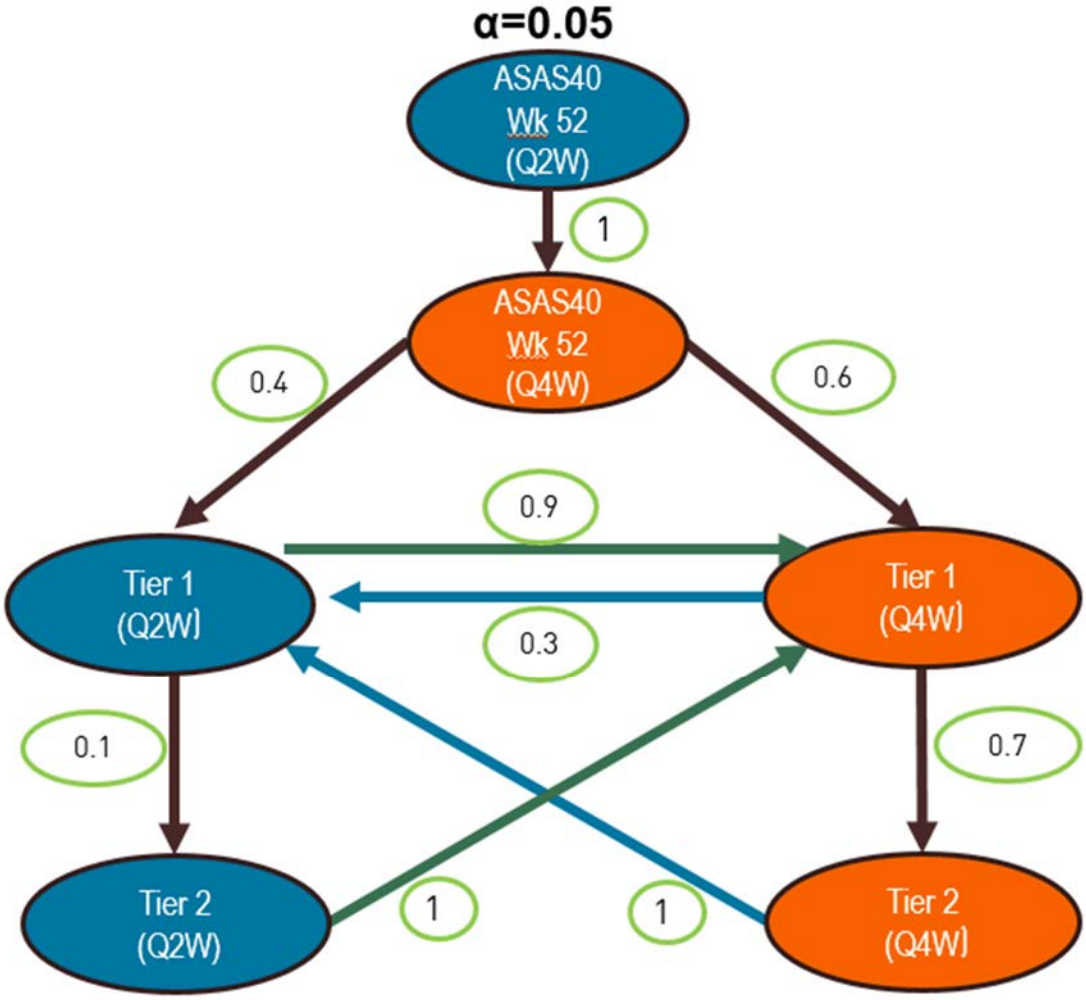
Step 3: α=0.02 (0.4*0.05) will be distributed to Tier 1 set of secondary outcomes for ixekizumab 80 mg Q2W (blue circles in Figure RHBX.6.4), and the remaining α=0.03 (0.6*0.05) will be distributed to Tier 1 set of secondary outcomes for ixekizumab 80 mg Q4W (orange circles in Figure RHBX.6.4).

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 RHBX.6.3 and Figure RHBX.6.4.

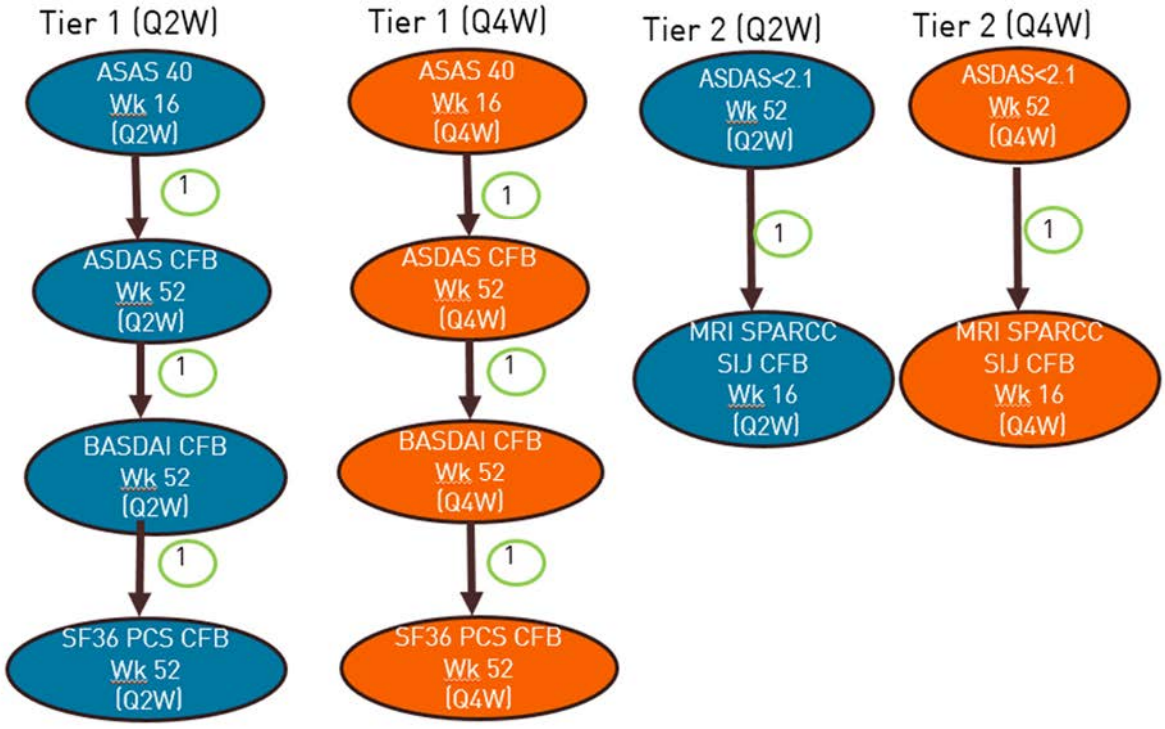
Multiple testing scheme for regulatory agencies that require Week 52 endpoints for approval purposes

All outcomes are assessed at Week 52 unless noted otherwise



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure RHBX.6.3. Graphical multiple testing scheme for regulatory agencies that require Week 52 endpoints for approval purposes.



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CFB = change from baseline; MRI = magnetic resonance imaging; SIJ = sacroiliac joints; Q2W = every 2 weeks; Q4W = every 4 weeks; SPARCC = Spondyloarthritis Research Consortium of Canada; SF-36 PCS = Short Form 36 physical component score; Wk = Week.

Figure RHBX.6.4. Graphical multiple testing scheme used within the Tier 1 and Tier 2 group of endpoints.

6.6. Patient Disposition

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 6.1.1):

- The number and percentage (where applicable) of patients randomized at Week 0 (Visit 2), completing Week 16 (Visit 8), completing Week 52 (Visit 15) on initially assigned treatment, or on biologic rescue of ixekizumab 80 mg Q2W, or on other rescue therapies such as TNF-i and completing Follow-Up Visits 801, 802, and 803, by the initial randomized treatment group (Analysis population: ITT).

- The number and percentage of patients completing Week 16 of Period 2 on initially assigned treatment and the number and percentage of patients discontinuing on/prior to Week 16 from Period 2, by treatment group and primary reason for discontinuation, including classified as Inadequate Responder at Week 16 (Analysis population: ITT). Fisher's exact test will be used to test for difference between treatment groups in the proportion of patients discontinuing on/prior to Week 16 from Period 2, and in the proportion of patients discontinuing for each reason on/prior to Week 16 during Period 2.
- The number and percentage of patients completing Week 52 of Period 2 on initially assigned treatment and the number and percentage of patients discontinuing on/prior to Week 52 from Period 2, by treatment group and primary reason for discontinuation, including classified as Inadequate Responder during Period 2 (Analysis population: ITT). Fisher's exact test will be used to test for difference between treatment groups in the proportion of patients completing their originally assigned treatment in Period 2.
- The number and percentage of Inadequate Responders completing Period 2 or prematurely discontinuing from Period 2 after Week 16, by treatment group and primary reason for discontinuation (Analysis population: IR).
- The number and percentage of patients completing Period 3 and the number and percentage of patients discontinuing from Period 3, by treatment group and primary reason for discontinuation (Analysis population: Follow-Up).
- The time to discontinuation of originally assigned treatment from Period 2 due to any reason (in weeks) may be graphically presented using Kaplan-Meier techniques. The time to discontinuation of originally assigned treatment from Period 2 will be calculated as:

$$\frac{Date\ of\ discontinuation\ of\ originally\ assigned\ treatment\ from\ Period\ 2 - Date\ of\ first\ dose\ in\ Period\ 2 + 1}{7}$$

Patients completing the treatment Period 2 on initially assigned treatment (ie, not initiated rescue therapy of ixekizumab 80 mg Q2W) will be censored at the date of completion (that is, the date of the last scheduled visit in Period 2). Inadequate Responder will be treated as discontinuing originally assigned treatment (ie, an event) on the date of initiating biologic rescue of ixekizumab 80 mg Q2W. Patients without a date of Period 2 completion or discontinuation but are still on initially assigned treatment will be censored at the latest non-missing date out of the following dates: date of last dose and date of last attended visit on the initially assigned treatment in Period 2 (scheduled or unscheduled) (Analysis population: ITT). The log-rank test will be used to test for differences in the time to discontinuation of initially assigned treatment among treatment groups.

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

- Patient disposition during each period, including the date of randomization at Visit 2, the date of first and last dose on initially assigned treatment during Period 2, date/reason of

initiation of biologic rescue ixekizumab 80 mg Q2W if any, date of initiating other biologic therapies if any, the date of completion or discontinuation of study treatment, and the primary reason for discontinuation of study treatment if applicable and date of study discontinuation. (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, IR Population (i.e. patients who initated with biologic rescue of ixekizumab 80 mg Q2W after Week 16) and non IR population (i.e. patient who completed Week 16 and did not initated with biologic rescue of ixkizumab 80 mg Q2W).

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 for ITT Population.

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 July 1st 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: <40 years, ≥40 years
- Age category: <50 years, ≥50 years
- Age category: <65 years, ≥65 years
- Sex
- Race
- Ethnicity
- Geographic region:
  - Europe or non-Europe
  - America, Asia, Europe
  - North America (United States, including Puerto Rico sites if any and Canada) or Rest of the World
  - US (including Puerto Rico sites if any), non-US
- Country
- Weight (kg)
- Weight category: <70 kg, or ≥70 kg

- Weight category: <70 kg, 70-90 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)
  - or 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:

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

- 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 AxSpA 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:

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

- Human leukocyte antigen B27 (HLA-B27) positive: 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 C-Reactive Protein (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), ASDAS <2.1 or ASDAS≥2.1, 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)
- Individual BASDAI items (question 1-6) : fatigue, spinal pain, peripheral arthritis, enthesits, intensity of morning stiffness and duration of morning stiffness
- 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 (%)
- Swollen Joint Count (SJC) based on 44 joints
    - SJC: mean (SD)
    - patients with >0 swollen joint: n (%)
- 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:

- Assessment of Spondyloarthritis International Society 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)
- 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) scores
- Quick Inventory of Depressive Symptomatology–Self-Report (16 Items) (QIDS-SR16) Total Score
- Quick Inventory of Depressive Symptomatology–Self-Report (16 Items) (QIDS-SR16) Item 12

Baseline concomitant therapy use:

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

Previous therapy: axial spondyloarthritis: n (%)

- non-biologic systemic agent
- non-biologic non-systemic agent.

Habit:

- Tobacco use: never, current, former
    - Cigarette use: ≤10 per day versus >10 per day
- Alcohol consumption: never, current, former
- Caffeine/xanthine ingestion: never, current, former.

Baseline NSAID/COX-2 inhibitors) use:

- Assessment of SpondyloArthritis international Society Nonsteroidal Anti-inflammatory Drug (ASAS-NSAID) score
- patients with NSAIDs/COX-2 inhibitors) use: n (%)

Baseline Imaging of Sacroiliac Joints

- Magnetic resonance imaging (MRI) of total SI joint SPARCC scores
    - SPARCC SIJ MRI: mean (SD)
    - SPARCC SIJ score ≥2: n (%)
- Magnetic resonance imaging of SI joint SPARCC SSS scores
    - SPARCC SIJ SSS MRI separately for fat metaplasis, erosion, backfill and anklyosis: mean (SD)

Screening MRI/CRP status: n (%)

- positive MRI and elevated CRP
- positive MRI and nonelevated CRP
- negative MRI and elevated CRP.
  Note: Positive MRI is defined by ASAS/Outcome Measures in Rheumatology (OMERACT) criteria, and elevated CRP is defined as >5.00 mg/L.

6.7.2. Historical Illness and Preexisting Conditions

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

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

Preexisting condition for Period 2 is defined as the condition/event recorded on the *Pre-Existing Conditions and Medical History* eCRF page or on the *Prespecified Medical History* eCRF page with a start date prior to the date of informed consent, and no end date (that is, the event is ongoing) or an end date on or after the date of informed consent. Pre-existing condition for subsequent treatment period is defined as those pre-existing conditions and AEs which are ongoing at the treatment period baseline. Notice if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on *Adverse Events* eCRF page from the date of worsening onwards.

The following summaries will be provided for the ITT Population and/or IR Population:

- The number and percentage of patients with historical illnesses by treatment group and overall, by System Organ Class (SOC) and Preferred Term (PT).
- The number and percentage of patients with preexisting conditions and adverse events prior to first dose by treatment group, and overall by SOC and PT (ITT Population only).
- The number and percentage of patients with preexisting conditions by treatment group and overall, by SOC and preferred term (IR 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 non-insulin dependent; coronary artery disease; history of stroke; dyslipidemia; psoriatic arthritis) by treatment group and overall.

For a condition/event that is gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender. The comparisons among treatment groups in the ITT Population will be conducted using Fisher's exact test.

By-patient listings of historical illnesses and preexisting 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 Period 2, 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 on initially assigned treatment for each patient during Period 2 prior to initiation of biologic rescue ixekizumab 80 mg Q2W 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 on initially assigned treatment, the number of injections prescribed (that is, expected) during Period 2 will be equal to 27 (2 injections at Week 0 and 1 injection Q2W from Week 2 to Week 50).
- 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.
- 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 initially assigned study treatment within Period 2 if he/she misses no more than 20% of the expected doses, does not miss 2 consecutive doses (all injections at an injection week are counted as 1 dose), and does not over-dose (that is, take more injections at the same time point than specified in the protocol).

Patient treatment compliance to initially assigned treatment by treatment week and overall will be summarized for the Safety Population. The comparisons between treatment groups for the Safety Population will be conducted using Fisher's exact test.

Patient treatment compliance to biological rescue therapy ixekizumab 80 mg Q2W will be summarized for IR Population.

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 spondyloarthritis therapy for the ITT Population will be provided.

6.9.1. Previous Therapy

Previous therapy is defined as the therapy that starts and ends prior to the date of first dose of study treatment in Period 2. If therapy start and/or end dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study treatment in Period 2. If there is clear evidence to suggest that the therapy stopped prior to the first dose of study treatment in Period 2, the therapy will be assumed to be previous only.

The following summaries will be provided for the ITT Population and IR Population:

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

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

6.9.2. Concomitant Therapy

Concomitant therapy for treatment period is defined as the therapy that starts before, on, or after the first day of study treatment in treatment period and before the last visit date in the treatment period, and continues into the treatment period, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment in treatment period. Note, concomitant therapy will belong to a treatment period if the therapy starts and ends on the exact same day as the first day of study treatment of the treatment period.

The following summaries will be provided for the following study periods and analysis populations:

- General concomitant therapy by WHO ATC Level 4 and WHO PT for:
  - Period 2 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W (ITT Population)
  - Period 2 after initiation of biologic rescue of ixekizumab 80 mg Q2W (IR Population)
- Concomitant DMARDs, systemic corticosteroids, NSAID (including COX-2 inhibitors) and opioids use for:
  - Period 2 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W (ITT Population)
  - Period 2 after initiation of biologic rescue of ixekizumab 80 mg Q2W (IR Population).

The definition of above medication is provided in Appendix 12.

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

6.10. Efficacy Analyses

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

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Assessment of Spondyloarthritis International Society 40 (ASAS40), ASAS20, ASAS Partial Remission, ASAS5/6	ASAS40, ASAS20, ASAS Partial Remission and ASAS5/6 are clinical responses derived based on the following ASAS domains (Sieper et al. 2009, ASAS Handbook): 1) Patient Global 2) Spinal Pain 3) Function 4) Inflammation (mean of BASDAI Q5 and Q6) 5) CRP 6) Spinal mobility (lateral spinal flexion)	ASAS40 **(Primary Outcome)**	The ASAS40 is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0–10) in ≥3 of the following 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain.	See Appendix 3 for derivation of observed response.
		ASAS20	An ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 units (range 0–10) in ≥3 of the following 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) and no worsening of 20% and ≥1 unit (range 0-10) in the remaining domain.	
		ASAS Partial Remission	ASAS partial remission is defined as a value not above 2 units (range 0-10, NRS) in each of the following 4 domains: Patient Global, Spinal Pain, Function, and Inflammation.	
		ASAS5/6	ASAS5/6 includes assessment of all 6 individual ASAS domains (Patient Global, Spinal Pain, Function, Inflammation, CRP, Spinal mobility) and represents improvement of ≥20% in at least 5 domains.	
Patient Global (Assessment of Disease Activity)	From the ASAS handbook (Sieper et al. 2009), the patient is asked to respond to the following question: "How active was your spondylitis on average during the last week?"	Patient Global, NRS	Range: 0 to 10: "0" (not active) and "10" (very active).	Single item, missing if missing
		Patient Global change from baseline and % improvement from baseline	Change from baseline calculated as: observed patient global – baseline patient global. % improvement from baseline calculated as: $100 \times \frac{Baseline - Observed\ score}{Baseline}$	Missing if baseline or observed value is missing
Spinal Pain	From the ASAS handbook (Sieper et al. 2009), the patient is asked to respond to the	Spinal Pain, NRS	Range: 0 to 10: "0" (no pain) and "10" (most severe pain). This question is used to derive response for ASAS40, ASAS20, ASAS5/6 and ASAS partial remission.	Single item, missing if missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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 change from baseline and % improvement from baseline	Change from baseline calculated as: observed spinal pain – baseline spinal pain. % 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 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. % 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 hours).	Missing if both Q5 and Q6 are missing; If Q6 is missing, then use Q5 as inflammation score.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		BASDAI score – **major secondary outcome**	BASDAI = (Q1+Q2+Q3+Q4+inflammation)/5 Range: 0 to 10: "0" (none) and "10" (very severe).	If only Q6 is missing, BASDAI is average of the other 5 questions; missing BASDAI if more missing than just Q6.
		BASDAI score, 6 individual item and inflammation change from baseline and % improvement from baseline	Change from baseline calculated as: observed score – baseline score. % improvement from baseline calculated as: $100 \times \frac{Baseline - Observed\ score}{Baseline}$	Missing if baseline or observed value is missing
		BASDAI50	BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline, ie, if the value of % improvement from baseline is ≥50, BASDAI50 is met.	Missing if observed value is missing (note: baseline BASDAI is part of inclusion criteria therefore should not be missing)
Bath Ankylosing Spondylitis Functional Index (BASFI)	The BASFI establishes a patient's functional baseline and subsequent response to treatment (Calin et al. 1995).	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

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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 change from baseline –% improvement from baseline	Change from baseline calculated as: observed BASFI – baseline BASFI. % 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 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><th>Measure</th><th>Description</th><th>Variable</th><th>Derivation / Comment</th><th>Imputation Approach if with Missing Components</th></tr>
<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).
• Lateral Spinal Flexion
• Tragus-to-wall distance
• Lumbar Flexion (modified Schober)
• Maximal intermalleolar distance
• Cervical rotation</td><td>BASMI Linear</td><td>The BASMI includes these 5 measurements which are each scaled to a score of 0-10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives the BASMI linear result (van der Heijde et al. 2008; Sieper et al. 2009).
<table>
<tr><th>Function</th><th>For</th></tr>
<tr><td>S = (21.1cm- A) / 2.1cm</td><td>Lateral Lumbar flexion (mean right/left)</td></tr>
<tr><td>S = (A-8cm) / 3cm</td><td>Tragus to wall distance</td></tr>
<tr><td>S = (7.4cm –A)/0.7 cm</td><td>Lumbar flexion (modified Schober)</td></tr>
<tr><td>S= (124.5 cm –A) /10cm</td><td>Maximal intermalleolar distance</td></tr>
<tr><td>S = (89.3 º –A)/8.5º</td><td>Cervical rotation angle (mean right/left)</td></tr>
</table>
The average score of the five assessments gives the BASMI linear result. The additional condition $0 \leq S \leq 10$ is always applied. A is the result of an assessment.
When 2 readings are taken for each of above measures, the better of the two will be used (for tragus, the smaller number is better; for the other 4 measurements, the bigger number is better).</td><td rowspan="2">Missing if >20% measurements (ie >1 of the 5 clinical measurements) are missing. If only 1 of 5 measurements missing, then averaging the other 4 nonmissing ones. In some individual component (eg, lateral lumbar flexion) with left and right measurements, if one side (either left or right) is missing, the other nonmissing side will be used as the mean.</td></tr>
<tr><td>BASMI Linear change from baseline</td><td>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>Calculated as: observed score – baseline score

Individual component will be converted to 0-10 scale for analysis.</td><td>Missing if baseline or observed value is missing</td></tr>
<tr><td>Chest Expansion</td><td>While patients have their hands resting on or behind the head, the assessor will</td><td>Chest Expansion score</td><td>One score measured in centimeter (cm).
When 2 readings are taken, the better of the two numbers (bigger one) will be used.</td><td>Single item, missing if missing</td></tr>
</table>

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	measure the chest encircled length by centimeter (cm) at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in 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 case report form (CRF).	Chest Expansion 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 two tries in cm (eg, 10.2 cm) is reported.	Occiput to Wall Distance score	One score measured in centimeter (cm). When 2 readings are taken, the better of the 2 numbers (smaller one) will be used.	Single item, missing if missing
		Occiput to Wall Distance change from baseline	Calculated as: observed Occiput to Wall – baseline Occiput to Wall	Missing if baseline or observed value is missing
Ankylosing Spondylitis Disease Activity Score (ASDAS)	The ASDAS is a composite index to assess disease activity in AS (Machado et al. 2011a, 2011b; Zochling 2011). The parameters used for the ASDAS (with CRP as acute phase reactant): 1) Total back pain (BASDAI	$ASDAS_{crp}$	$ASDAS_{crp}$ (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). C-reactive protein is in mg/liter, the range of other variables is from 0 to 10; Ln represents the natural logarithm.	Missing if any of the components is missing. If CRP <2 mg/L or below the limit of detection, then use 2 mg/L in the calculation (Machado et al. 2015).

