Statistical Analysis Plan: I1F-MC-RHBY (V2)

A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal-Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients With Axial Spondyloarthritis

NCT03129100

Approval Date: 19-Jun-2020

1. Statistical Analysis Plan: I1F-MC-RHBY: A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal-Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients with Axial Spondyloarthritis

Ixekizumab (LY2439821) Axial Spondyloarthritis

Study I1F-MC-RHBY is a Phase 3, multicenter, long-term extension study of 104 weeks in patients with axial spondyloarthritis that includes a double-blind, placebo-controlled, randomized withdrawal-retreatment period. The study duration will be up to 2 years for ixekizumab administration, and up to 2 years and 6 months for study participation over 4 periods.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

Approval Date: 19-Jun-2020 GMT

2. Table of Contents

Section **Page**

CCI

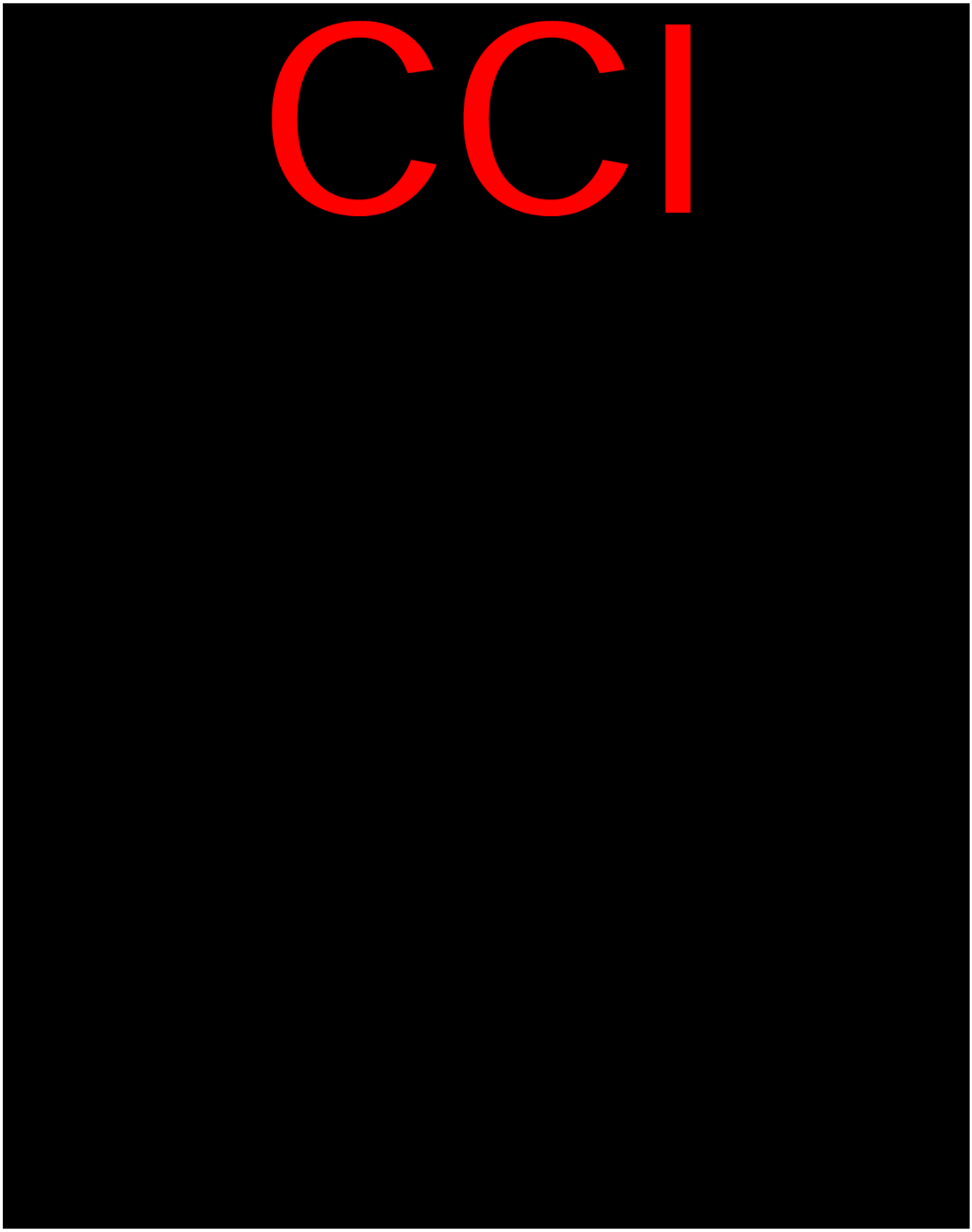
Table of Contents

Table **Page**

Table of Contents

Figure **Page**

Table of Contents


CCI


CCI

4. Study Objectives

Objectives	Endpoints
Primary	
• To evaluate in patients having achieved a state of sustained remission, whether the combined ixekizumab treatment group is superior to the placebo group in maintaining response during Period 2	• The proportion of patients in the randomized withdrawal population who do not experience a flare during Period 2
Major Secondary	
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response after randomized withdrawal	• The proportion of patients in the randomized withdrawal population who do not experience a flare during Period 2
• To evaluate in patients having achieved a state of sustained remission whether the combined ixekizumab treatment group is superior to the placebo group in maintaining response after randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during Period 2
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg Q4W treatment group is superior to placebo in maintaining response after randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during Period 2
Other Secondary	
• To evaluate in patients having achieved a state of sustained remission whether the combined ixekizumab treatment group, ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W is superior to the placebo group in maintaining response during Period 2	• The proportion of patients in the randomized withdrawal population with a 20% improvement in the Assessment of Spondyloarthritis International Society criteria (ASAS20), a 40% improvement (ASAS40), and improvement of at least 20% and improvement of at least 1 unit in at least 5 of 6 domains in the ASAS (ASAS5/6), ASAS partial remission, clinically important improvement (change of Ankylosing Spondylitis Disease Activity Score [ASDAS] ≥1.1 units), major improvement (change of ASDAS ≥2.0 units), inactive disease (ASDAS <1.3), and ASDAS <2.1 during Period 2 • Change from baseline in the individual components of the ASAS response criteria • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Proportion of patients with Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response