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	Q2) 2) Patient global 3) Peripheral pain/swelling (BASDAI Q3) 4) Duration of morning stiffness (BASDAI Q6) 5) CRP in mg/L	$ASDAS_{crp}$ 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): • ASDAS <1.3 defines inactive disease • 1.3 ≤ ASDAS <2.1 defines low disease activity • 2.1 ≤ ASDAS ≤3.5 defines high disease activity • ASDAS > 3.5 defines very high disease activity	Set the disease activity state to worst state (i.e. very high) if observed ASDAS score is missing
		ASDAS <2.1 **Major secondary outcome**	Defined as ASDAS < 2.1 (low or inactive disease activity)	
		Clinical important improvement	Defined as at least 1.1 unit change in ASDAS from baseline	Missing if baseline or observed ASDAS score is missing
		Major improvement	Defined as at least 2.0 unit change in ASDAS from baseline or reached the minimum of ASDAS score (0.6361) at postbaseline visit	

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
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 1 = activity	Missing if >20% (ie, ≥3) sites are missing. If ≤20% missing, then imputed sum = sum of scores from nonmissing sites x 13/ no. of nonmissing sites
		MASES change from baseline	Calculated as: observed MASES – baseline MASES	Missing if baseline or observed value 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 observed value is missing
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	SPARCC enthesitis	The SPARCC is the sum of all site scores Range: 0–16, higher scores indicate more severe enthesitis.	Missing if >20% (ie, ≥4) sites are missing. If ≤20% missing, then imputed sum = sum of scores from nonmissing sites x 16/ no. of nonmissing sites.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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), Achilles tendon insertion into calcaneum (L/R), and Plantar fascia insertion into calcaneum (L/R).	SPARCC enthesitis change from baseline	Calculated as: observed SPARCC enthesitis – baseline SPARCC enthesitis	Missing if baseline or 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 observed value is missing
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.	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 baseline or observed value is missing
		Proportion of patients with TJC = 0 when baseline TJC > 0	Analysis of TJC = 0 only applies to patients whose baseline TJC > 0.	Missing if observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		Proportion of patients with TJC = 0 for patients with current or historical peripheral arthritis at baseline	Analysis of TJC = 0 only applies to patients with current or historical peripheral arthritis at baseline	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.	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 Only applies to patients whose baseline SJC >0.	Missing if baseline or observed value is missing
		Proportion of patients with SJC = 0 when baseline SJC > 0	Analysis of SJC = 0 only applies to patients whose baseline SJC > 0.	Missing if observed value is missing
		Proportion of patients with SJC = 0 for patients with current or historical peripheral arthritis at Baseline	Analysis of SJC = 0 only applies to patients with current or historical peripheral arthritis at Baseline	Missing if observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
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 patients with or without prior anterior uveitis, separately. Anterior uveitis is identified using the preferred term "iridocyclitis".	Not applicable (NA)
Non-Steroidal Anti-Inflammatory Drug (NSAID) Intake	Information regarding NSAIDs (including COX-2 inhibitors) intake will be collected in the eCRF and the ASAS-NSAID score will be calculated (Dougados et al. 2011).	Proportion of patients taking NSAID	Proportion of patients taking NSAID (including COX-2 inhibitor) at specified visit	NA
		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	If NSAID dose is missing, the maximum efficacy dose (Appendix 5) is assumed. If frequency is missing, 'every day' intake is assumed. If start/stop dates are missing, follow missing date rule in Section 6.9.2
		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.	

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
MRI Sacroiliac Joint (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] Score)	Both left and right SIJ are scored for bone marrow edema. Each side has 6 slices and each slice has 6 scoring units, score of 0 or 1. Total SIJ SPARCC scores can range from 0 to 72 with higher scores reflecting worse disease. Scoring will be performed by a central reader.	SPARCC SIJ Score	The SPARCC SIJ Score is sum of 72 scoring units; the sum ranges from 0 to 72.	See "MRI Data Programming Guidance for AxSpA Studies' for missing rule and imputation method.
		SPARCC SIJ change from baseline – **major secondary outcome (Week 16 only)**	Calculated as: observed SPARCC SIJ – baseline SPARCC SIJ	Missing if baseline or observed value is missing
Spondyloarthritis Research Consortium of Canada –SIJ Structure Score (SSS)	Structural lesions in MRIs of the SIJ are assessed using the SPARCC SSS method for both left and right side. Each site has 5 slices. For fat metaplasia and bone erosion,	SPARCC SIJ SSS Score	For each feature, sum all corresponding scoring units. The sum ranges are fat metaplasia (0 to 40), erosions (0 to 40), backfill (0 to 20), and ankylosis (0 to 20)	See "MRI Data Programming Guidance for AxSpA Studies" for missing rule and imputation method.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	each slice has 1 scoring unit in each of the 4 quadrants; for backfill and ankyloses, each slice has 1 scoring unit in each of the upper and lower half. Each scoring unit has score of 0 or 1. (Maksymowych et al. 2015). Scoring will be performed by central readers.	SPARCC SIJ SSS change from baseline	Calculated as: observed SPARCC SIJ SSS – baseline SPARCC SIJ SSS	Missing if baseline or observed value is missing

Abbreviations: MRI = magnetic resonance imaging; no. = number; NRS = numeric rating scale; Q = question; rad-axSpA = radiographic axial spondyloarthritis; V = visit.

Table RHBX.6.5. Description of Primary and Secondary Efficacy Analyses

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	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 Week 52	Primary analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Week 52 (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 (PPS)	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Additional analyses of primary outcome (Section 6.10.3).
		Categorical MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 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 Weeks 16 and 52 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 Weeks 16 and 52	Sensitivity analyses (Section 6.10.5.1)
		Tipping point analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Sensitivity analyses (Section 6.10.5.2)
		Subgroup analyses	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Subgroup analyses (Section 6.15.1)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
		Descriptive statistics of ASAS40 response rate	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
ASAS20	ASAS20	Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 as well as 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 Weeks 16 and W52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Logistic regression analysis with NRI	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 ASAS20 response rate	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
ASDAS	$ASDAS_{crp}$ change – **Major Secondary**	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Major secondary efficacy analysis is MMRM analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 (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	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		pMI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Sensitivity analyses (Section 6.10.5.1)
		Tipping point analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Sensitivity analyses (Section 6.10.5.2)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
ASDAS	ASDAS <2.1 (**Major Secondary endpoint – ASDAS <2.1)** ASDAS Inactive Disease	Logistic regression analysis with NRI	ITT population with baseline ASDAS ≥2.1 for ASDAS <2.1 ITT Population for ASDAS inactive disease;	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	.Major secondary efficacy analysis is logistic regression analysis with NRI for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 (Section 6.10.2) for ASDAS <2.1. Other secondary efficacy analyses (Section 6.10.4) for ASDAS inactive disease.
		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 (for ASDAS <2.1 only)	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Logistic regression analysis with NRI (for ASDAS <2.1 only)	ITT Population	IXE80Q2W & IXE80Q4W Starting Dose 160 mg and 80 mg during Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Subgroup analyses (for ASDAS <2.1 only)	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Subgroup analysis (Section 6.15.1)
		Descriptive statistics of ASDAS <2.1	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
ASDAS	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)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
ASDAS	ASDAS clinical important improvement; major improvement	Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Logistic regression analysis with NRI	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 response rate	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
BASDAI	BASDAI50	Logistic regression analysis with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Descriptive statistics of BASDAI50 response rate	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
BASDAI	BASDAI change **(Major Secondary)** and % improvement from baseline (incl. 6 individual item and inflammation)	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is MMRM mean change analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 (Section 6.10.2).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Descriptive statistics	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
BASFI	BASFI change from baseline and % improvement	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Other secondary efficacy analyses (Section 6.10.4).
		MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	from baseline	ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 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	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Exploratory analyses (Section 6.10.6.1)
SPARCC SIJ Score	SPARCC SIJ score change from baseline **(major secondary)**	ANCOVA with observed case analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 16	Major secondary efficacy analyses (Section 6.10.4).
		ANCOVA with observed case analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Week 52	Other secondary efficacy analyses (Section 6.10.4).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Other secondary efficacy analyses (Section 6.10.4).
SPARCC SIJ Structural Score (SSS)	SPARCC SIJ SSS score change from baseline for each of the 4 features: fat metaplasia, bone erosion, backfill and anklyosis	ANCOVA with observed case analysis	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	Other secondary efficacy analyses (Section 6.10.4).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52	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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
Patient Global	Patient Global change and % improvement from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
Spinal Pain	Spinal Pain and Spinal Pain at night change and % improvement from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	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 Weeks 16 and 52 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 Weeks 16 and 52 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).
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 Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	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 Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
		ANCOVA with mBOCF	ITT Population with Current or Historical Enthesitis at Baseline	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population with Current or Historical Enthesitis at Baseline	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	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 Weeks 16 and 52 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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
		ANCOVA with mBOCF	ITT Population with Current or Historical Enthesitis at Baseline	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).
	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 Weeks 16 and 52 and all other postbaseline visits in Period 2	Other secondary efficacy analyses (Section 6.10.4).

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	TJC = 0 when patients had current or historical peripheral arthritis at baseline (similarly SJC = 0 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 52 and all other postbaseline visits in Period 2	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).
NSAID (including COX-2 inhibitor) Intake	Proportion of patients taking NSAID (including COX-2 inhibitor)	Descriptive statistics	ITT Population	At Baseline (Week 0), Weeks 16, 20, 24, 28, 32, 36, 44, 52.	Analyses on NSAID intake (Section 6.10.4.1)
	Change from baseline in ASAS-NSAID	Descriptive statistics	ITT Population who have NSAID (including COX-2 inhibitor) intake at Baseline	At Weeks 16, 20, 24, 28, 32, 36, 44, 52.	Analyses on NSAID intake (Section 6.10.4.1)

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	ASAS-NSAID50	Descriptive statistics	ITT Population who have NSAID (including COX-2 inhibitor) intake at Baseline	At Weeks 16, 20, 24, 28, 32, 36, 44, 52.	Analyses on NSAID intake (Section 6.10.4.1)

Abbreviations: ANCOVA = analysis of covariance; ASAS40 = Assessment of Spondyloarthritis International Society 40; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI50 = 50% of the Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = C-reactive protein; ITT = intent-to-treat; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; NSAID = non-steroidal anti-inflammatory drug; pMI = placebo multiple imputation; SJC = swollen joint count; SPARCC SIJ = Spondyloarthritis Research Consortium of Canada Score Sacroiliac Joint; TJC = tender joint count.

6.10.1. Primary Outcome and Methodology

The primary outcomes are the proportion of patients achieving ASAS40 at Week 16 (Visit 8) for regulatory agencies that accept Week 16 as primary endpoint, and ASAS40 at Week 52 (Visit 15) for regulatory agencies that require Week 52 as primary endpoint. These are de-facto (effectiveness) estimands (that is, the effect attributable to the originally randomized treatment, ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo, at the primary time points of Week 16 and Week 52 in all randomized patients). For inadequate responders who were treated with biologic rescue of ixekizumab 80 mg Q2W, only data up to the time of initiation of biologic rescue of ixekizumab 80 mg Q2W will be included in the primary analysis. These patients will be considered nonresponders to categorical assessment per the NRI imputation method after initiation of biologic rescue with ixekizumab 80 mg Q2W.

The primary analysis will be based on the ITT Population for Period 2 comparing each ixekizumab treatment group and placebo at Week 16 (Visit 8) and at Week 52 (Visit 15). The primary analysis is a logistic regression analysis with treatment, geographic region, and screening MRI/CRP status in the model (Section 6.1.2).
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 RHBX.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for primary outcome.

6.10.2. Major Secondary Efficacy Analyses

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

- Proportion of patients achieving ASAS40 response at Week 16 (for regulatory agencies that require Week 52 as primary endpoint)
- Change from baseline in ASDAS at Week 16
- Change from baseline in SF-36 PCS at Week 16
- Proportion of patients achieving ASDAS low disease activity (<2.1) at Week 16
- Change from baseline in BASDAI at Week 16
- Change from baseline in MRI of the SIJ [SPARCC score] at Week 16

The major secondary outcomes at Week 52 (Visit 15) are:

- Change from baseline in ASDAS at Week 52
- Change from baseline in SF-36 PCS at Week 52
- Proportion of patients achieving ASDAS low disease activity (<2.1) at Week 52
- Change from baseline in BASDAI at Week 52

The major secondary analysis will be based on the ITT Population for Period 2 comparing each ixekizumab treatment group and placebo at Week 16 and/or Week 52 as appropriate. 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, and screening MRI/CRP status in the model (Section 6.1.2). For inadequate responders who were treated with biologic rescue of ixekizumab 80 mg Q2W, only data up to the time of initiation of biologic rescue of ixekizumab 80 mg Q2W will be included in the primary analysis. These patients will be considered nonresponders to categorical assessment per the NRI imputation method (Section 6.3.1) after initiation of biologic rescue with ixekizumab 80 mg Q2W.

The primary analysis for continuous major secondary outcomes (except MRI of SIJ SPARCC score) is an MMRM analysis with treatment, geographic region, screening MRI/CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors (Section 6.1.2). Data after initiation of biologic rescue of ixekizumab 80 mg Q2W will not be included in MMRM analyses.

The primary analysis for change from baseline in MRI of SIJ SPARCC score at Week 16 is an observed case analysis using ANCOVA with treatment, geographic region, screening MRI/CRP status and baseline value in the model (Section 6.1.2). Only patients with both baseline and Week 16 MRI of SIJ SPARCC 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 RHBX.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 beyond the aforementioned primary and major secondary analyses in Sections 6.10.1 and 6.10.2.

In the additional analyses of primary outcome 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 Populations for Period 2 at Week 16 (Visit 8) [using PPS-16] and Week 52 (Visit 15) [using PPS-52] using a logistic regression analysis with treatment, geographic region, and screening MRI/CRP status in the model (Section 6.1.2) [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 Weeks 16 and 52 using logistic regression analysis with treatment, geographic region, screening MRI/CRP status in the model (Section 6.1.2) [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 Weeks 16 and 52 and all other postbaseline visits using categorical MMRM analysis with treatment, geographic region, screening MRI/CRP status, visit, treatment-by-visit as fixed factors (Section 6.1.2) [de-jure estimand]. Data after initiation of biologic rescue of ixekizumab 80 mg Q2W will not be included in the categorical MMRM analyses.
- Comparisons of each ixekizumab treatment group and placebo at Weeks 16 and 52 and all other postbaseline visits using Fisher's exact test with NRI (Sections 6.1.2 and 6.3.1) [de-facto estimand]. Missing data will be imputed using the NRI method (Section 6.3.1).

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

Table RHBX.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 analyses include:

- ASAS40: analyses other than primary analysis (Section 6.10.1), and additional analysis of the primary outcome (Section 6.10.3)
- ASAS20, 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
- Change from baseline in ASDAS: analyses other than major secondary efficacy analysis (Section 6.10.2)
- ASDAS inactive disease (ASDAS<1.3)
- 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
- Change from baseline in mobility (BASMI linear and individual components, chest expansion, occiput to wall distance)
- Change from baseline in SPARCC SIJ score: analyses other than major secondary efficacy analysis (Section 6.10.2)
- Change from baseline in SPARCC SIJ structural score (SSS) for each of the 4 features: fat metaplasia, bone erosion, backfill and ankyloses.

- Change from baseline in enthesitis score (MASES and SPARCC)
- Change from baseline in TJC and SJC scores
- Incidence of peripheral arthritis by TJC and SJC scores of 46/44 joints.
- Incidence rate of anterior uveitis
- Change from baseline in ASAS-NSAID score, Section 6.10.4.1.

Treatment comparisons of each ixekizumab treatment group and placebo at Weeks 16 and 52 and all other postbaseline visits during Period 2 for the ITT Population will be provided. For inadequate responders who were treated with biologic rescue of ixekizumab 80 mg Q2W, only data up to the time of initiation of biologic rescue of ixekizumab 80 mg Q2W will be included in these analysis.

The impact of ixekizumab starting doses will be evaluated for the selected categorical responses and mean change in selected continuous efficacy and health outcome measures at Weeks 16 and 52 and earlier time point as described in Section 6.1.2.

Descriptive statistics (that is, no inferential testing) will be provided for each treatment group for the Inadequate Response Population during Period 2.

Table RHBX.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

The ASAS-NSAID score is used to present the NSAID (including COX-2 inhibitor) intake by considering the type of NSAID, the total daily dose, and the number of days on which NSAID has been taken during a period of interest (Dougados et al. 2011). Appendix 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, 400 mg sulindac, 1200 mg dexibuprofen, 75 mg deketoprofen, 1110 mg talniflumate. For Vimovo, esomeprazole strontium w/naproxen, esomeprazole w/naproxen and naproxen w/omeprazole, use the score for naproxen; for caffeine w/ibuprofen, CAROL-F, and famotidine w/ibuprofen, use the score for ibuprofen; for dioxaflex protect 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 (1–3 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).

The 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 and mean change in ASDAS at Weeks 16 and 52 will be analyzed based on the ITT Population using the pMI method, as described in Section 6.3.4. Analyses for ASAS40 will be based on the logistic regression analysis with treatment, geographic region, and screening MRI/CRP status in the model (Section 6.1.2). Analysis for mean change in ASDAS will be based on MMRM analysis. The model will include treatment, geographic region, screening

MRI/CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors (Section 6.1.2).

6.10.5.2. Tipping Point Analysis

ASAS40 and mean change in ASDAS at Weeks 16 and 52 will be analyzed based on the ITT Population using the tipping point method (Section 6.3.5).

6.10.6. Exploratory Analyses

6.10.6.1. Exploratory Analyses Post Biologic Rescue for Inadequate Responders

For inadequate responders who initiated biologic rescue of ixekizumab 80 mg Q2W, summary statistics will be provided for categorical measures (ASAS40/20, BASDAI50, ASDAS <2.1, ASDAS clinical important improvement and major improvement) and continuous measures (CRP, BASFI, BASDAI, SF-36 PCS) to describe the treatment response post biologic rescue. For patients who further initiated other biologic rescues (such as TNF-i), a listing of ASAS40 and its domains, BASDAI score and CRP value will be produced. The length of exposure on initially randomized therapy, and biologic rescue of ixekizumab 80 mg Q2W will be summarized separately for the IR Population.

6.10.6.2. Use of Rescue Therapy During Period 2 for ITT Population

The time to initiation of biologic rescue of ixekizumab 80 mg Q2W (in weeks) will be summarized by treatment group and graphically presented using Kaplan-Meier techniques for Period 2. The time to initiation of biologic rescue of ixekizumab 80 mg Q2W will be calculated as:

(Date of initiating biologic rescue ixekizumab 80 mg Q2W in Period 2-Date of first dose in Period 2+1) / 7

Patients who did not initiate biologic rescue of ixekizumab 80 mg Q2W will be censored at the date of completion (that is, the date of the last scheduled visit in the period) or discontinuation. Patients without a date of Period 2 completion or discontinuation will be censored at the latest non-missing date out of the following dates: date of last dose on the initially assigned treatment and date of last attended visit in Period 2 (scheduled or unscheduled) (Analysis population: ITT).

6.11. 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.

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

Table RHBX.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 RHBX.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 (WWW)].
		ASAS HI change from baseline	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.	Missing if baseline or observed value is missing
		Proportion of patients reaching Good ASAS HI (defined as ASAS HI ≤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 physical well-being are captured by the Mental Component Summary and Physical Component Summary scores. The	8 associated domain scores: • Physical Functioning, • Role Physical, • Bodily Pain, • General Health, • Vitality, • Social Functioning, • Role Emotional, • Mental 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 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	All collected data will be imported into SF-36 software and "Maximum Data Recovery" will be selected for "Missing Score Estimator"

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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]).	2 component Scores: • MCS Score • PCS Score	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.	
		PCS, MCS and domain scores (for both transformed and norm-based scores) change from baseline – **major secondary for PCS**	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–Spondyloarthritis	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, hours actually worked, the degree to which spondyloarthritis affected work productivity while at work, and the	percentage of absenteeism	% 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 missing
		percentage of presenteeism	% impairment while working due to problem: (Q5/10)*100	if Q5 is missing, then missing
		percentage of presenteeism -	Calculated as: observed value – baseline value	if baseline or observed value is missing, then missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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 (Reilly Associates Health Outcomes Research [WWW]).	change from baseline		
		overall work impairment score	% overall work impairment due to problem: (Q2/(Q2+ Q4) + [(1-Q2/(Q2+Q4))*(Q5/10)])*100	if any of Q2, Q4, or Q5 is missing, then missing
		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	% activity impairment due to problem: (Q6/10)*100	if Q6 is missing, then missing
		percentage of activity impairment - change form 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) 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	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
		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	See Section 6.13.6 for description of QIDS-SR16	9 Domains	See Section 6.13.6 for description of each domain	See Section 6.13.6

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Symptoma-tology-self report 16 items		Change from baseline in each domain	Calculated as: observed domain score – baseline domain score	Missing if baseline or observed value is missing
		Item 12 Thought of Death or Suicide	Range: 0 to 3.	Missing if the item is missing.
		Change from baseline in Item 12 Thought of Death or Suicide	Calculated as: observed item score – baseline individual item score	Missing if baseline or item is missing
		QIDS-SR16 total score	See Section 6.13.6 for description of QIDS-SR16 total score	See Section 6.13.6
		Change from baseline in QIDS-SR16 total score	Calculated as: observed total score – baseline total score	Missing if baseline or observed value is missing
		Proportion of patients with at least a 50% decrease in QIDS-SR16 total score	% reduction from baseline calculated as: $100 \times \frac{Baseline - Observed\ score}{Baseline}$ 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: ADaM = Analysis Data Model; ASAS = Assessment of Spondyloarthritis International Society; axSpA = axial spondyloarthritis; CSV = comma-separated values; MCS = mental component summary; NRS = numeric rating scale; PCS = physical component summary; SDTM = Study Data Tabulation Model; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SpA = spondyloarthritis.

Table RHBX.6.7. Description of Health Outcomes and Quality-of-Life Analyses

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
36 item Short Form Health Survey (SF-36)	PCS **(Major Secondary),** change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Major secondary efficacy analysis is MMRM analysis for ITT Population comparing IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 (Section 6.10.2).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
		Descriptive statistics	IR Population	Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W	Health Outcomes/ QOL analyses (Section 6.11).
	MCS, domain scores (for both transformed and norm-based scores), change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
ASAS Health Index (ASAS HI)	ASAS HI change from baseline -	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16, 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
	Proportion of patients with ≥3 points	Logistic regression with NRI;	ITT population With Baseline Score ≥3	IXE80Q2W & IXE80Q4W vs. placebo at Week 16, 52 and all other	Health Outcomes/ QOL analyses

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	improvement from baseline	Fisher's exact test with NRI		postbaseline visits in Period 2	(Section 6.11).
	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, 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
Fatigue Severity Numeric Rating Scale	Fatigue Severity change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
Work Productivity and Activity Impairment Questionnaire—Spondyloarthritis	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 and 52 in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
JSEQ	JSEQ score change from baseline	MMRM	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
		ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
Quick Inventory of Depressive Symptomatology-self report 16 items	Change from baseline in the 9 QIDS-SR16 domains and Item 12 score	ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	Health Outcomes/ QOL analyses (Section 6.11).
	Change from baseline		ITT Population with at		

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	in QIDS-SR16 total score		least moderate depression at baseline (QIDS-SR16 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 at least moderate depression at baseline (QIDS-SR16 total score)	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52 and all other postbaseline visits in Period 2	

Abbreviations: ANCOVA = analysis of covariance; ASAS HI = Assessment of Spondyloarthritis International Society Health Index; IR = inadequate responder; ITT = intent-to-treat; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; JSEQ = Jenkins Sleep Evaluation Questionnaire; mBOCF = modified baseline observation carried forward; MCS = mental component summary; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; PCS = physical component summary; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self-Report (16 Items); QOL = quality of life.

6.12. 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 PK and the exposure-response relationship between ixekizumab exposure and clinically important efficacy measures (for example, ASAS40 or ASAS20 at Week 16 and/or Week 52) may be explored using graphical methods and/or a modeling approach. Pharmacokinetic (PK) 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.

The relationship between select AEs of special interest and exposure estimates 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 anti-drug antibody (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 neutralizing anti-drug antibody (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/pharmacodynamic (PD) analysis plan.

6.13. 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 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W 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 patients who initiated biologic rescue of ixekizumab 80 mg Q2W on or after Week 16, categorical safety data post biologic rescue treatment will be summarized with incidence rates by initially assigned treatment group for the IR Population (that is, TEAEs, serious adverse events [SAEs], AEs as reason for study treatment discontinuation, treatment-emergent clinical laboratory assessments, treatment-emergent vitals).

For **Period 3**, safety data will be summarized according to the treatment patients were on or prior to 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 non-missing assessment recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Treatment-emergent abnormal laboratory and vital signs: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Change from baseline to minimum or maximum: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).

6.13.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group for the Safety Population and IR Population during Period 2 using descriptive statistics.

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

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

Date of last visit on initially assigned treatment (scheduled or unscheduled) or the first date of biologic rescue in Period 2 (for inadequate responders) – Date of first dose in Period 2+1

Note that patients who are inadequate responders and therefore rescued by ixekizumab 80 mg Q2W during Period 2 will only have their exposure calculated up until the date of rescue.

The duration of ixekizumab exposure for IR Population will be calculated as:

Date of last visit (scheduled or unscheduled) on or prior to ixekizumab treatment discontinuation in Period 2 –
Date of first injection of biologic rescue of ixekizumab 80 mg Q2W+1

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

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥150 days, ≥183 days, ≥210 days, ≥273 days and ≥365days. 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 to <150 days, ≥150 to <183 days, ≥183 to <210 days, ≥210 to <273 days, ≥273 to <365 days and ≥365 days.

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

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

- Mean and median total dose. Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose.
    - For those randomized to ixekizumab 80 mg (Q2W or Q4W), the total dose (in mg) taken during Period 2 prior to biologic rescue of ixekizumab 80 mg Q2W will be calculated as:

Total number of active injections (including loading doses, if any) received in Period 2 before biologic rescue of ixekizumab 80 mg Q2W x 80

    - For those patients receiving biologic rescue ixekizumab 80 mg Q2W, the total dose (in mg) on rescue ixekizumab will be calculated as:

Total number of injections of biologic rescue of ixekizumab 80 mg Q2W x 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. Information from the *Exposure as Collected: Rescue Therapy* eCRF page will be used to determine which injection is biologic rescue of ixekizumab.

6.13.2. Adverse Events

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

A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the defined treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. Treatment-emergent AEs will be assigned to the study period to which it's considered treatment-emergent:

- The MedDRA Lowest Level Term (LLT) will be used when classifying AEs as treatment-emergent.
- The maximum severity recorded for each LLT prior to the first dose date/time in the treatment Period will be used as the 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 (ie, a patient has no preexisting conditions with that LLT), or if the severity is greater than the pre-treatment 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 prior to 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 follow-up emergent event was already counted as treatment-emergent during the prior treatment period, it will not be counted as a follow-up emergent event.

Adverse events and TEAEs will be summarized for the following time period and analysis populations:

- Period 2 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W (Safety Population)
- Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W (IR Population)
- Period between Week 0 and Week 16 (Safety population).

Treatment comparisons between treatment groups for Safety Population in Period 2 and Period between Week 0 and 16 will be conducted using a Fisher's exact test.

The following summaries/analyses will be performed for the Safety and IR Populations, unless noted otherwise:

- 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.
- Treatment-emergent adverse event by PT (Safety Population only)
- Treatment-emergent adverse event by maximum severity, SOC, and PT.

Follow-up emergent AEs will be summarized for the Follow-Up Population for Period 3:

- Follow-up emergent adverse event 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.

The exposure-adjusted incidence rates (that is, person-time-adjusted incidence rates) over the entire time period for overall summary of AEs and TEAE by maximum severity, SOC, and PT will also be summarized for the following populations:

- Safety Population in Period 2 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W
- Inadequate Response Population in Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W

Summary tables comparing exposure-adjusted incidence rates will be generated for patients with AEs and TEAEs where total number of patients experienced the TEAE will be divided by the sum of all patients' time (in 100 years) of exposure during the above mentioned treatment period. Tables will include the total number of patients in each treatment group, the total person years, and the incidence rate ((number of patients with the event / total person years)*100). The relative risk and p-value will be produced for the Safety population in Period 2 prior to initiation

of biologic rescue of ixekizumab and will be derived from a Poisson regression model with treatment as explanatory variable. The p-value will be based on the likelihood ratio test.

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

6.13.2.1. 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 based on Safety Population for Period 2. 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.

- common TEAEs by SOC and PT
- common TEAEs by PT
- common TEAEs by maximum severity, SOC, and PT

6.13.3. 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 3 after discontinuation of study drug

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

The following summary tables will be provided for the Safety Population for Period 2 and Period between Week 0 and 16, and for the IR Population:

- serious adverse events by PT
- adverse events that lead to treatment discontinuation (including death) by PT

Treatment comparisons between treatment groups for Safety Population in Period 2 will be conducted using a Fisher's exact test.

The exposure-adjusted incidence rates for patients with SAEs and AEs leading to treatment discontinuation will also be summarized for the Safety Population and IR population in Period 2.

6.13.3.1. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AEs of special interest (AESIs) will be presented by treatment group for the Safety Population in Period 2. Selected AESIs (ie, Hepatic, Allergic Reactions/Hypersensitivities, Injection Site Reactions, and Inflammatory Bowel Disease [IBD]) will also be summarized by treatment group for the Safety Population in the period between Week 0 and Week 16. In addition, summaries for TEAEs for AESIs will be provided for the IR Population during biologic rescue including ixekizumab 80 mg Q2W. No separate summaries for SAEs or AEs leading to discontinuation for AESIs will be provided for these patients since the incidences of these events are expected to be low and they will be summarized in the overall SAEs and AEs leading to discontinuation reports for the IR Population.

Exposure-adjusted incidence rates will also be summarized for selected AESIs (ie, Hepatic, Allergic Reactions/Hypersensitivities, Injection Site Reactions, and IBD) for the Safety Population in Period 2, and for IR population.

Table RHBX.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 and during period between Week 0 and Week 16.

In general, an AESI summary will not be provided for Follow-Up Population during Period 3 except for hepatic laboratory tests.

Table RHBX.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)	**Fisher's exact test for Safety Population in Period 2 and Period between Week 0 and Week 16, and summary for IR Population**: TEAE by PT within SMQ or sub-SMQ. Number and percentage of patients, as well as the exposure-adjusted incidence rates will be presented for the Safety Population and IR Population in Period 2. **Listing:** TEAE (to be prepared in Spotfire)
	Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using Performing Lab Reference Ranges are defined as: • Include scheduled visits, unscheduled visits, and repeat measurements. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST): maximum postbaseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing Lab upper limit of normal (ULN) for all patients with a postbaseline value. o The analysis of 3× ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN, or missing. o The analysis of 5× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN, or missing. o The analysis of 10× ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN, or missing. o The analysis of 20× ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN to <20× ULN, ≥20× ULN, or missing.	**Fisher's exact test for Safety Population and summary for IR Population**: Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum postbaseline category

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

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	bilirubin/GGT by visit, treatment start and stop dates, and reason for treatment discontinuation.	
	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.	**for Safety Population and IR Population**: 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)	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by PT within sub-SMQ **Listing:** TEAE(to be prepared in Spotfire)
Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections, and infections resulting in anti-infective medication administration therapeutic intervention (ie, antibacterial, antivirals, antifungals, antiparasitic treatments).	**Fisher's exact test for Safety Population and summary for IR Population**: SAE by PT, AE leading to treatment discontinuation by PT
	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:** TEAE with anti-infective medications (to be prepared in Spotfire).

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	The list of MedDRA terms used to identify infections that are predefined as potential opportunistic infections (OI) are found in Appendix 11. This list contains PTs as contained within categories (narrow and broad) from the Infections and infestations SOC and the Investigations SOC which can assist in identifying potential OIs. The narrow terms are considered OIs unless medical review determines that the reported term is not consistent with the patient's clinical history/presentation/course. Medical review of broad terms is needed for final determination of patients meeting the program definition of OIs. Listing of patients experiencing a TEAE of OIs will be provided including the following additional information: 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).	**Summary for Safety Population and IR Population** TEAE of OIs by PT TEAE of OIs by maximum severity by PT **Listing:** TEAE of OIs (to be prepared in Spotfire)
	The duration of each common (≥1% of total ixekizumab) TEAE PT of Infections, and duration of narrow terms for Opportunistic infections are defined as: Duration of treatment-emergent AE Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7 Only TEAEs of infections beginning during treatment Period 2 will be included in the summary. If an AE has not ended by the date of completion of the treatment periods 2 , or date of early discontinuation, it will be censored as of that date (last visit within the treatment period 2 , 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.	**Summary for Safety Population**: Duration of Common TEAE – Infections
Allergic Reactions/Hy-persensitivities	Allergic reactions/hypersensitivity events will be categorized as either anaphylaxis or non-anaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. Allergic Reactions/Hypersensitivity Events, Anaphylaxis: Anaphylaxis has been broadly defined as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson et al. 2006). Identification of cases of potential anaphylaxis from the clinical trial data involves two criteria: 1) designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). Criterion 1 for anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ: • Anaphylactic reaction • Anaphylactic shock • Anaphylactoid reaction • Anaphylactoid shock • Kounis Syndrome	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by maximum severity by PT within Category (also for Safety Population Period between Week 0 and 16), SAE by PT within Category, AE leading to treatment discontinuation by PT within Category. For the TEAE by maximum severity by PT within

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• Type 1 hypersensitivity 2) to identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 2 for anaphylaxis requires having TEAEs from two or more of four categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident based on recording of events on CRFs. All qualifying event must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: • Category A: Involvement of the skin-mucosal tissue • Category B: Respiratory compromise • Category C: Reduced blood pressure or associated symptoms • Category D: Persistent gastrointestinal symptoms The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in 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. Allergic Reactions/Hypersensitivity Events, Non-Anaphylaxis: TEAEs of allergic reaction/hypersensitivity categorized as non-anaphylaxis events are defined by the narrow terms within Hypersensitivity SMQ (20000214) excluding the PTs noted in Appendix 9 and excluding the anaphylactic events as defined above.	Category analysis, number and percentage of patients, as well as the exposure-adjusted incidence rates will be presented for the Safety Population and IR Population in Period 2.
	A by-patient listing will be provided for all patients experiencing TEAE of allergic	**Listing:**

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	reactions/hypersensitivities at any time, including status/criterion of anaphylaxis or non-anaphylaxis, and the associated information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page if identified by the investigator.	TEAE including information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page (to be prepared in Spotfire)
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 [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	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by maximum severity by PT within HLT (also for Safety Population in Period between Week 0 and Week 16), SAE by PT within HLT (Safety Population only), AE leading to treatment discontinuation by PT within HLT (Safety Population only). TEAE identified by the investigator PT within HLT: by maximum severity, by maximum redness category, by maximum swelling category, by maximum pain category For the TEAE by maximum severity by PT within HLT analysis, number and percentage of patients, as well as the exposure-adjusted incidence rates will be presented for the Safety Population and IR Population in Period 2.

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	[4] Clear bump 2 mm thick or more Pain (including burning) (Scored 0-3) [0] None [1] Mild [2] Moderate [3] Severe	**Listing:** TEAE including information collected on *Injection Site Reaction* eCRF page (to be prepared in Spotfire)
Cerebro-cardiovascular Events	Cerebro-cardiovascular events will be externally adjudicated by the Central Events Committee (CEC) at the Cleveland Clinic, as outlined in the Manual of Operations. The CEC will adjudicate investigator-reported events selected for adjudication and render an assessment as to whether the event represents a confirmed event (meeting the event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient documentation for confirmation of an event. All events which qualify for CEC adjudication will be used for the analysis of cerebro-cardiovascular events. The categories and subcategories of adjudicated events used for the analysis will include the following: • Cardiovascular o Death (Cardiovascular) o Cardiac Ischemic Event: Myocardial Infarction and Hospitalization for Unstable Angina o Serious Arrhythmia o Hospitalization for Heart Failure o Hospitalization for Hypertension o Resuscitated Sudden Death o Cardiogenic Shock o Coronary Revascularization • Neurologic o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Hemorrhagic, Ischemic and Undetermined) • Peripheral Vascular Events o Peripheral Arterial Event o Peripheral Revascularization Events will be analyzed using MedDRA PT nested within the CEC assessment (confirmed event, no event, or insufficient documentation for event determination) and the subcategory. Subtypes of stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed in the analyses nested within Cerebrovascular Event. Subtypes of Serious Arrhythmia (Atrial Arrhythmia, Ventricular Arrhythmia, Heart	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by PT within Subcategory **Listing:** TEAE (to be prepared in Spotfire)

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	Block, Other, Unknown) will be displayed nested within Serious Arrhythmia.	
Major Adverse Cerebro-Cardiovascular Events (MACE)	MACE (requiring adjudication as defined above) is defined as: • Vascular Death (including cardiovascular and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system) • Non-fatal myocardial infarction • Non-fatal stroke (subtypes: hemorrhagic stroke, ischemic stroke, undetermined stroke type) Where, • Vascular death should be captured as an *Event on Adjudication - Death* eCRF page with Adjudication Death Type = 'Cardiovascular'. • Non-fatal myocardial infarction should be captured as an *Event on Adjudication - Cardiac Ischemic Event* eCRF page with Type of Ischemic Event = "Myocardial Infarction" and the Event is NOT on Adjudication - Death eCRF page. • Non-fatal strokes (ischemic, hemorrhagic) should be captured as an *Event on Adjudication - Cerebrovascular Event* eCRF page with Stroke Cerebrovascular Event Subtype in 1 of the following categories: hemorrhagic stroke, ischemic stroke, undetermined stroke type, and the *Event is NOT on Adjudication - Death* eCRF page. Subcategories of non-fatal stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed nested within non-fatal stroke category.	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by maximum severity by PT within category **Listing:** TEAE (to be prepared in Spotfire)
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as specified in MedDRA (SMQ: 20000091, which includes the sub-SMQs: • 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours] • 20000195 [Tumours of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy] • 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	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by PT within category **Listing:** TEAE (to be prepared in Spotfire)

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	
Depressions	Depression is defined using the PTs from the Depression and suicide/self-injury SMQ as specified in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excl suicide and self-injury)]).	**Fisher's exact test for Safety Population and summary for IR Population**: TEAE by PT within SMQ and sub-SMQ **Listing:** TEAE (to be prepared in Spotfire)
Inflammatory Bowel Disease (IBD)	IBD will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered IBD. IBD (Narrow terms) • Inflammatory Bowel Disease: Inflammatory bowel disease • Crohn's Disease: Crohn's disease • Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative Non-Specific Terms (Events That Can Occur with IBD (Broad Terms)): The PTs in this category are listed in Appendix 10.	**Fisher's exact test for Safety Population in Period 2 and Period between Week 0 and Week 16 and summary for IR Population**: TEAE by PT within subcategory Number and percentage of patients, as well as the exposure-adjusted incidence rates will be presented for the Safety Population and IR Population in Period 2. **Listing:** TEAE (to be prepared in Spotfire)
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)	**Listing**: TEAE (to be prepared in Spotfire)

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	○ Hypereosinophilic syndrome (Narrow) ○ Loeffler's syndrome (Narrow) ○ Pulmonary eosinophilia (Narrow) ○ Pulmonary vasculitis (Narrow)	

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; eCRF = electronic case report form; GGT = gamma-glutamyl transferase; HLT = high-level term; IR = inadequate responder; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA Query; TEAE = treatment emergent adverse event; ULN = upper limit of normal.

6.13.4. Clinical Laboratory Evaluation

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

- Period 2 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W (Safety Population)
- Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W(IR Population, for categorical safety analyses only)
- Period between Week 0 and Week 16 (Safety Population, for categorical safety analyses only)

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

Treatment group comparisons will be conducted for Safety Population for Period 2 and the period between Week 0 and Week 16 using an ANCOVA model with treatment group and baseline value for continuous data and Fisher's exact test for categorical data as described in Section 6.1.2.1. Only categorical safety data will be summarized for the IR Population.

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.
- Data will be analyzed based on original scale.

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

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The 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 one 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. The comparisons between and among treatment groups will be conducted using Fisher's exact test for the Safety Population for Period 2 and Period between Week 0 and Week 16.

- All scheduled, unscheduled and repeated measurements will be included.
- Performing laboratory will be used to define the low and high limits reference ranges except for leukocyte, neutrophil, lymphocyte and platelet counts, where Lilly defined lower limit of normal will be used for these 4 labs.
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), neutrophils, leukocytes, platelets, and lymphocytes will not be included in the treatment-emergent abnormal, high, or low summary as a separate analysis addressing the risk of liver injury is described in Section 6.13.3.1 and a separate analysis addressing leukocytes (white blood cell [WBC]) and platelets is described in Section 6.13.4.1.
- 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.

6.13.4.1. 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 Periods 2 and Period between Week 0 and Week 16, respectively:

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

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

6.13.4.2. Neutrophil Follow-Up

Neutrophil counts will be followed throughout the study. Patients will continue in Period 3until 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 ETV prior to entering Period 3 and less than the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0). These patients are monitored during Period 3 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 prior to first study drug injection at Week 0.

If a patient's neutrophil count has not recovered, within 12 weeks after entering the follow-up period (Visit 802), the 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 3. The number and percentage of patients with an absolute neutrophil cell count that is at least 25%, 50%, 75%, or 100% of the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

6.13.5. 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) and BMI (kg/m^2).

Treatment group comparisons will be conducted for Safety Population for Period 2 using an ANCOVA model with treatment group and baseline value for continuous data and Fisher's exact test for categorical data as described in Section 6.1.2.1. Only categorical safety data will be summarized for the IR Population.

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, respectively:

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- Data will be analyzed based on original scale.

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

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.

- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least 1 postbaseline result, mean, SD, 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 Week 0 and any visit where biologic rescue of ixekizumab 80 mg Q2W was initiated, vital signs will be measured before the first injection and approximately 1 hour after the injection. The box plots will be produced for pre-dose and post-dose vital signs at Week 0 (Visit 2), Week 16 (Visit 8), and any visits after for patients who have pre- and post-dose vital signs.

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 and 3, 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 RHBX.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 RHBX.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.

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

The QIDS-SR16 is a self-administered 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's (APA's) *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* (APA 1994). The QIDS-SR16 scale is used to assess the potential impact of treatment on new onset or changes in depression, thoughts of death, and/or suicidal ideation severity. A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS resource page (WWW).

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 the Safety Population during the Period 2:

- 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 Safety Population during Period 2:

- 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.

6.13.7. 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 C-SSRS resource page (Columbia resources page [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 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide.

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

Composite endpoints based on the above categories are defined below.

- **Suicidal ideation:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- **Suicidal behavior:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
- **Suicidal ideation or behavior:** A "yes" answer at any time during treatment to any 1 of the ten 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 that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient's answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/behavior or self-injurious behavior without suicidal intent at any time point, then all their ideation and behavior will be displayed, even if not positive. Note, missing data should not be imputed.

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

6.13.8. Immunogenicity

6.13.8.1. Definitions and Terms

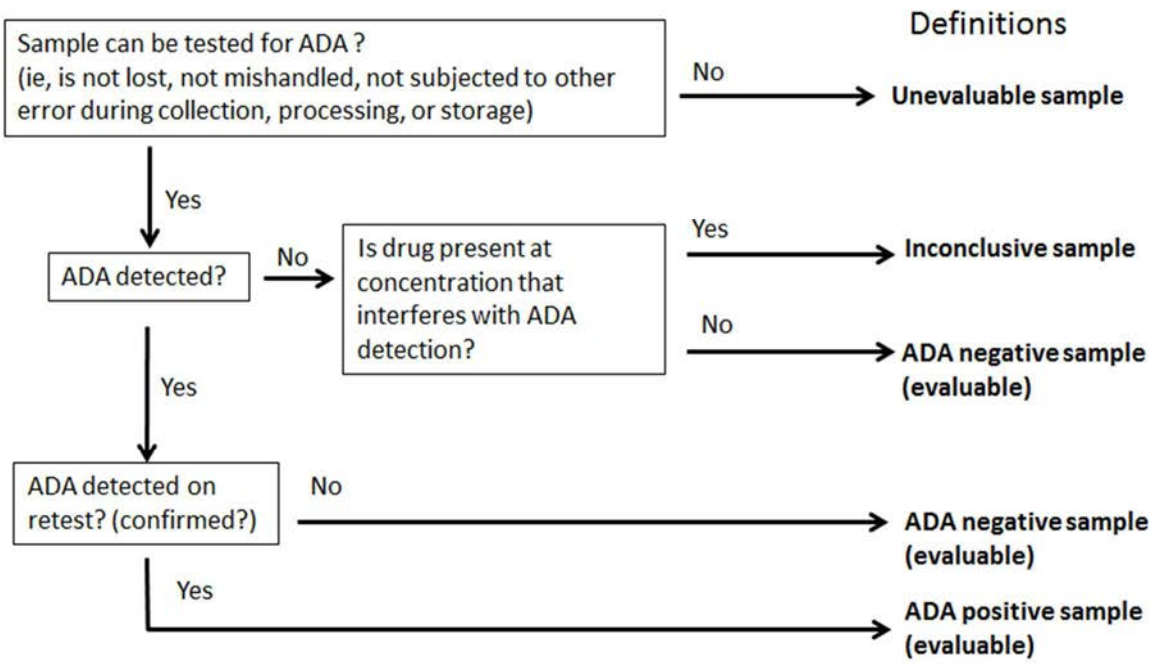
The following sample- and patient-related definitions and parameters will be used to describe the immunogenicity data.

6.13.8.1.1. Sample Category Definitions

Samples are classified into the following categories:

- **Unevaluable sample:** Sample could not be tested for ADA due to sample loss, mishandling, or errors in collection, processing, storage, and so on.
- **Anti-drug antibody (ADA) Positive sample:** The presences of ADA is detected and confirmed. The samples are reported as positive. If the sample is positive, a titer value is reported.
- **Neutralizing anti-drug antibody (NAb) Positive sample:** NAb are reported as detected.
- **Anti-drug antibody (ADA) Negative sample:** The presence of ADA is not detected and the assay drug tolerance level is not exceeded.
- **Neutralizing anti-drug antibody (NAb) Negative sample:** The presence of NAb is not detected and the assay drug tolerance level is not exceeded.
- **Anti-drug antibody (ADA)/NAb Inconclusive sample:** when ADA/NAb is not detected in a sample but drug is present in the same sample at a level that can cause interference in the ADA/NAb detection method. The negative ADA/NAb result cannot be confirmed and the sample should be considered inconclusive.
    - Confirmation of a negative ADA result is based on ixekizumab concentrations and on the limit of drug tolerance of the NAb assay.

Figure RHBX.6.5 illustrates the relationship of some of the above terms.



Abbreviation: ADA = anti-drug antibody.