from baseline • Change from baseline in ASDAS • Change from baseline in high sensitivity C-reactive protein (CRP) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Change from baseline in the measures of axial mobility: o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear), and BASMI individual components o Chest expansion o Change from baseline in occiput to wall distance • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and Spondyloarthritis Research Consortium of Canada Score (SPARCC) enthesitis score

Other Secondary	
	• The recovery (Tender Joint Count [TJC]=0, Swollen Joint Count [SJC]=0) and change from baseline of peripheral arthritis by TJC and SJC of 46/44 joints • The incidence rate of anterior uveitis or uveitis flares since baseline • Change from baseline in the following health outcomes measures: o Fatigue numeric rating scale (NRS) score o Quick Inventory of Depressive Symptomatology Self-Report-16 (QIDS-SR16) o 36-item Short Form Health Survey (SF-36), both physical and mental component scores o Assessments of Spondyloarthritis International Society–Health Index (ASAS HI) o European Quality of Life - 5 Dimensions 5 Level (EQ-5D-5L) o Work Productivity Activity Impairment-Spondyloarthritis (WPAI-SpA) o Jenkins Sleep Evaluation Questionnaire (JSEQ)
• To assess the combined ixekizumab treatment group, ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W for 2-year radiographic progression in spine in patients with active radiographic axSpA (rad-axSpA)	• Change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS score) from baseline of originating study • Proportion of patients with change in mSASSS score <2 from baseline of originating study to Week 56 in RHBY • Proportion of patients with no new syndesmophyte formation from baseline of originating study to Week 56 in RHBY
• To assess the efficacy of retreatment with ixekizumab following a flare during Period 2	• Proportion of patients who regain ASDAS <1.3 within 16 weeks after ixekizumab retreatment • Proportion of patients who regain ASDAS <2.1 within 16 weeks after ixekizumab retreatment • Proportion of patients who achieve/maintain an ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement, ASDAS clinically important improvement, ASDAS inactive disease, and ASDAS <2.1 within 16 weeks after ixekizumab retreatment • Proportion of patients who achieve/maintain an ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement, ASDAS clinically important improvement, ASDAS inactive disease, and ASDAS <2.1 through Week 64
• To determine the long-term treatment effect of 80 mg ixekizumab Q2W and 80 mg ixekizumab Q4W through Week 104	• The proportion of patients with ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, clinically important improvement, major improvement, ASDAS <2.1, and inactive disease • Change from baseline in the individual components of the ASAS criteria • Change from baseline in BASDAI • Proportion of patients with BASDAI50 response • Change from baseline in ASDAS • Change from baseline in CRP • Change from baseline in BASFI • Change from baseline in the measures of axial mobility: o BASMI (linear), and BASMI individual components