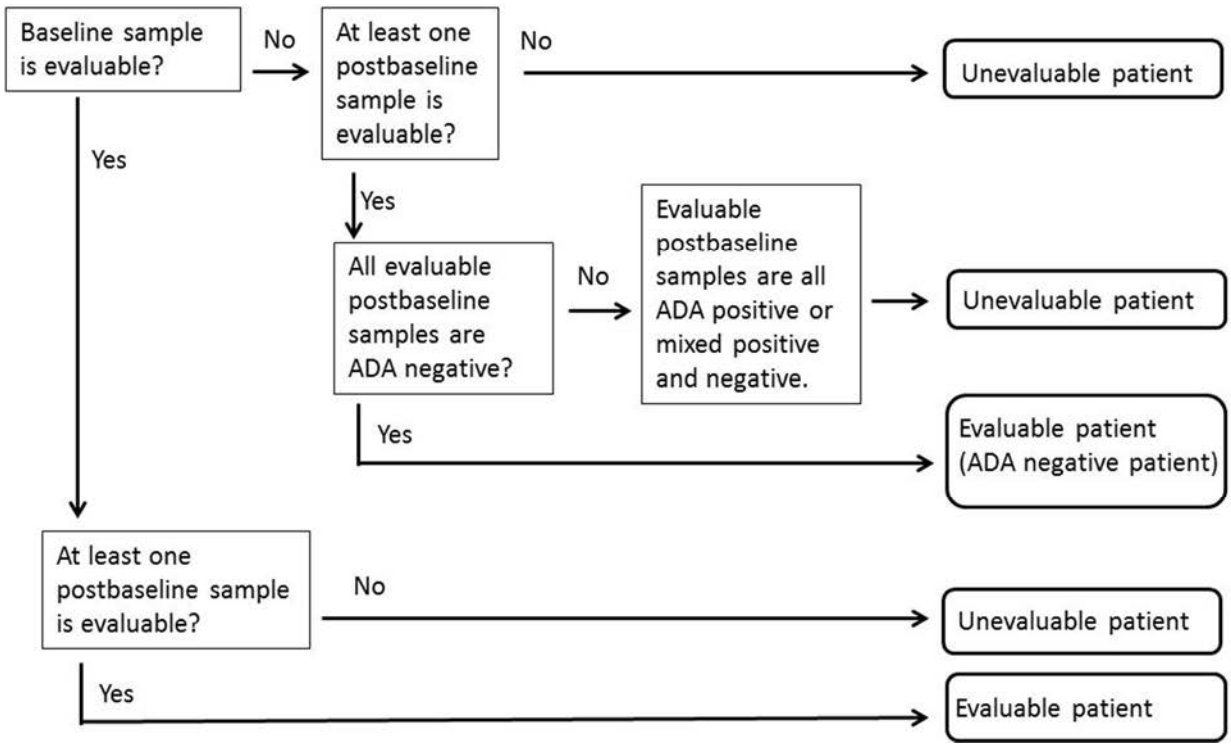
Figure RHBX.6.5. Sample definitions.

6.13.8.1.2. 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 RHBX.6.6 illustrates the relationship of the above terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHBX.6.6. Patient category definitions.

6.13.8.1.3. Definitions for Clinical Interpretation of Assay Results

Baseline and postbaseline

Baseline and postbaseline definition for immunogenicity analyses are defined in Table RHBX.6.10 based on the purpose of the analyses.

Table RHBX.6.10. Baseline and Postbaseline Definition for Immunogenicity Analyses in Period 2

Analysis Purpose	Analysis Population	Treatment Group	Baseline Definition	Postbaseline Definition
Incidence of TE-ADA during Week 0-16	Safety Population	Group 1: PBO IXE 80mg Q4W IXE 80mg Q2W Total Ixe	Last non-missing observation on, or prior to the date of the first injection of study drug at Week 0 (before drug administration)	Week 0-16
Incidence of TE-ADA during Week 0 -52 while patients on Ixekizumab exposure	All Ixekizumab Exposure Safety Population[a]	Group 2: IXE 80mg Q2W – Q2W[b] IXE 80mg Q4W – Q4W[c] PBO - IXE 80mg Q2W[d] IXE 80mg Q4W – Q2W[e] All IXE 80mg Q2W[f]	Last non-missing observation on, or prior to the date of the first injection of ixekizumab, that is, PBO – ixe 80mg Q2W, baseline is before ixekizumab 80mg Q2W rescue. For other groups, it is Week 0	Time period between the first ixekizumab injection to the last visit. For patients who may take other biologic rescues (e.g. TNFi), the postbaseline period ends prior to the start of other biologic therapy.

Abbreviations: IXE = ixekizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; TE-ADA = treatment-emergent anti-drug antibody; TFFi = tumor necrosis factor inhibitor.

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

[b] includes patients with only ixekizumab 80mg Q2W exposure, regardless of whether patients were rescued by ixekzimab 80mg Q2W

[c] Includes patients with only ixekizumab 80mg Q4W exposure. Patients who were rescued by ixekizuamb 80mg Q2W are not included.

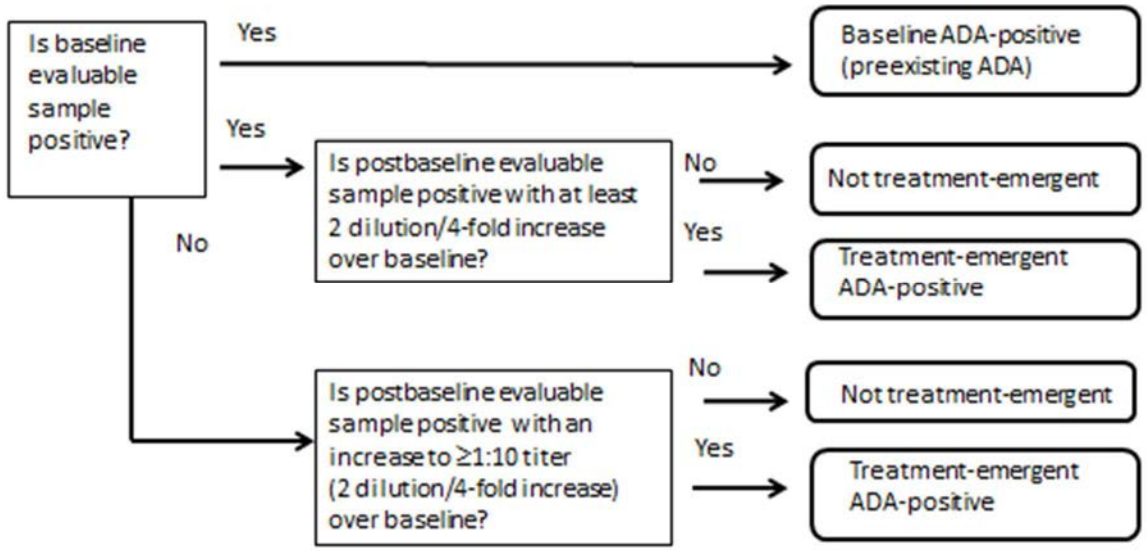
[d] Includes patients who were originally assigned to placebo and were later on rescued by ixekizumab 80mg Q2W.

[e] Includes patients who were originally assigned to ixekizumab 80mg Q4W and were later on rescued by Ixekizumab 80mg Q2W.

[f] includes groups 1 and 3.

- **baseline ADA positive (preexisting antibody):** ADA detected in a sample collected at baseline.
- **baseline ADA-negative:** ADA is not detected in a sample collected at baseline.
- **treatment-emergent anti-drug 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.
- **treatment-emergent anti-drug antibody (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.
- **treatment-emergent anti-drug antibody (TE-ADA negative patient:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.

Figure RHBX.6.7 illustrates the relationship of some of these terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHBX.6.7. Relationship of terms for clinical interpretation of assay results for evaluable patients.

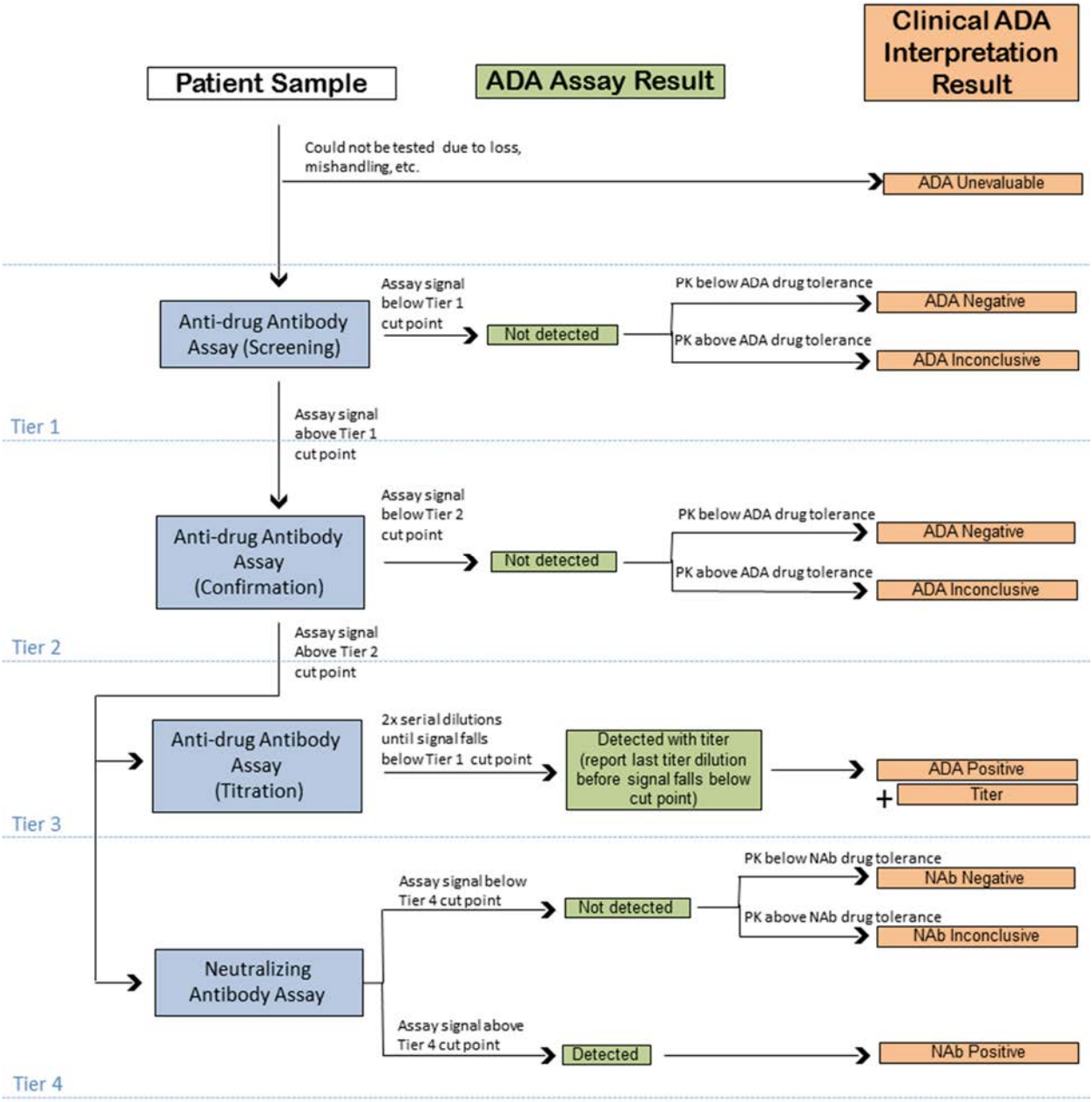
- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment period. This excludes unevaluable patients.

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 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 RHBX.6.8.



Abbreviations: ADA = anti-drug antibody; NAb = neutralizing antibody; PK = pharmacokinetics.

Figure RHBX.6.8. Flow chart of ADA assessment with clinical interpretation of the various result possibilities.

6.13.8.2. 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 6.13.8.1.2 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
- TE-ADA titer groups for TE-ADA positive patients:
  - Low Titer: TE-ADA titer value (last observation carried forward [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 RHBX.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 RHBX.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 anti-drug antibody.
Note: For purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive."
Note: A TE-ADA low is defined as a TE-ADA positive with a titer value <1:160; a TE-ADA moderate is defined as a TE-ADA positive with a titer value ≥1:160 and <1:1,280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1,280.

For each TE-ADA status dichotomous variable, a time-varying TE-ADA status will be computed. At time *t*, the TE-ADA status is taken to be the highest of the TE-ADA values bracketing time *t*. More formally, the TE-ADA status at time *t* is given by the greater of (a) the TE-ADA status at the most-recent postbaseline measurement prior to *t*, and (b) the TE-ADA status at the first TE-ADA postbaseline measurement at or after time *t*. In this computation, "greater" is given by the greater-TE-ADA status of Table RHBX.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.

6.13.8.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of characteristics of ADA response will be conducted on all immunogenicity evaluable patients within the Safety Population for the first 16-weeks of Blinded Treatment Dosing Period 2 (Week 0 to 16), and for the All Ixekizumab Exposures Safety Population for the entire 52-week Blinded Treatment Dosing Period 2 when patients are on ixekizumab, including open label rescue with ixekizumab of 80 mg Q2W (time period when patients are on placebo will be excluded), according to Table RHBX.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-ADA (TE-ADA positive, low titer, moderate titer, high titer, and NAb positive) will be calculated as follows:

Time to development of TE-ADA/NAb (in weeks) = (Date of development of TE-ADA/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 RHBX.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, ADA result, TE-ADA result, NAb result, ADA titer value, and 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.

6.13.8.2.2. Analyses of ADA Effects on Efficacy

Efficacy analyses for Period 2 will be conducted on all evaluable patients within the safety populations n for Blinded Treatment Dosing Period for Groups 1 and 2, separately. Groups 1 and 2 are illustrated in Table RHBX.6.10.

Assessment of Spondyloarthritis International Society 40 and ASDAS <2.1 (for patients with baseline ASDAS ≥2.1) at Weeks 16 with NRI will be summarized by the TE-ADA status groups as described in Section 6.13.8.2.1 for the Safety Population.

A logistic regression model with treatment group, TE-ADA status group (excluding patients in the TE-ADA inconclusive category for TE-ADA, excluding TE-ADA positive and co-occurring NAb inconclusive subgroups for NAb) and the interaction of treatment group-by-TE-ADA status group included as factors will be used to test the interaction of treatment group -by-TE-ADA status group during Period 2 at Week 16. The p-value associated with the interaction term will be used to assess if the treatment effect is consistent across the TE-ADA status groups. When the interaction term is statistically significant, the association between responder status and treatment depends, in some manner, on the TE-ADA status group. The interaction will be tested at the 10% significance level. Treatment differences will be evaluated within each subgroup using Fisher's exact test regardless of whether the interaction is statistically significant.

Assessment of Spondyloarthritis International Society 40 and ASDAS <2.1 (for patients with baseline ASDAS ≥2.1) at Weeks 52 with NRI will be summarized by the TE-ADA status groups as described in Section 6.13.8.2.1 for the All Ixekizumab Exposures Safety Population. No statistical testing will be performed.

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

The analyses of TE-ADA effects on safety will be conducted on all immunogenicity evaluable patients for the All Ixekizumab Exposures Safety Population for the Blinded Treatment Dosing Period (Period 2 Week 0 to 52) when patients are on ixekizumab, including open label rescue with ixekizumab 80 mg Q2W (time period when patients are on placebo will be excluded). All patients will be analyzed in one group.

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

For each TE-ADA status dichotomous variable (as defined in Table RHBX.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.

6.14. Analysis for Submission to Japan - Regulatory Body

A subset of the planned efficacy and safety analyses will be summarized based on patients from Asian sites (Japan and Korea), in support of the regulatory submission in Japan. The list of tables, listings, and figures for the patients from Asian sites (Asian population) will be in a separate document.

In addition, a by-patient listing of patients from Asian sites with the number of self-injections will be provided for Period 2. The self-injection is defined as the injection administered either by study subject or by caregiver during Period 2.

6.15. Subgroup Analyses

6.15.1. Efficacy Subgroup Analyses

Subgroup analysis will be conducted for the primary endpoints of proportion of patients achieving an ASAS40 response at Weeks 16 and 52 (NRI) using the ITT Population for the Period 2. The proportion of patients achieving ASDAS <2.1 (NRI) at Weeks 16 and 52, will also be conducted.

For ASAS40, ASDAS <2.1, a logistic regression analysis with treatment, subgroup, and treatment-by-subgroup interaction as factors will be used. The treatment-by-subgroup interaction will be tested at the 10% significance level. Treatment group differences will be evaluated within each subgroup using the Fisher's exact test, regardless of whether the interaction is statistically significant. If any group within the subgroup (for example, yes, no) is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

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

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: Europe, non-Europe
  - Geographic region: America, Asia, Europe
  - Geographic region: North America (US, including Puerto Rico if any, Canada) or Rest of the World
  - Geographic region: US (including Puerto Rico if any), non-US
  - Geographic region: South America (Argentina, Brazil and Mexico), Rest of the World (non-South America)
- 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:
    - SPARCC SIJ score ≥2 or <2
  - Screening MRI/CRP status:
    - positive MRI and elevated CRP
    - positive MRI and nonelevated CRP
    - negative MRI and elevated CRP

      Note: Positive MRI is defined by Assessment of SpondyloArthritis international Society/ Outcome Measures in Rheumatology Clinical Trials (ASAS/OMERACT) criteria and elevated CRP is defined as >5.00 mg/L.
  - 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 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
- Baseline analgesics use: yes or no

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

6.15.2. Safety Subgroup Analyses

Safety subgroup analysis for common TEAEs and AESI of infections will be summarized by treatment group and overall, using Safety Population for Period 2 using Spotfire. The common TEAEs will be presented by MedDRA PT within SOC. 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 group 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 less than 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, and are defined in Section 6.15.1.

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

6.16. 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 RHBX.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, the source of

identification for the deviations, and the statistical programming guidance for the clinical study report (CSR).

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

- Period 2 prior to initiation of biologic rescue of ixekizumab 80 mg Q2W (ITT Population)
- Period 2 post initiation of biologic rescue of ixekizumab 80 mg Q2W (IR Population)

A by-patient listing of important protocol deviations will be provided.

Table RHBX.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		
Subcategory: Inclusion/Exclusion		
[1] Not meeting 'sacroiliitis on MRI and have at least 1 SpA feature'; and not meeting 'positive for HLA-B27 and have at least 2 additional SpA features' 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
[3] No active nonrad-axSpA defined as BASDAI ≥4 and total back pain ≥4 on an NRS at screening and baseline	Exclude from PPS	Monitor and Stats
[4] Not have objective signs of inflammation by presence of sacroiliitis on MRI and not have elevated CRP (defined as CRP >5.00 mg/L).	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 (for Japan patients, not have had NSAID or had 1 NSAID for a duration of less than 12 weeks)	Exclude from PPS	Monitor
[6] Not have a history of prior therapy for axSpA of at least 12 weeks prior to screening	Exclude from PPS	Monitor
[7] Not ≥18 years of age at time of screening	Exclude from PPS	Monitor and Stats
[8] 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
[10] Fulfillment of the mNY criteria with sacroiliitis defined radiographically, based on central reading	Exclude from PPS	Monitor and Stats
[11] 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
[12] Have active Crohn's disease (CD) or active ulcerative colitis (UC) at screening	Do not exclude from PPS	Monitor and Stats
[13] Have evidence of active anterior uveitis (an acute episode) within the last 4 weeks prior to baseline randomization	Do not exclude from PPS	Monitor and Stats
[14] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease; or have active or history of	Do not exclude from PPS	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
malignant disease within 5 years prior to Visit 2		
[15] Have had fluid overload, MI or new onset ischemic heart disease, uncompensated heart failure, or other serious cardiac disease within 12 weeks prior to Visit 2	Do not exclude from PPS	Monitor
[16] Presence of significant, uncontrolled cerebro-cardiovascular events at screening	Do not exclude from PPS	Monitor
[17] Presence of respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorder at screening that pose unacceptable risk to patient or with interpretation of data	Do not exclude from PPS	Monitor
[18] Presence of neurologic or neuropsychiatric disorders at screening that pose unacceptable risk to patient or with interpretation of data	Do not exclude from PPS	Monitor
[19] Presence of significant uncontrolled neuropsychiatric disorder, recent history (30 days prior to 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 Visit 1 or Visit 2, or at risk for suicide	Do not exclude from PPS	Monitor and Stats
[20] In the past 12 weeks prior to V2, had a serious infection, hospitalization or IV antibiotics for an infection; in the past 24 weeks prior to V2, had a serious bone or joint infection; ever had an infection of an artificial joint, or infection that occurs in increased incidence in an immunocompromised host. Japan patients with a positive beta-D-glucan test at screening and a confirmed diagnosis of PCP.	Do not exclude from PPS	Monitor
[21] 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
[22] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of Visit 2	Do not exclude from PPS	Monitor
[23] Have any other active or recent infection within 4 weeks of Visit 2 that would pose an unacceptable risk to the patient	Do not exclude from PPS	Monitor
[24] 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
[25] Have had surgical treatment of a joint to be assessed in the study within 8 weeks prior to baseline randomization or will require such	Exclude from PPS depending on the clinical significance	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
during the first 16 weeks of the trial		
[26] Had any major surgery within 8 weeks prior to Visit 2, or will require such during the study that would pose an unacceptable risk to the patient	Do not exclude from PPS	Monitor
[27] Not have stable dose for NSAID or COX-2 for at least 2 weeks prior to baseline randomization, if taking NSAID or Cox-2 inhibitors	Only Exclude from PPS if: 1. Stopped or decreased dose for a current med <3 days before randomization; or 2. Start or increased dose for a current med or started a new med <2 wks before randomization	Monitor and Stats
[28] 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 prior to baseline randomization.	Exclude from PPS if: 1.Stopped or decreased dose for a current med ≤3 days before randomization; or 2. Started new treatment or increased dose for current med or started a new med <4 wks before randomization. Patients with Combo cDMARD drug use will be removed from PPS	Monitor and Stats
[29] Current use of oral corticosteroids >10 mg/day prednisone or its equivalent	Exclude from PPS if: 1. Dose >10 mg/day any time within 4 weeks; or 2. Stopped or decreased dose for a current med <10 days before randomization; or 3.Started new treatment or increased dose for current one or started a new one <4 wks before randomization	Monitor and Stats
[30] 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, TNF inhibitors, IL-1, IL-6 , IL-23 , IL-17 (including ixekizumab), IL-17R, T	Exclude from PPS	Monitor and Stats

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
cell, or B cell targeted therapies).		
[31] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 30 days prior to screening or a period of at least 5 half-lives of the last administration of the drug, whichever is longer	Exclude from PPS	Monitor
[32] Are currently 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	Exclude from PPS	Monitor
[33] Are currently receiving or have received treatment with denosumab within 6 months prior to baseline randomization	Do not exclude from PPS	Monitor and Stats
[34] Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks prior to baseline randomization, or a parenteral injection of glucocorticosteroids is anticipated during the Period 2.	Exclude from PPS	Monitor and Stats
[35] 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 prior to baseline randomization. For Japan patients, use of pregabalin >300 mg/day or use of variable doses of pregabalin within 2 weeks prior to baseline randomization.	Exclude from PPS if: 1. 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; or 3.Started new treatment or increased dose for current one or started a new one <6 wks before randomization	Monitor and Stats
[36] Had a live vaccination or participated in a vaccine clinical study within 12 weeks prior to Visit 2, or intend to have a live vaccination during the study or within 12 weeks of completing study treatment	Do not exclude from PPS	Monitor
[37] Had a vaccination with BCG within 12 months prior to Visit 2, 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
[38] Have a body temperature ≥38°C (100.5°F) at Visit 2	Do not exclude from PPS	Monitor and Stats
[39] Have evidence or suspicion of active or latent TB	Do not exclude from PPS	Monitor
[40] Are positive for human immunodeficiency virus serology (HIV)	Do not exclude from PPS	Monitor and Stats

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
[41] Have evidence of or test positive for hepatitis B virus (HBV) and are HBV DNA positive	Do not exclude from PPS	Monitor and Stats
[42] Have evidence of or test positive for hepatitis C virus (HCV)	Do not exclude from PPS	Monitor and Stats
[43] 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
[44] Patients having contraindications to MRI	Do not exclude from PPS	Monitor
[45] At Visit 1, have a neutrophil count <1.50 GI/L	Do not exclude from PPS	Monitor and Stats
[46] At Visit 1, have a lymphocyte count <0.80 GI/L; for Japan patients, lymphocyte count <1.0 GI/L	Do not exclude from PPS	Monitor and Stats
[47] At Visit 1, have a platelet count <100 GI/L	Do not exclude from PPS	Monitor and Stats
[48] At Visit 1, 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 Visit 1, have a total white blood cell (WBC) count <3.00 GI/L; for Japan patients, WBC count <4.0 GI/L	Do not exclude from PPS	Monitor and Stats
[50] At Visit 1, 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 Visit 1 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 prior to Visit 1, 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 prior to use of rescue ixekizumab 80 mg Q2W	Monitor
[57] Have any other condition that precludes the patient from following and completing the protocol	Exclude from PPS	Monitor

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
Subcategory: other		
Rescreened patients were screened but did not meet rescreening criteria per protocol	Do not exclude from PPS	Monitor
Category: Study Procedures		
Subcategory: Violation of Discontinuation Criteria		
[D1] Lilly medical not consulted when patient met hepatic lab criteria for consideration of discontinuation. For patients from German sites, not discontinued IP for abnormal liver tests.	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 for non-German patients). For patients from German site, any malignancy	Do not exclude from PPS	Monitor
[D7] Enrolled in prohibited medical research	Exclude from PPS when occurred in Period 2 prior to use of rescue ixekizumab 80 mg Q2W	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 has a confirmed diagnosis of PCP during the study for patients from Japan sites; Patients develop a severe infection for patients from German sites	Do not exclude from PPS	Monitor and Stats

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
Category: Study Procedures		
Subcategory: Excluded Con-meds		
	Exclude from PPS (Excluded Con-meds refers to clinically meaningful change in con-meds (Appendix 13) occurred during Period 2 prior to use of rescue ixekizumab 80 mg Q2W and prescribed for primary study condition	Monitor and Stats
Subcategory: 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 post-baseline	Do not exclude from PPS	Stats
Subcategory: Other		
Missing QIDS total score: missing baseline or any scheduled visit prior to discontinuation visit	Do not exclude from PPS	Stats
Missing Columbia scale at any visit except Visit 1	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 non-responder 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		
Subcategory: Treatment Assignment/Randomization Error		
Took incorrect study medication	Do not exclude from PPS. Analyze 'As randomized' or 'As assigned'.	Stats and monitor
Subcategory: Compliance		
	Exclude from PPS when occurred during Period 2 prior to use of rescue ixekizumab 80 mg Q2W	Stats

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]
Subcategory: Patient took medication not fit for use		
	Do not exclude from PPS	Monitor
Subcategory: Unblinding		
	Exclude from PPS	Monitor
Subcategory: Other		
Randomized but did not take any study medication	Exclude from PPS	Stats
Category: Safety		
Subcategory: SAEs		
SAE not reported within designated timeline	Do not Exclude from PPS	Monitor
Category: Informed Consent		
Subcategory: Informed Consent not Obtained/Missing/Late[b]		
	Exclude from PPS	Monitor
Subcategory: Improper Consent		
	Do not Exclude from PPS	Monitor
Category: administrative/oversight		
Subcategory: Reg/Ethic Approvals		
	Exclude from PPS	Monitor
Subcategory: 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; cDMARD = conventional disease-modifying antirheumatic drug; CRP = C-reactive protein; ECG = electrocardiogram; GCP = good clinical practice; IL = interleukin; ITT = intent-to-treat; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; NRS = numerical rating scale; MI = myocardial infarction; mNY =modified New York; MRI = magnetic resonance imaging; PCP = pneumocystis pneumonia; PPS = per protocol set; QIDS = Quick Inventory Depressive Symptomatology; Q2W = every 2 weeks; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self-Report 16 items; rad = radiographic; SAE = serious adverse event; TB = tuberculosis; TNF = tumor necrosis factor; 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 as the last column. 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.

[b] This deviation will be summarized in CSR table and listing as listed in this document. Issue Management Plan and the monitor's list is slightly different with subcategory as 'Informed Consent not Obtained.' These 2 subcategories will be grouped in the clinical study report table and listing as "Informed Consent not Obtained/Missing/Late."

6.17. Interim Analyses and Data Monitoring

An interim database lock and unblinding will occur, and the analysis will be performed at the time (that is, a cut-off date) the last patient completes Visit 15 (Week 52) or ETV. This interim database lock will include all data collected by the cut-off date including follow-up data from patients who have begun the Post-Study Follow-Up Period (Period 3). Because the study will still be ongoing for the Post-Study Follow-Up Period at the time of this database lock, the analysis will be referred to as an interim analysis. The analyses from the Week 52 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

Unblinding details are specified in the blinding/unblinding plan.

6.18. Planned Exploratory Analyses

- To assess the psychometric properties (including reliability, validity, and responsiveness) of the ASAS HI in the ITT Population
- To assess the psychometric properties (including reliability, validity, and responsiveness) of the SF-36 components and norm-based domain scores in the ITT Population.
- To explore the impact of each ixekizumab regimen on change from baseline in measures of health utility (EQ-5D); and healthcare resource utilization in the double-blind dosing period in the ITT Population.

6.18.1. Psychometric Properties of ASAS HI

Unless stated otherwise, the analysis population of the psychometric properties of ASAS HI is ITT Population. The psychometric properties of the ASAS HI will be evaluated per the following analyses:

- Descriptive statistics for ASAS HI including sample size, mean, median, SD, min, max, % min, % max and % missing, will be provided for the baseline and at Week 16. The number and percentage of ASAS HI of 0,1,…, and 17 will also be summarized at baseline and at Week 16. Number and percentage of patients with each ASAS HI item score will also be summarized.
- Convergent and discriminant validity will be assessed by Pearson correlation and Spearman rank-based correlation coefficient at baseline and at Week 16 between ASAS HI and other clinical assessments, including BASFI, BASDAI, Spinal Pain (BASDAI item 2), EQ-5D UK Index, SF-36 MCS, SF-36 PCS, Patient Global Assessment of disease activity and fatigue NRS. Cohen's conventions (any absolute correlation at or of value greater than 0.5 is large, 0.3 to <0.5 is moderate, 0.1 to <0.3 is small, and anything smaller than 0.1 is insubstantial) will be used to interpret the results. It is hypothesized there will be small to moderate correlations at baseline and moderate to large correlations at Week 16 between the ASAS HI and all clinical measures, except for CRP. The correlations between ASAS HI and CRP at baseline and Week 16 are hypothesized to be small to moderate.

- Known groups validity of ASAS HI will be evaluated using one-way ANOVA with Scheffe's correction for post-hoc pairwise comparison, in distinguishing ASAS HI scores at baseline and Week 16 (mBOCF) between subgroups defined on the basis of ASDAS category: ASDAS <2.1, 2.1 ≤ ASDAS ≤3.5 and ASDAS >3.5. If the sample size for any ASDAS category is less than 10% of the total sample size, the ASDAS category will be collapsed with lower category.
- Responsiveness will be evaluated by the correlations of ASAS HI changes from baseline to Week 16 (mBOCF) with changes from baseline in other clinical assessments, including BASFI, BASDAI, ASDAS, and Patient Global Assessment of disease activity to Week 16 (mBOCF). Moderate to large correlations are hypothesized based on Cohens' conventions. Additionally, responsiveness will be evaluated using one-way ANCOVA comparing mean change in ASAS HI (mBOCF) between subgroups defined on the basis of (1) ASAS response status at Week 16: not achieving ASAS20; achieving ASAS20 but not ASAS40; and achieving ASAS40, and (2) BASDAI response status at Week 16 (NRI): BASDAI50 nonresponder and BASDAI50 responder, and (3) ASDAS disease activity: ASDAS <1.3, 1.3≤ASDAS<2.1 and at ASDAS ≥2.1, (4) ASDAS improvement<1.1, 1.1≤ASDAS improvement<2.0 and 2.0≤ASDAS improvement, after with and without controlling for baseline ASAS HI. Missing ASAS response status will be treated as not achieving ASAS20. It is hypothesized that an overall statistically significant difference will be observed ($p<0.05$) with at least one statistically significant subgroup comparisons.
- Test-retest reliability will be assessed in stable patients during the interval between screening and baseline assessment (the 2 assessments will be separated by 4 - 42 days). Stable patients will be defined as those with no more than ±1.5 points difference in BASDAI ratings between screening and baseline. Intraclass correlation coefficients (ICCs) and change scores will be calculated between the initial and retest to evaluate test-retest reliability. An ICC of 0.70 is considered acceptable agreement (Nunnally and Bernstein 1994). The analysis population for test-retest reliability will be all patients with both screening and baseline assessments.
- Internal consistency of ASAS HI total score at baseline and at Week 16 will be evaluated using Cronbach's alpha. Inter-item correlation will be quantified using two metrics: simple agreement and Yule's Q coefficient.
- The responder definition of ASAS HI will be derived using both anchor-based and distribution-based methods. In the distribution-based method, 1.00 and 1.96 times the standard error of measurement (SEM) bears alignment with meaningful change over time (Wyrwich 2004) and are are considered thresholds for minimal detectable change. The anchor-based method will utilize the empirical cumulative distribution function (eCDF) and probability density function (PDF) plots to explore the relationship between selected anchors, including ASAS40, ASAS20, BASDAI50, sPGA change of ≤-4, -3, -2, -1, 0, 1, 2, 3, and ≥4 and ASDAS<2.1 response status at Week 16 (NRI) and the change in ASAS HI from baseline to Week 16 (mBOCF). The eCDF and PDF plots of the ASAS HI total score change from baseline to Week 16 using pooled sample will be provided, including sample sizes and median scores in each plot's legend.

- The empirical cumulative distribution function (eCDF) and probability density function (PDF) plots for change in ASAS HI from baseline to Week 16 (mBOCF) will be presented by treatment group (including placebo).

6.18.2. Psychometric Properties of SF-36 components and norm-based domain scores

- Test-retest reliability will be assessed in stable patients during the interval between screening and baseline assessment (the 2 assessments will be separated by 4 - 42 days). Stable patients will be defined as those with no more than ± 1.5 point difference in BASDAI ratings between screening and baseline. Intraclass correlation coefficients (ICCs) and change scores will be calculated between the initial and retest to evaluate test-retest reliability. An ICC of 0.70 and above is considered acceptable agreement (Nunnally and Bernstein 1994). The analysis population for test-retest reliability will be all stable patients with both screening and baseline assessments.
- Known groups validity of SF-36 scores will be evaluated using one-way ANOVA with Scheffe's correction for post-hoc pairwise comparison at baseline and Week 16 (mBOCF) between subgroups defined on the basis of ASDAS category: ASDAS <2.1, ASDAS ≤2.1 to ≤3.5, and ASDAS >3.5.
- Convergent and discriminant validity will be assessed by Pearson correlation and Spearman rank-based correlation coefficient at baseline and at Week 16 between SF-36 scores and other clinical assessments, including BASFI, BASDAI, Spinal Pain (BASDAI item 2), EQ-5D UK Index, Patient Global Assessment of disease activity, CRP, WPAI work productivity loss, WPAI activity impairment and fatigue NRS. Cohen's conventions (any absolute correlation at or value greater than 0.5 is large, 0.3 to <0.5 is moderate, 0.1 to <0.3 is small, and anything smaller than 0.1 is insubstantial) will be used to interpret the results. It is hypothesized there will be small to moderate correlations at baseline and moderate to large correlations at Week 16 between SF-36 and all clinical measures, except for CRP. The correlations between SF-36 and CRP at baseline and Week 16 are hypothesized to be small to moderate.
- Responsiveness will be evaluated by the correlations of SF-36 changes from baseline to Week 16 (mBOCF) with changes from baseline in other clinical assessments, including BASFI, BASDAI, ASDAS, and Patient Global Assessment to Week 16 (mBOCF). Moderate to large correlations are hypothesized based on Cohens' conventions. Additionally, responsiveness will be evaluated using one-way ANCOVA comparing mean change in SF-36 (mBOCF) between subgroups defined on the basis of (1) ASAS response status at Week 16: not achieving ASAS20; achieving ASAS20 but not ASAS40; and achieving ASAS40, and (2) BASDAI response status at Week 16 (NRI): BASDAI50 nonresponder and BASDAI50 responder, and (3) ASDAS disease activity: ASDAS <1.3, ASDAS ≤1.3 to <2.1, and at ASDAS ≥2.1, (4) ASDAS improvement <1.1, ASDAS improvement ≤1.1 to <2.0, and 2.0 ≤ASDAS improvement, after with and without controlling for baseline SF-36 score. Missing ASAS response status will be

treated as not achieving ASAS20. It is hypothesized that an overall statistically significant difference will be observed ($p<0.05$) with at least one statistically significant subgroup comparisons.

The anchor-based eCDF and PDF plots of the SF-36 change scores from baseline to week 16 using pooled sample will be provided for anchor ASAS40, ASAS20, BASDAI50, sPGA change of ≤-4, -3, -2, -1 0, 1, 2, 3, and ≥4 and ASDAS<2.1 response status at Week 16 (NRI) and change in SF-36 score from baseline to Week 16 (mBOCF), including sample sizes and median scores in each plot's legend.The eCDF and PDF plots of the SF-36 change scores from baseline to week 16 using pooled sample will be provided, including sample sizes and median scores in each plot's legend.

6.18.3. Association Between Clinical Outcomes and Health Outcomes/Quality-of-Life Measures

The objective of the following analysis is to determine whether greater improvement in clinical outcomes from baseline to Week 16, as assessed by categorized ASAS, BASDAI, and ASDAS is associated with larger improvement from baseline to Week 16 in the following continuous health outcome measurements:ASAS HI, Fatigue NRS, SF-36 PCS, SF-36 MCS, and WPAI-SpA. Association between clinical outcomes and categorical health outcomeswill also be investigated.

Clinical outcomes will be categorized according to Table RHBX.6.13.

Table RHBX.6.13. Categorization of Clinical Outcomes

	Clinical Outcomes at Week 16[a]			
Categorization	**ASAS**	**BASDAI**	**ASDAS static**	**ASDAS improvement**
(1)	ASAS40 Nonresponder	BASDAI50 Nonresponder	ASDAS very high disease (ASDAS > 3.5)	ΔASDAS<1.1
(2)	ASAS40 Responder	BASDAI50 Responder	ASDAS high disease (2.1≤ASDAS ≤3.5)	1.1≤ ΔASDAS<2.0
(3)			ASDAS inactive/moderate disease activity (ASDAS<2.1)	2.0≤ ΔASDAS

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.

[a] Above association analyses between clinical outcomes and health outcomes/quality-of-life measures may be conducted at Week 52 as well.

Missing categorical clinical outcomes and continuous health outcomes at Week 16 will be imputed by NRI and mBOCF methodology described in Sections 6.3.1 and 6.3.2, respectively. Missing categorical health outcomes will also be imputed using NRI method as described in Section 6.3.1.

The association analysis will be performed using the ITT Population with all treatment groups combined and the ITT Population with total ixekizumab groups.

6.18.4. Planned Exploratory Health Outcomes/Quality-of-Life Analyses

Table RHBX.6.14 includes the description and derivation of the exploratory health outcomes and QOL measures.

Table RHBX.6.15 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for the exploratory health outcomes and QOL analyses.

Table RHBX.6.14. Description and Derivation of Exploratory Health Outcomes and Quality-of-Life Measures

Measure	Description	Variable	Derivation / Comment	Missing Items
European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L)	EQ-5D-5L: is a standardized measure of health status used to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: item 1: mobility item 2: self-care item 3: usual activities item 4: pain/discomfort item 5: anxiety/depression The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions.	EQ-5D mobility, EQ-5D self-care, EQ-5D usual activities, EQ-5D pain/ discomfort, EQ-5D anxiety/ depression	Five health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems 5 = extreme problems It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a primary score.	Each dimension is a single item, missing if missing.
		EQ-5D-5L UK Population-based index score	Uses the concatenation of the value of each EQ-5D-5L dimension score in the order: item1; item2; item3; item4; item5. Derive EQ-5D-5L UK Population-based index score according to the link by using the UK algorithm (Szende et al. 2007) to produce a patient-level index score between -0.59 and 1.0 (continuous variable): https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/	If any of the items is missing, the index score is missing
	The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled 100 = "best imaginable health state" and 0 = "worst imaginable health state".	EQ-5D VAS	Range from 0 = "worst imaginable health state" to 100 = "best imaginable health state." Note: higher value indicates better health state.	Single item, missing if missing

Measure	Description	Variable	Derivation / Comment	Missing Items
Healthcare Resource Utilization	Healthcare resource utilization data regarding the number of visits to medical care providers, such as general practitioners, specialists, physical, or occupational therapists, and other nonphysical care providers for services outside of the clinical trial; emergency room admissions; hospital admissions; and concomitant medications will be recorded by the investigator in the study's CRF.	Visits to medical care providers (except hospitals)	Derivation will be performed within each treatment period	NA
		Days in hospital		
		Number of hospital admissions (Medical ICU, surgical ICU, coronary ICU, general ward, trauma unit, unknown or other)		
		Healthcare providers (type of specialist for healthcare practitioner)		

Abbreviations: ICU = intensive care unit; NA = not applicable; UK = United Kingdom; VAS = visual analog scale.

Table RHBX.6.15. Description of Exploratory Health Outcomes and Quality-of-Life Analyses

Measure	Variable	Analysis Method (Sections 6.1 and 6.3)	Population (Section 6.1.1)	Comparison / Time Point
European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L)	EQ-5D mobility, EQ-5D self-care, EQ-5D usual activities, EQ-5D pain/discomfort, EQ-5D anxiety/depression	For each EQ-5D dimension, the proportion of patients with "no problems" will be analyzed by: Logistic regression analysis with NRI; Fisher's exact test with NRI	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52
	Change from baseline in: EQ-5D-5L UK Population-based index score, EQ-5D VAS	ANCOVA with mBOCF	ITT Population	IXE80Q2W & IXE80Q4W vs. placebo at Weeks 16 and 52
Healthcare Resource Utilization	Visits to medical care provider; Days in Hospital; Number of hospital admissions; Healthcare provider	Descriptive statistics	ITT Population	Overall comparison in Period 2 by Kruskal Wallis test

Abbreviations: ANCOVA = analysis of covariance; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; ITT = intent-to-treat; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; mBOCF = modified baseline observation carried forward; NRI = nonresponder imputation; UK = United Kingdom; VAS = visual analog scale.

6.19. Annual Report Analyses

Annual report analyses will be documented in a separate document.

6.20. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include summary of AEs, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA 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 Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures such as the CSR.