Other Secondary	
	○ Chest expansion ○ Change from baseline in occiput to wall distance • Change from baseline in MASES and SPARCC • The recovery (TJC=0, SJC=0) and change from baseline of peripheral arthritis by TJC and SJC of 46/44 joints • The incidence rate of anterior uveitis or uveitis flares • Change from baseline in the following health outcomes measures: ○ Fatigue NRS score ○ QIDS SR16 ○ SF-36 (both physical and mental component scores) ○ ASAS HI ○ EQ-5D-5L ○ WPAI-SpA ○ JSEQ
• To evaluate the development of anti-ixekizumab antibodies and its impact on the efficacy of ixekizumab	• Efficacy response rates listed below at Weeks 64 and 104 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: ○ Proportion of patients achieving ASAS40 ○ Proportion of patients achieving ASAS20 Proportion of patients achieving ASDAS <2.1
CCI	

5. Study Design

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

5.1. Summary of Study Design

Study RHBY is a Phase 3, multicenter, long-term extension study that includes a double-blind, placebo-controlled, randomized withdrawal-retreatment (RWR) period. The study duration will be up to 2 years for ixekizumab administration, and up to 2 years and 6 months for study participation over 4 study periods:

- Lead-In [**Period 1**]: 24 weeks (Week 0 to Week 24)
- Extension Period including Double-Blind, Placebo-Controlled, Randomized Withdrawal-Retreatment [**Period 2**]: 40 weeks (Week 24 to Week 64)
- Long-Term Extension Period [**Period 3**]: 40 weeks (Week 64 to Week 104)
- Post-Treatment Follow-Up [**Period 4**]: at least 12 weeks and up to 24 weeks after the date of the patient's early termination visit [ETV] or last regularly scheduled visit).

Patients who completed an originating study (RHBV, RHBW, or RHBX) through Week 52 may be eligible for enrollment into Study RHBY provided they fulfill study entry criteria for Study RHBY (see Protocol Section 6).

Study RHBY will evaluate the sustainability of clinical benefits, safety, and tolerability of ixekizumab treatment as well as the impact of ixekizumab on structural progression in patients with axial spondyloarthritis (axSpA). In addition, maintenance of response after treatment withdrawal will be evaluated in those patients having achieved a state of sustained remission, defined as 1 of the following:

- Ankylosing Spondylitis Disease Activity Score (ASDAS) <1.3 at Week 16 and Week 20.

OR

- ASDAS <1.3 at Week 16 and ASDAS <2.1 at Week 20

OR

- ASDAS <2.1 at Week 16 and ASDAS <1.3 at Week 20.

Figure RHBY.5.1 illustrates the study design. During the 24-Week Lead-In Period [Period 1]), all patients will receive active treatment in the form of ixekizumab 80 mg every 4 weeks (IXE80Q4W) or ixekizumab 80 mg every 2 weeks (IXE80Q2W).

[**Group A**]: Patients who DO NOT meet entry criteria for participation in the 40-week double-blind placebo-controlled RWR period will continue to receive the ixekizumab dose regimen that they are receiving at Week 24 during Periods 2 and 3.

[**Group B**]: For patients who DO meet entry criteria for participation in the 40-week double-blind, placebo-controlled RWR period (that is, patients having achieved a state of sustained remission),

- Patients in the ixekizumab 80 mg Q2W treatment group (IXE80Q2W) will be re-randomized to either IXE80Q2W or placebo at 2:1 ratio and will be stratified by geographic region (see Table RHBY.6.2) and originating study.
- Patients in the ixekizumab 80 mg Q4W treatment group (IXE80Q4W) will be re-randomized to either IXE80Q4W or placebo at 2:1 ratio and will be stratified by geographic region (see Table RHBY.6.2) and originating study.

After completion of the 40-week RWR period, patients will continue the same treatment that they are receiving at the end of Period 2, and will continue in the Long-Term Extension Period (Period 3).

Patients who have taken at least 1 study dose and who discontinue study treatment are to complete an early termination visit (ETV) and enter into Post-Treatment Follow-Up Period (Period 4) for at least 12 weeks and up to 24 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 study dose are not required to enter into the Post-Treatment Follow-Up Period.