7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

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9. Appendices

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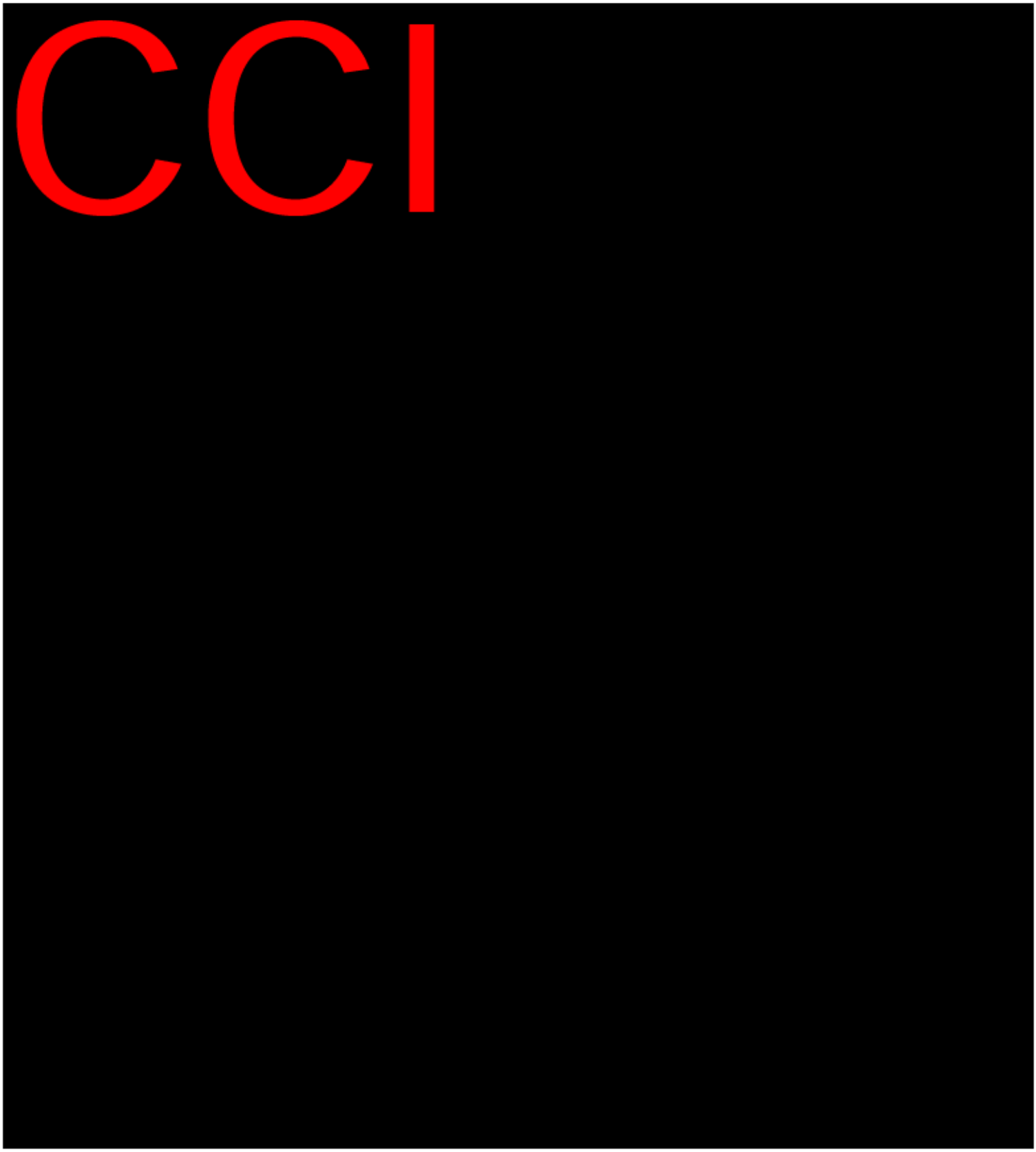
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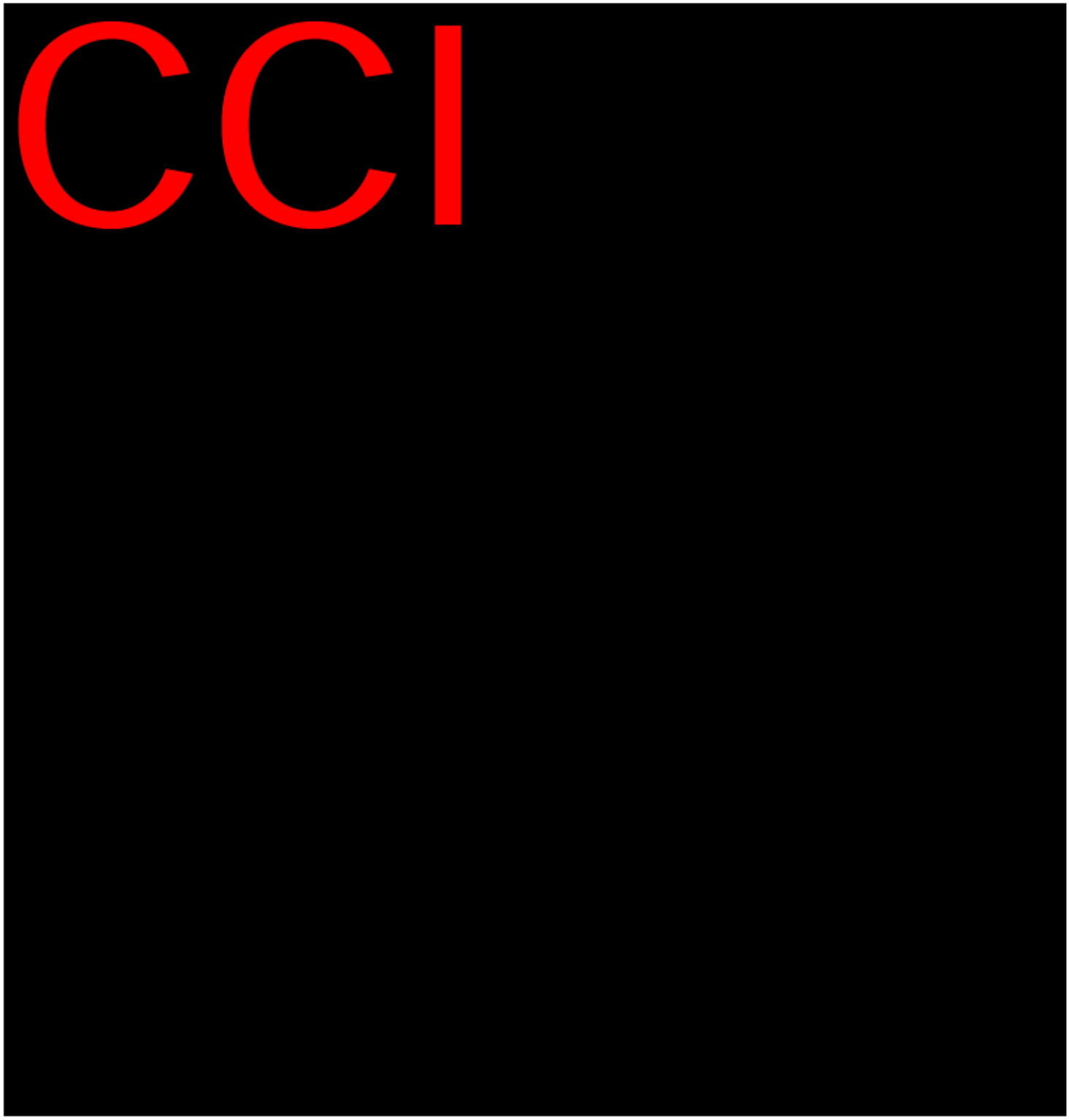
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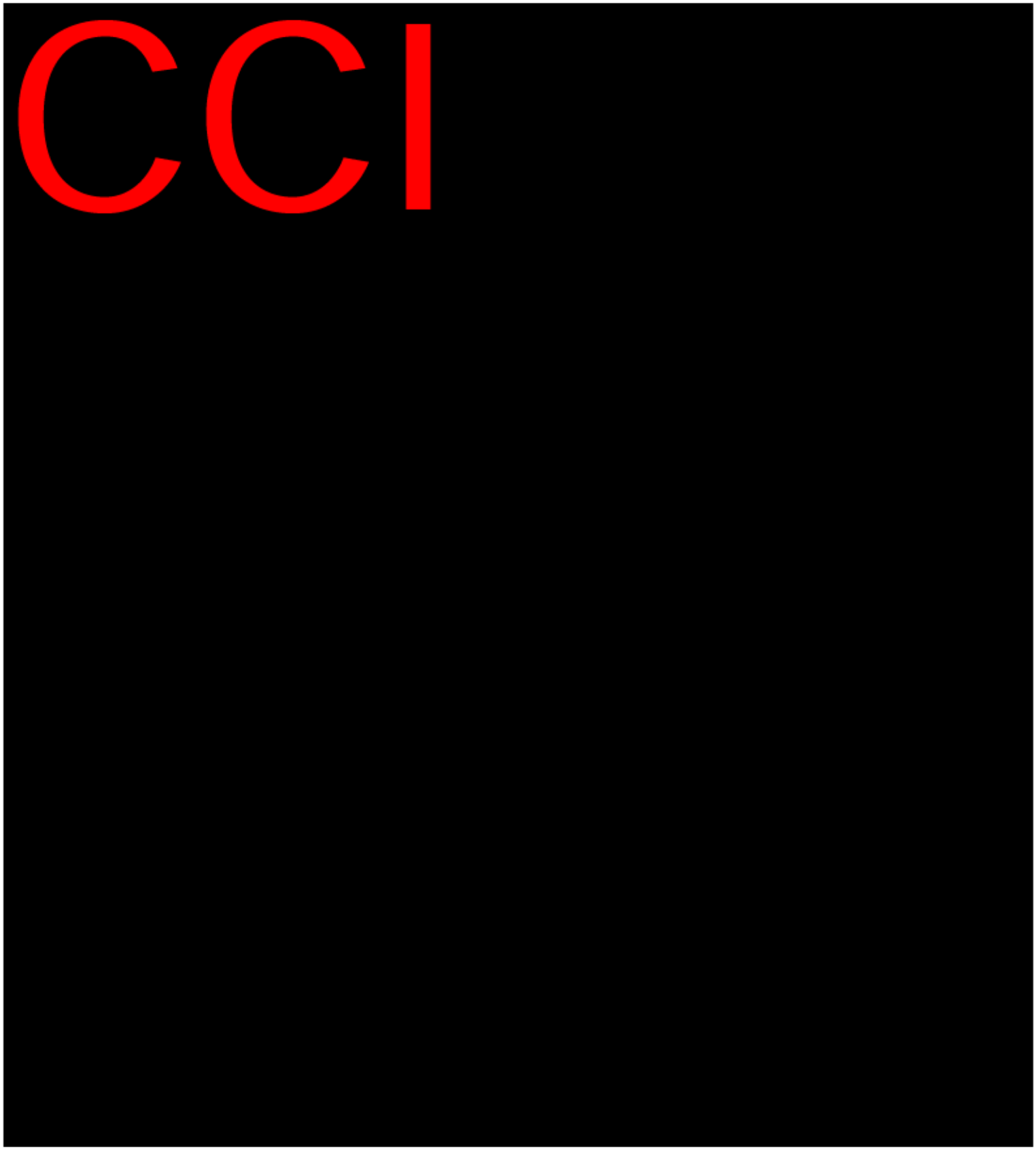
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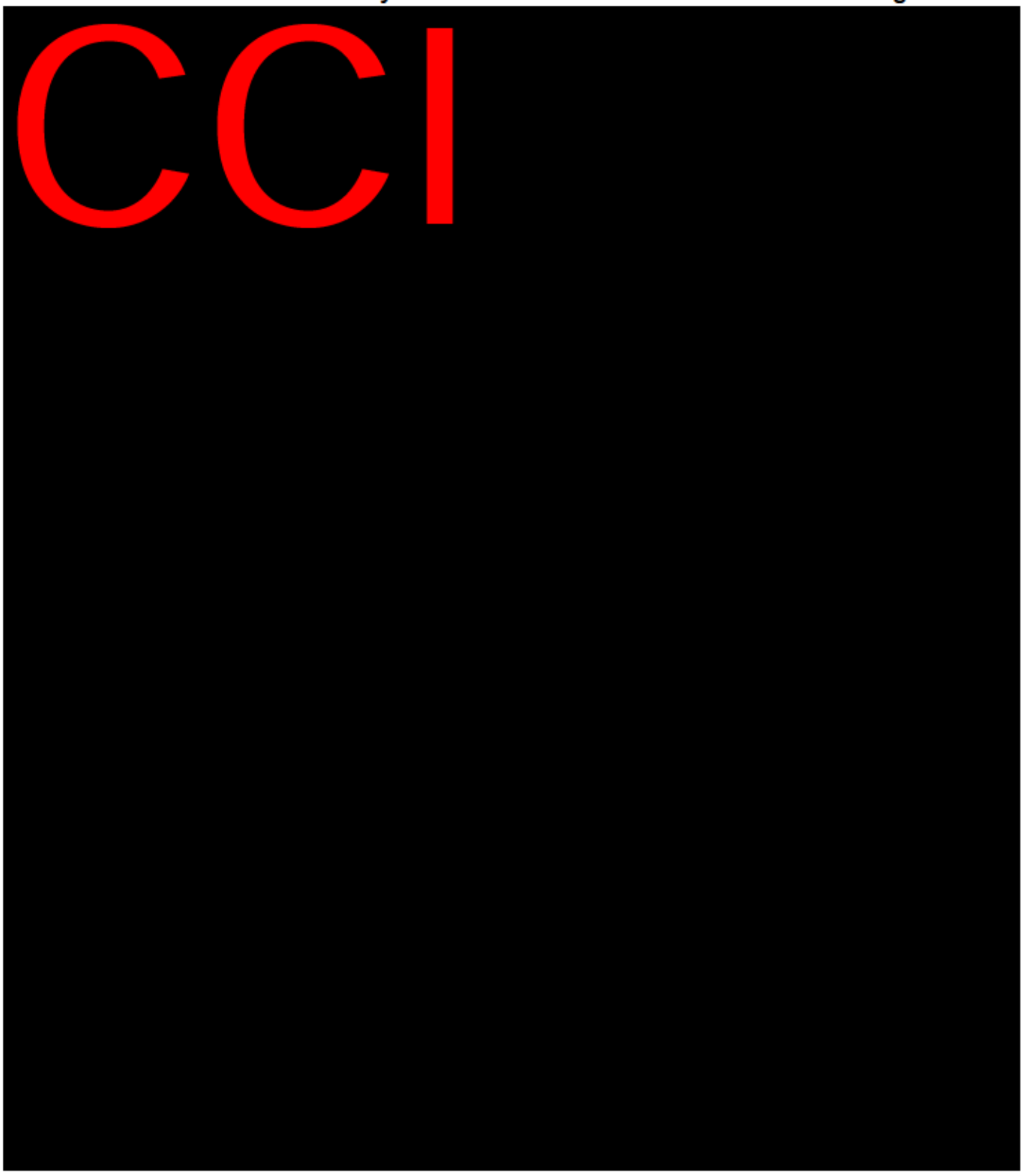
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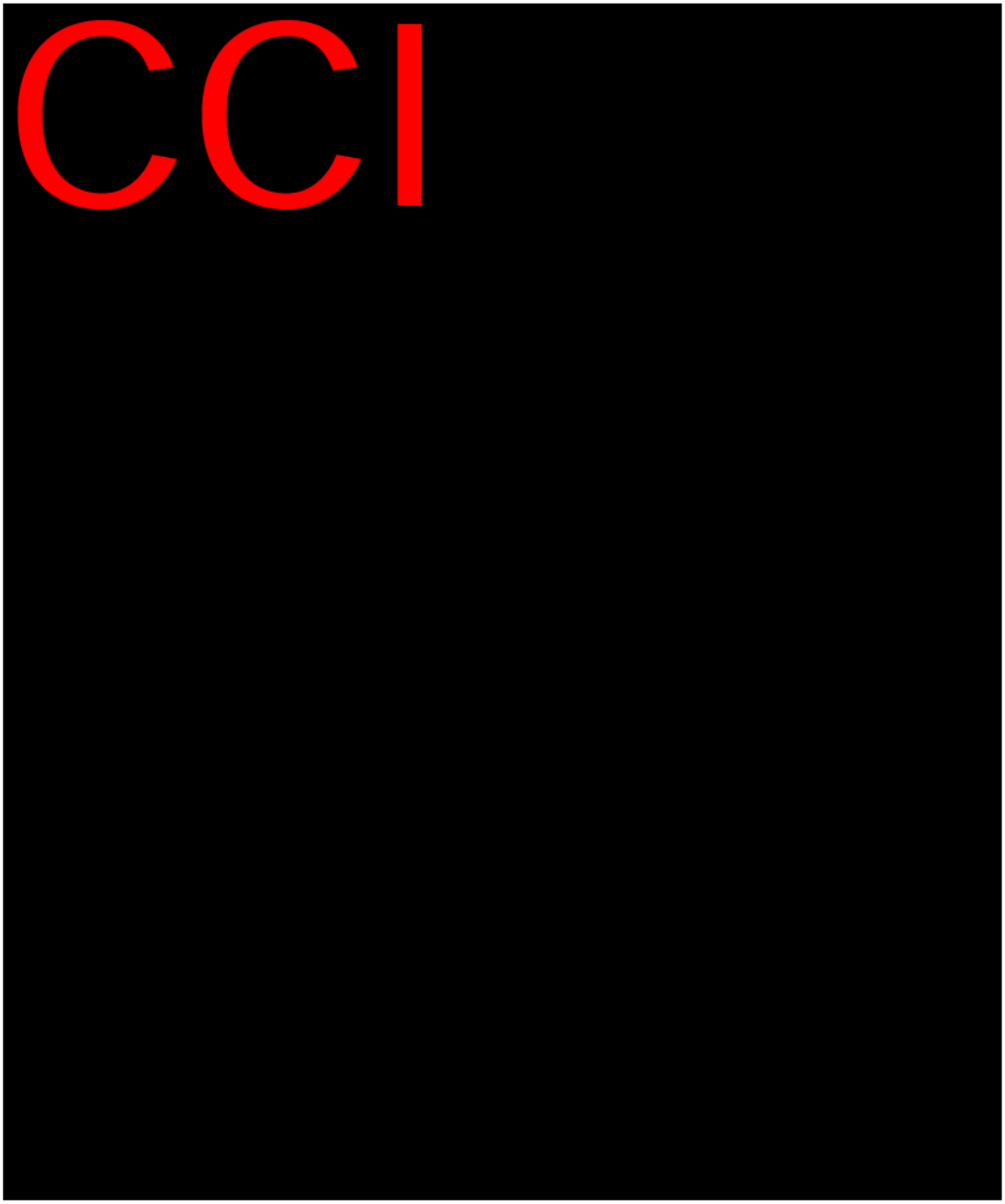
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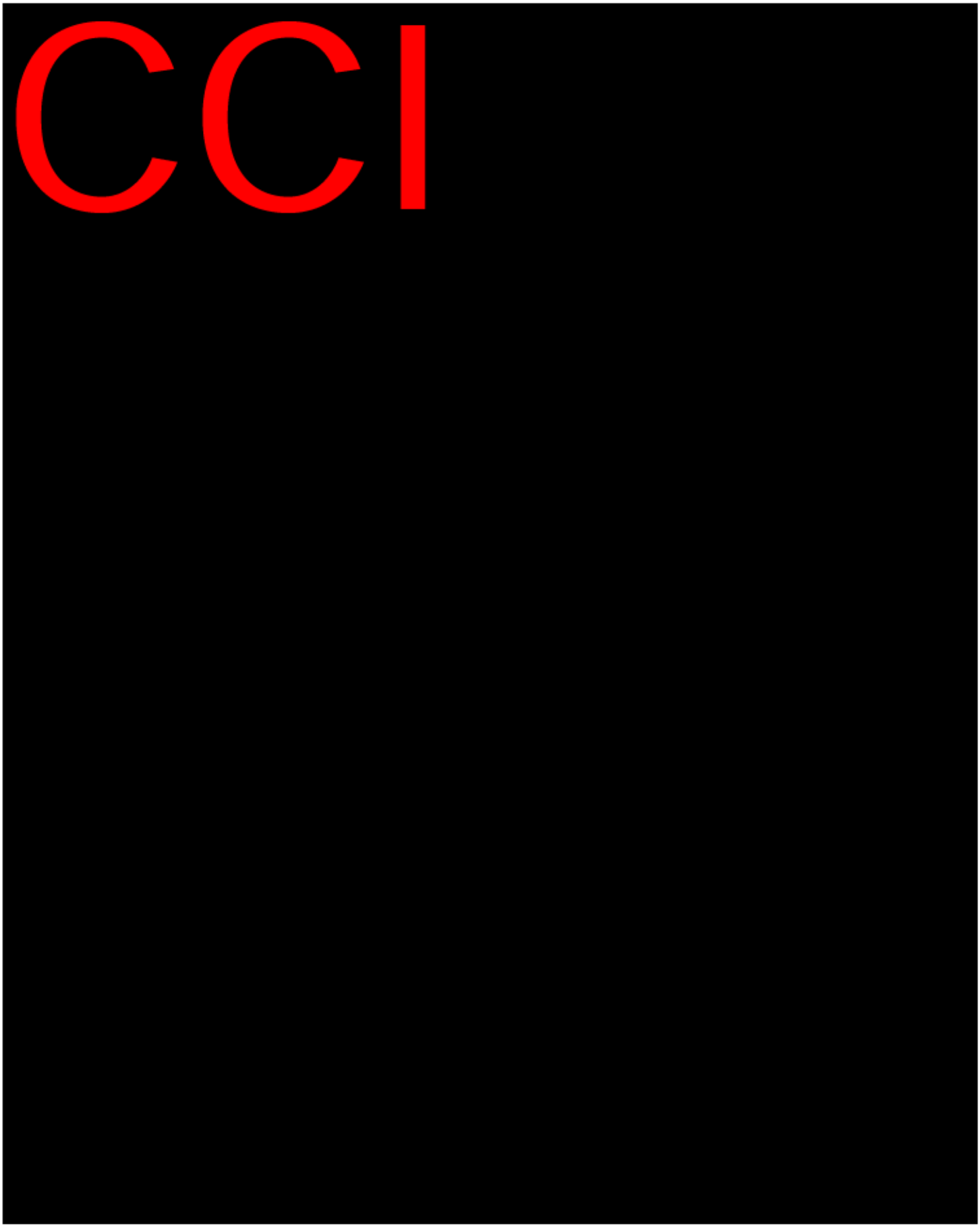
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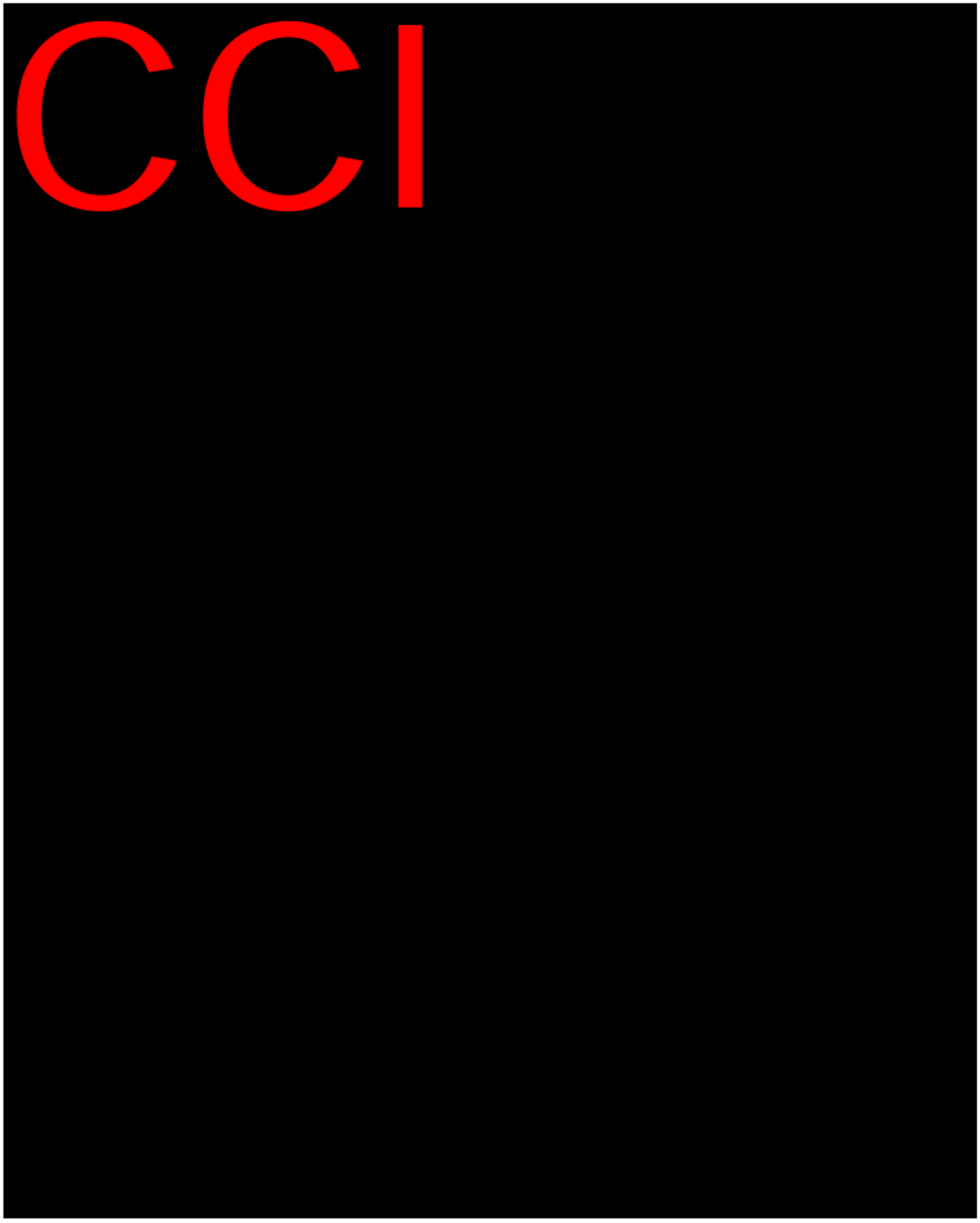
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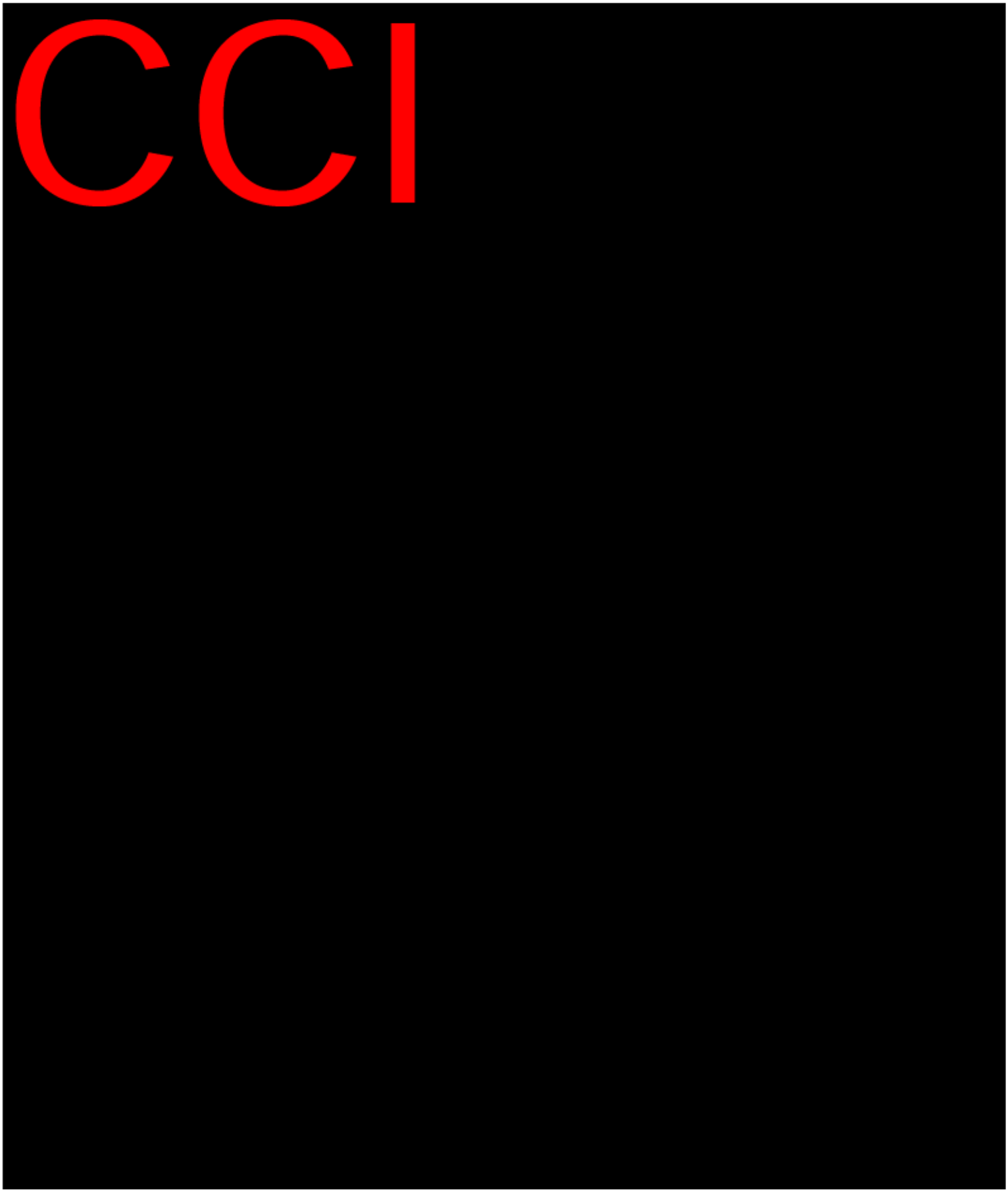
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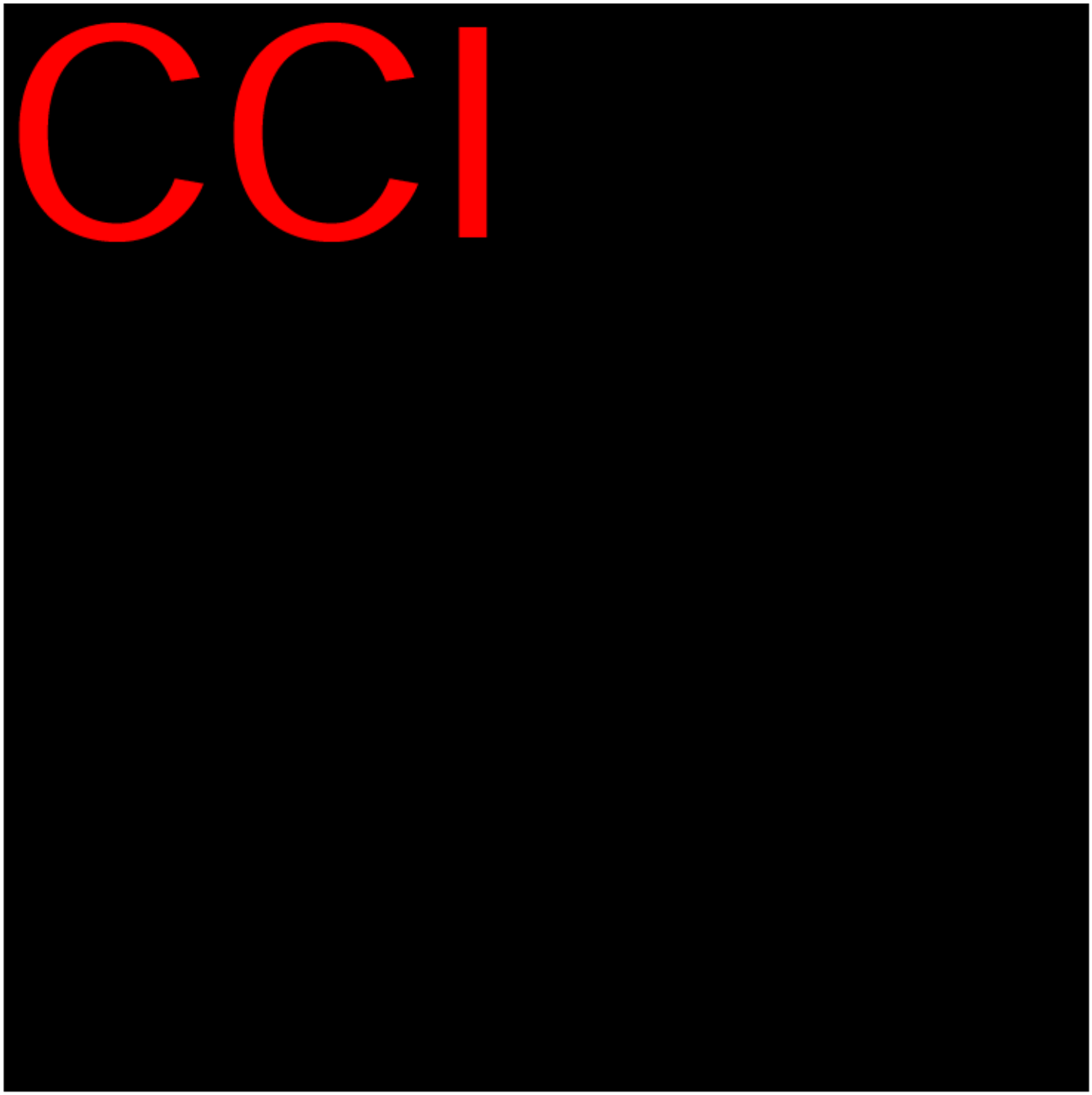
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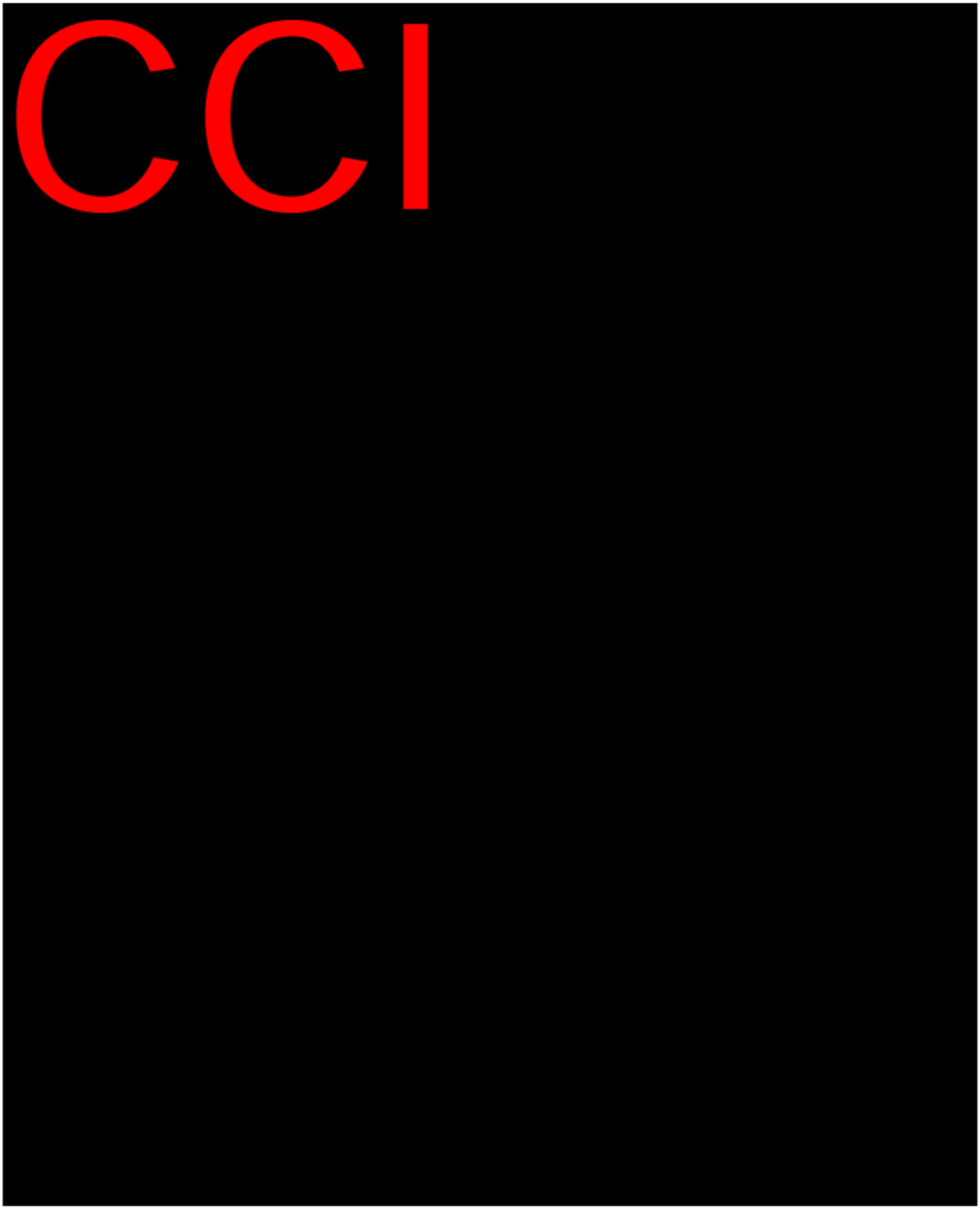
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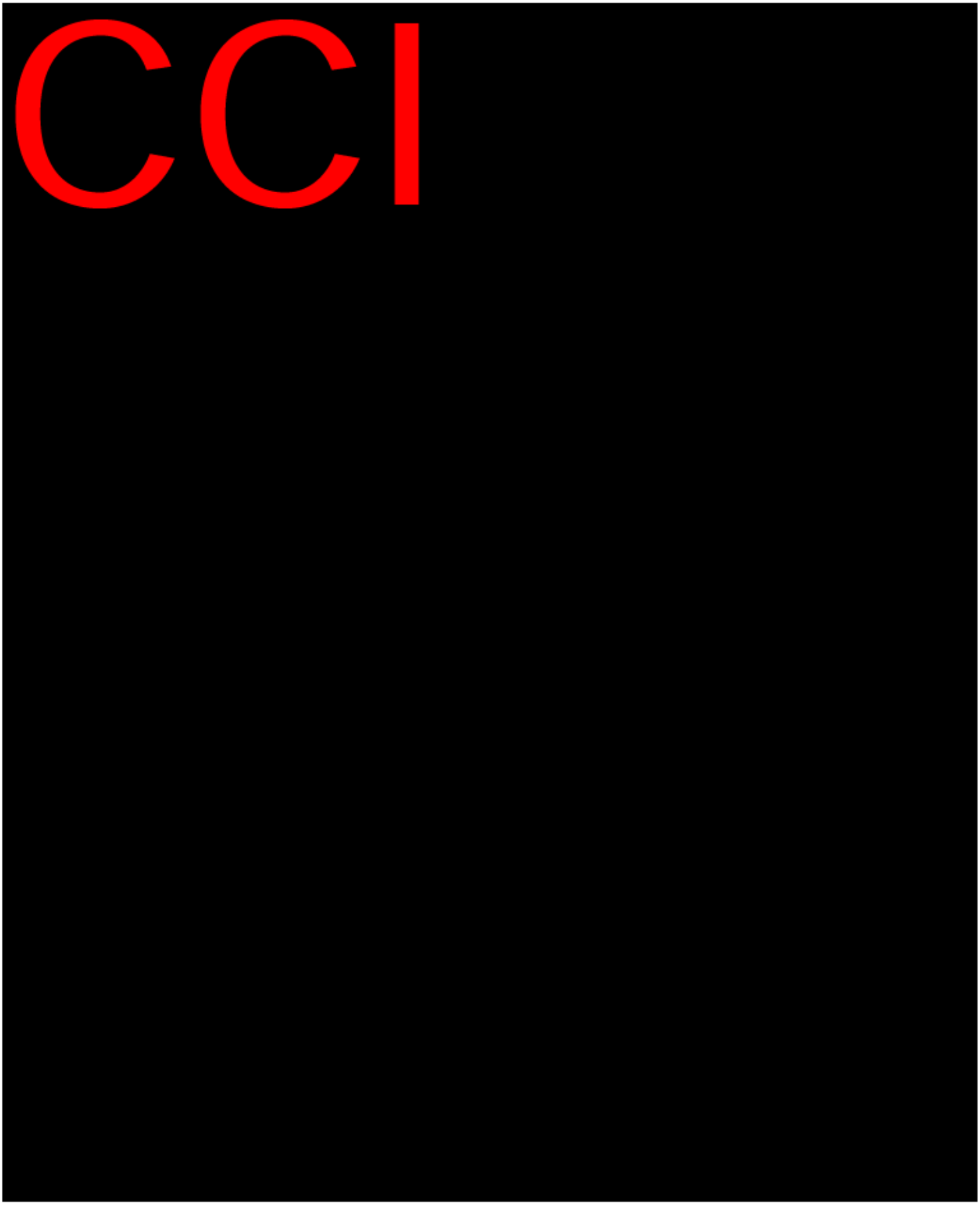
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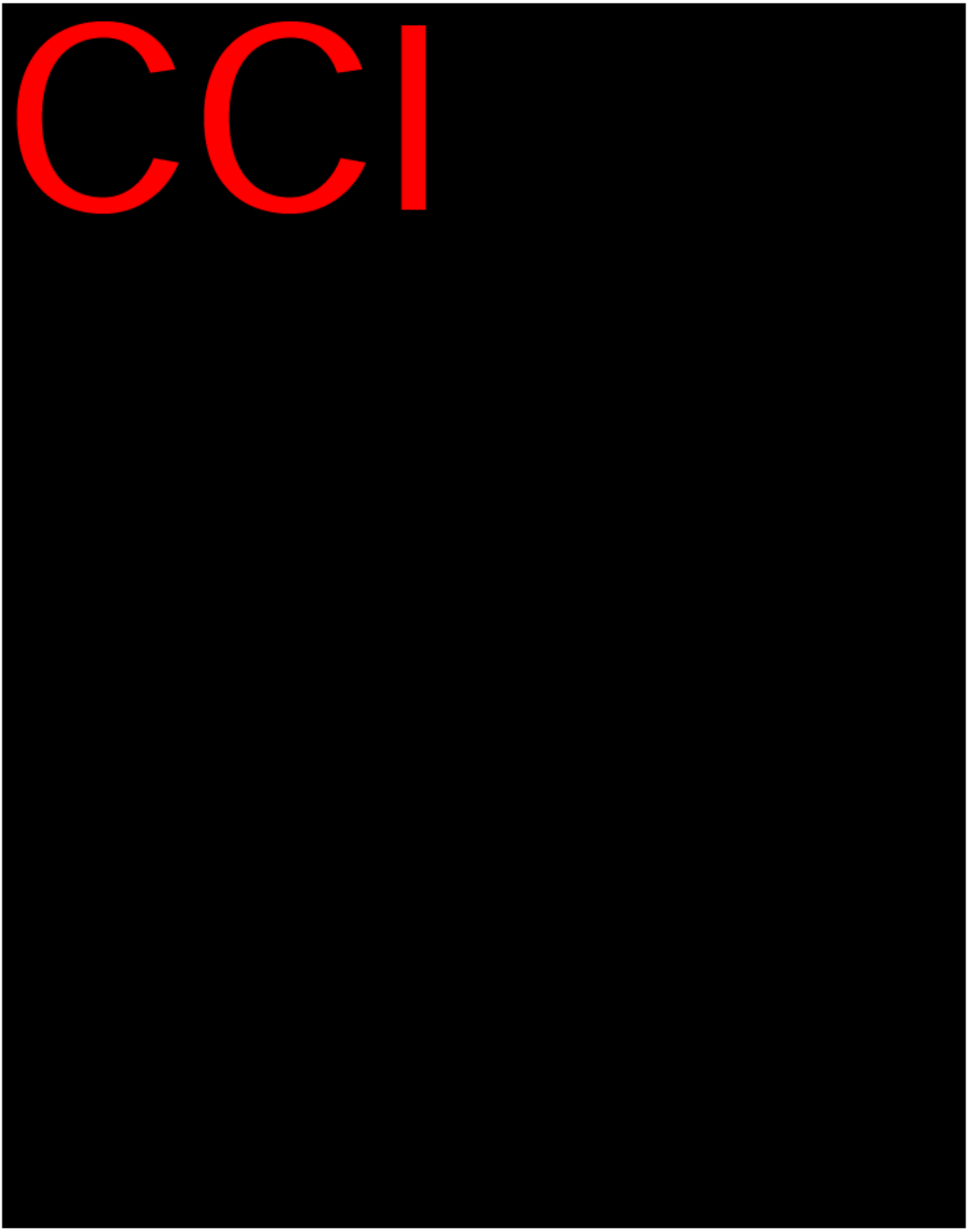
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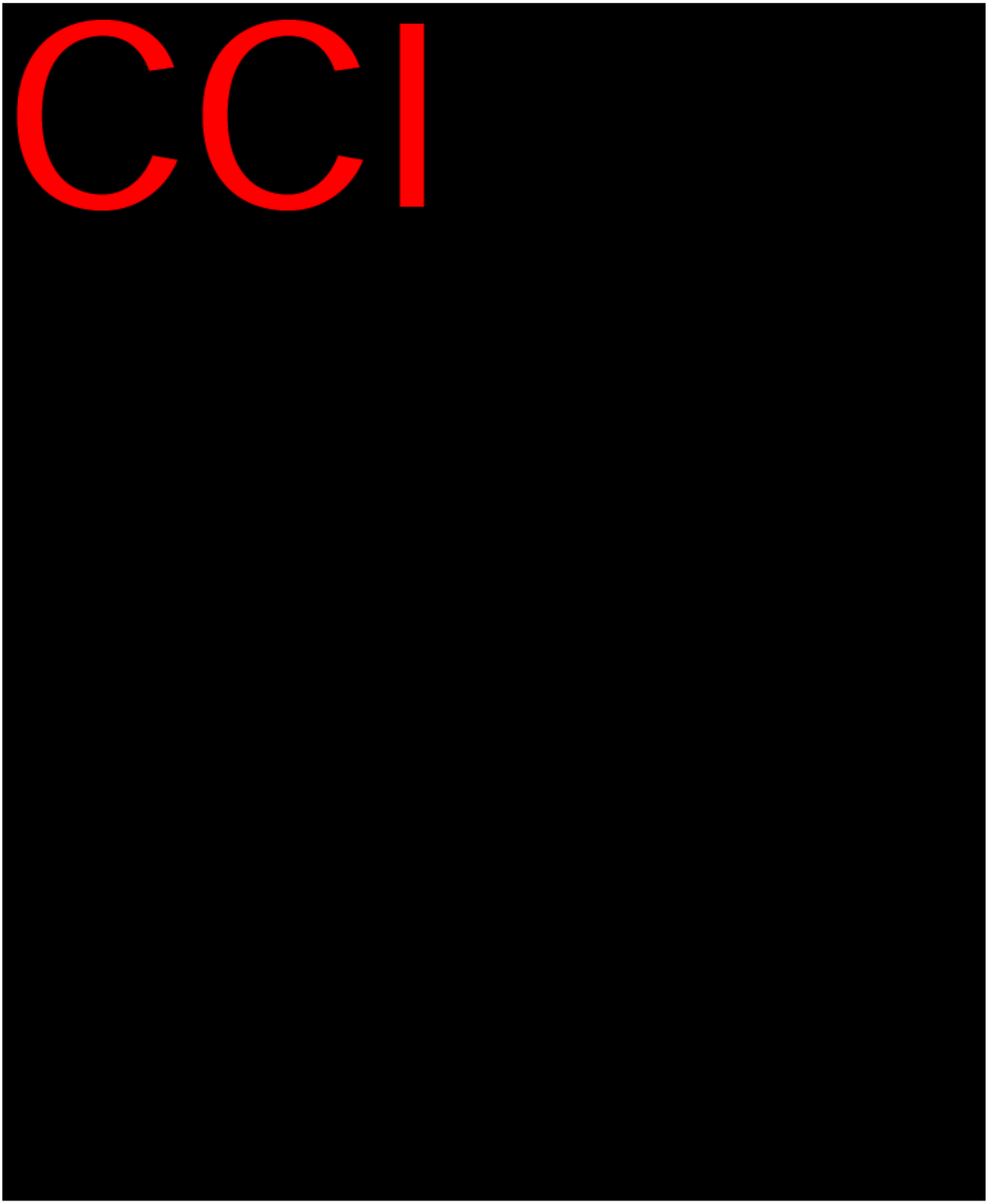
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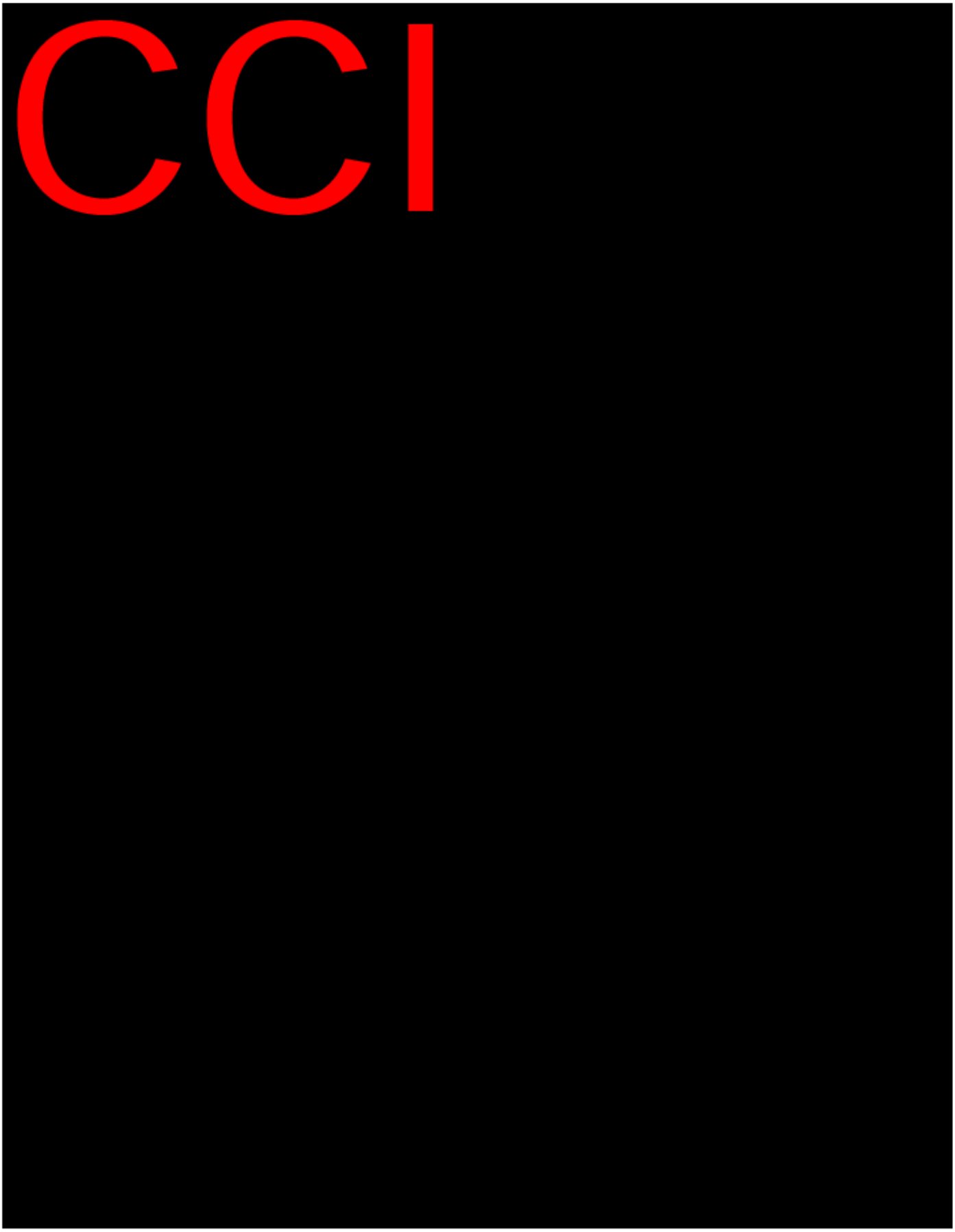
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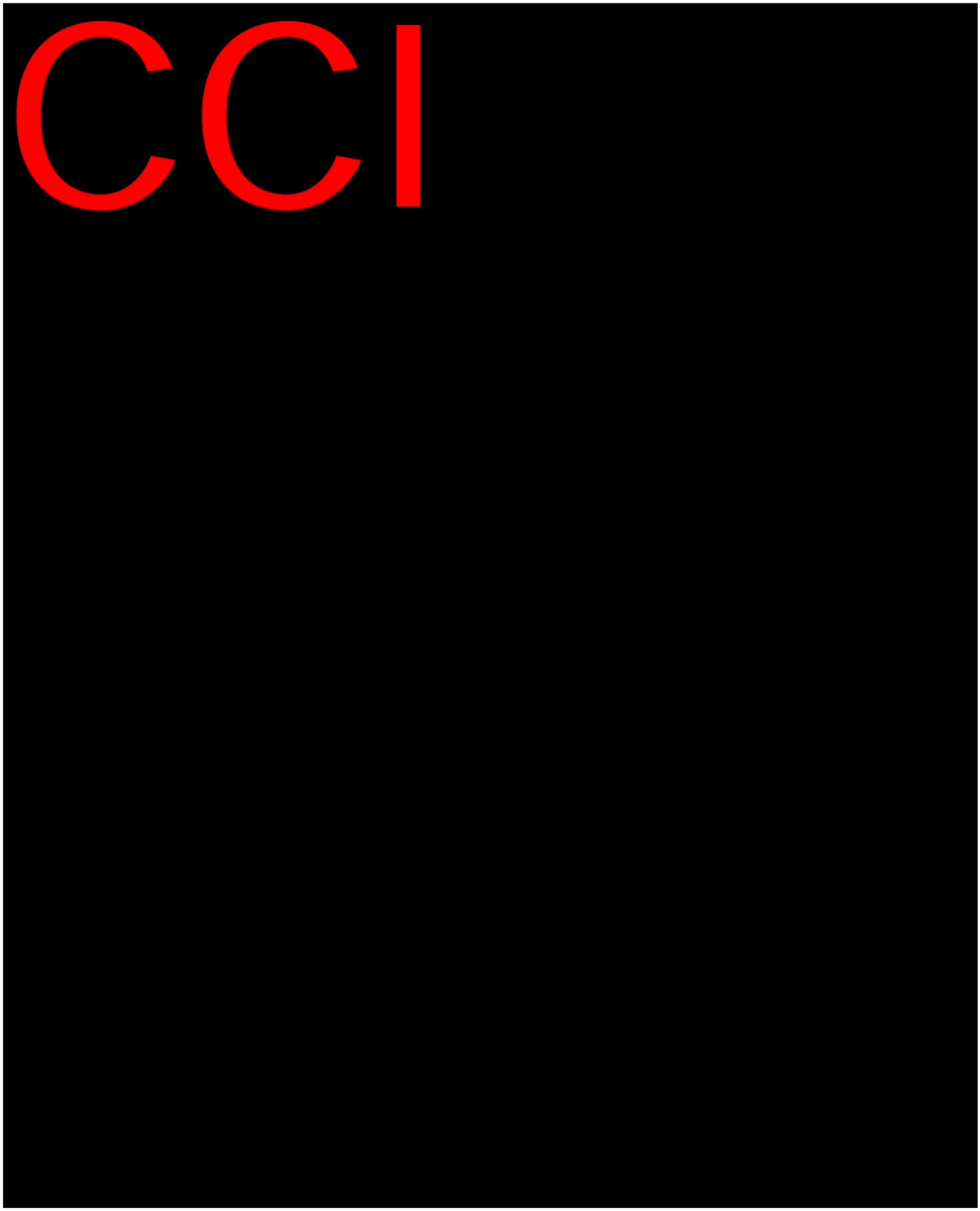
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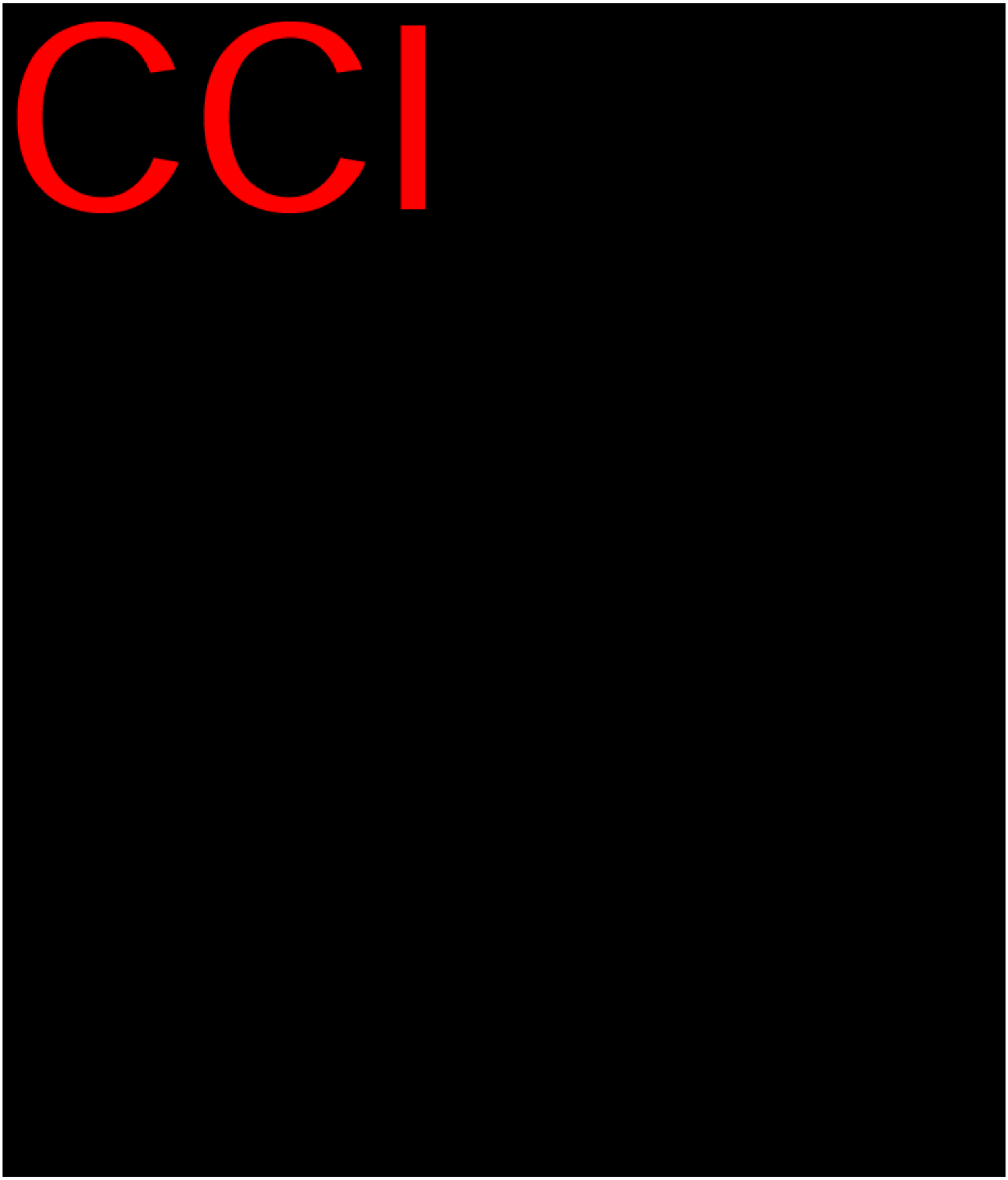
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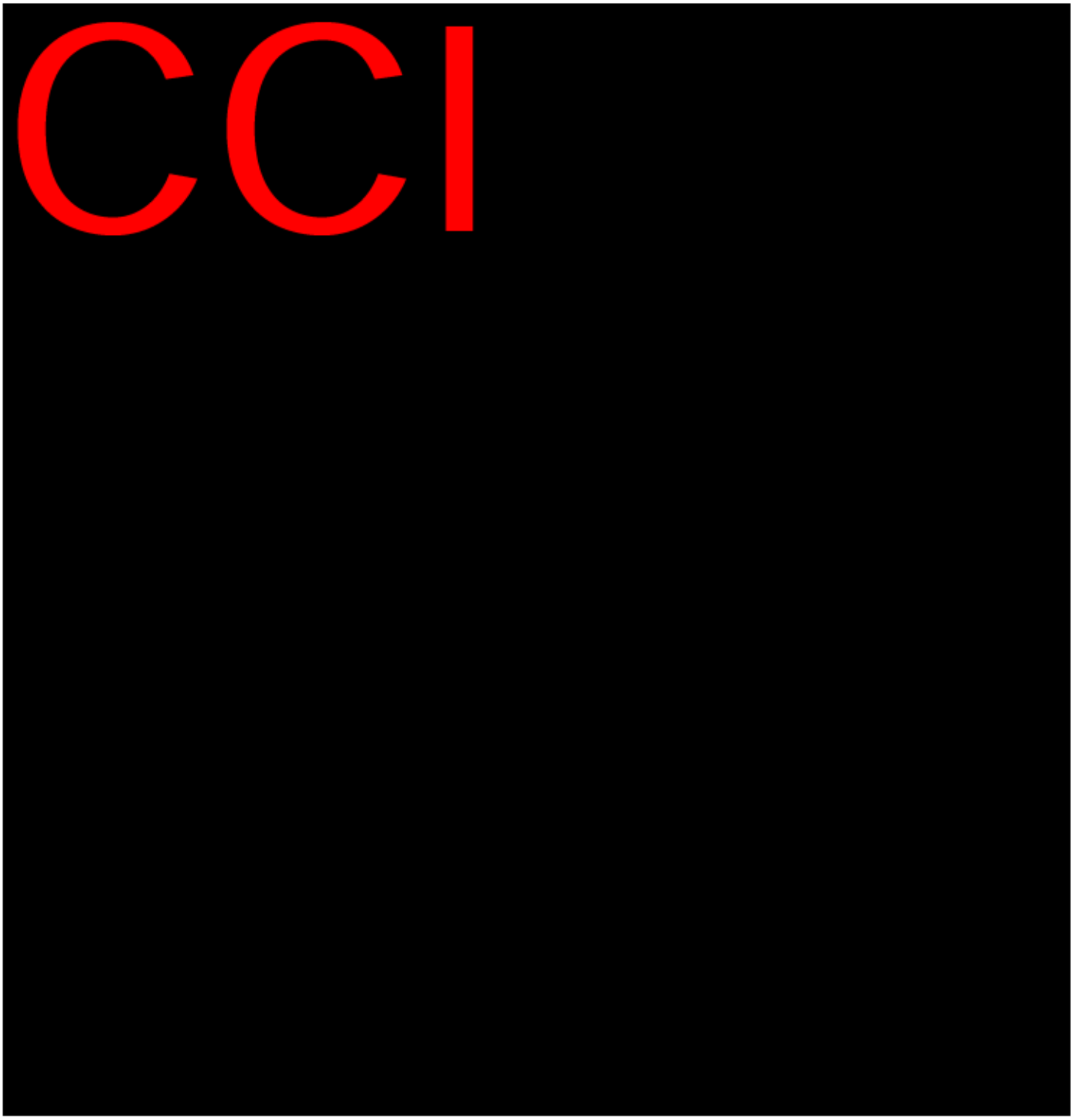
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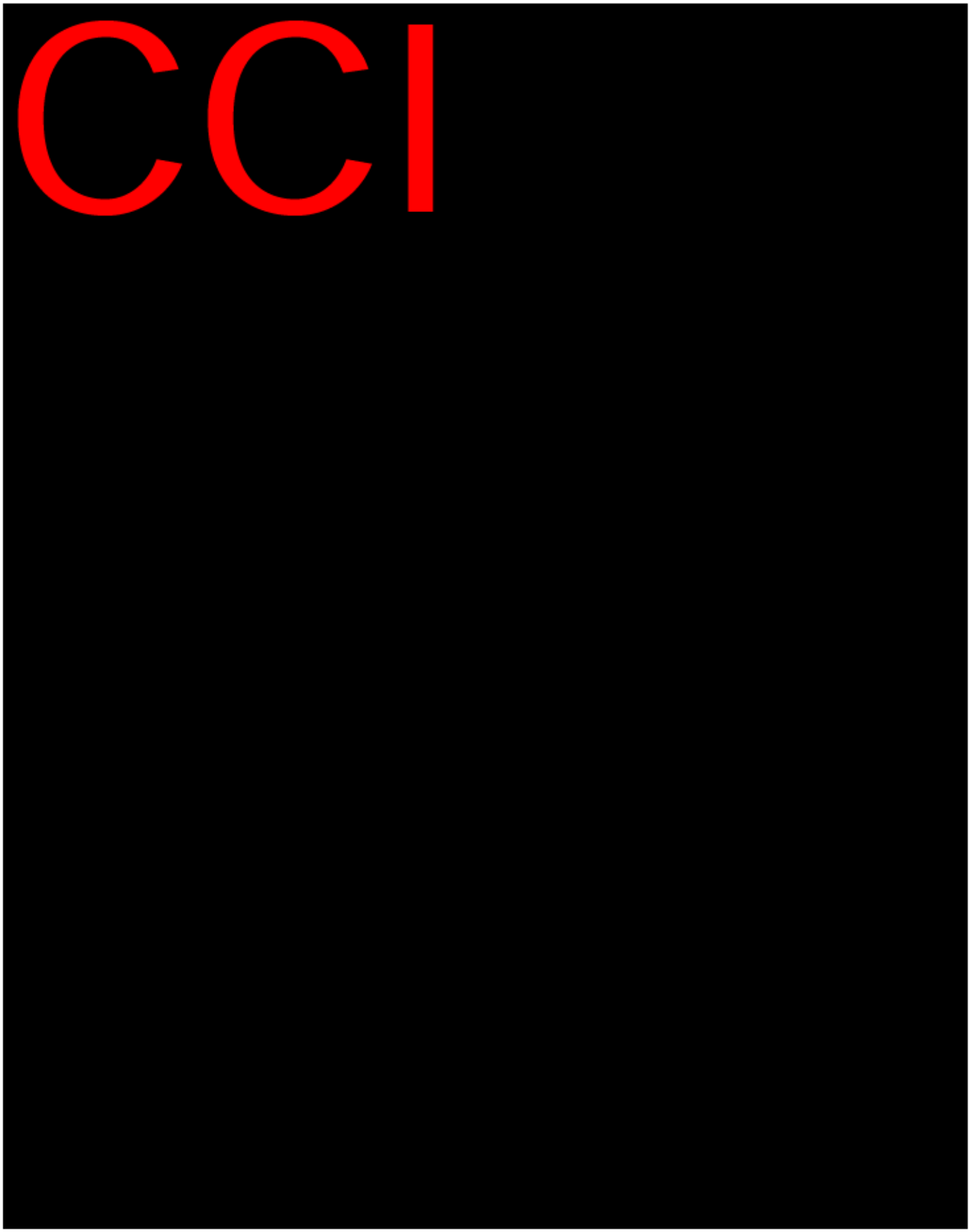
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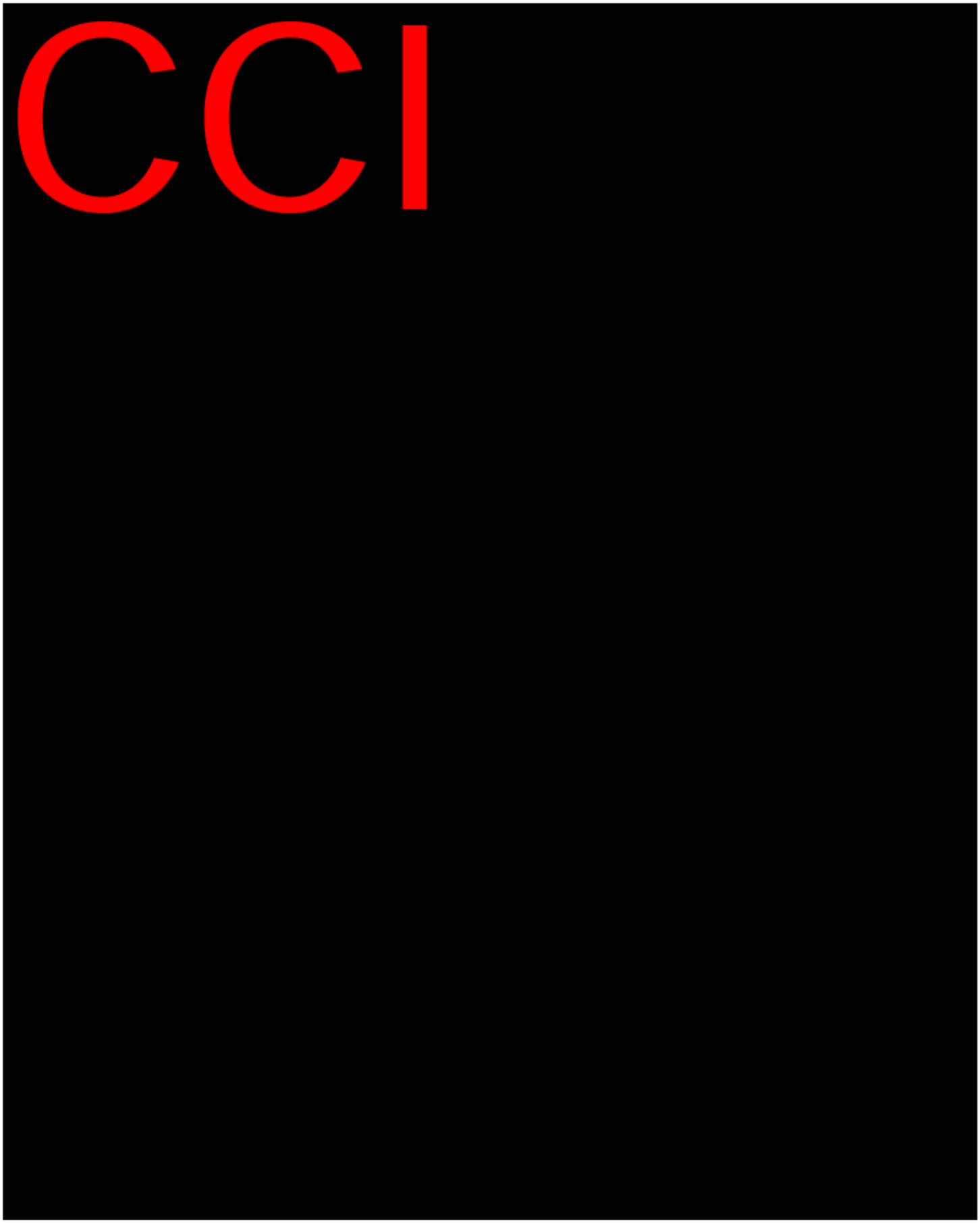
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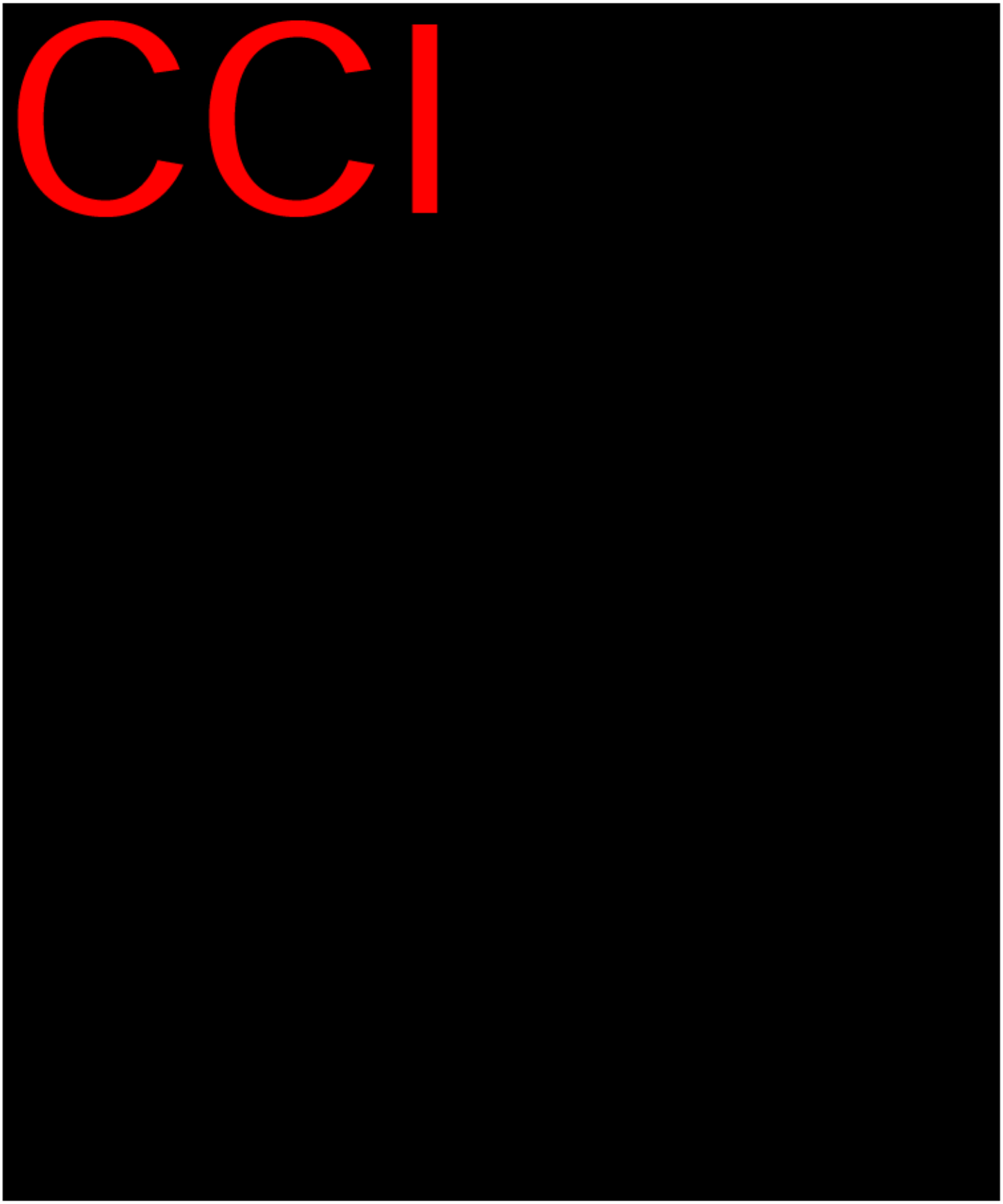
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