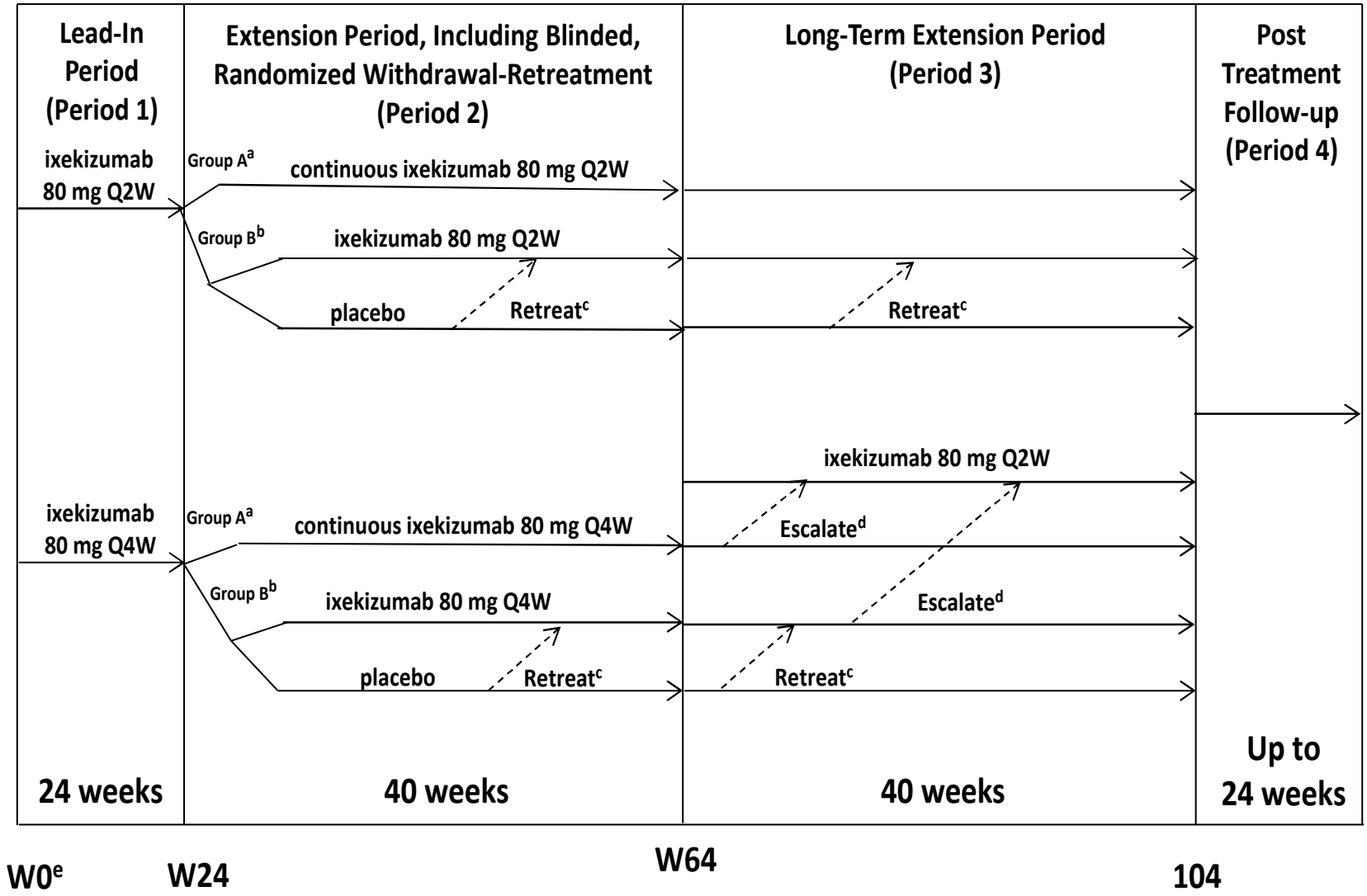


Figure RHBY.5.1. Illustration of study design for Clinical Protocol I1F-MC-RHBY.

(footnotes on next page)

Abbreviations: Q2W = once every 2 weeks; Q4W = once every 4 weeks; W = week.

[a] Patients in Group A will continue to receive the same ixekizumab dose regimen that they were receiving during Period 1.

[b] Only patients having achieved a state of sustained remission (Group B) are eligible for participation in the randomized withdrawal–retreatment period.

[c] Patients who experience a flare will be retreated with the ixekizumab treatment regimen that they were receiving prior to withdrawal. Flare status is determined by ASDAS score (Table RHBY.6.4). The interactive web-response system uses the flare status to dispense drug. Therefore, no missing data is allowed before discontinuation. If a component score is missing (eg, missing C-reactive protein due to COVID-19 mitigation plan) at an intermittent visit, the last nonmissing score is carried forward for the assessment.

[d] As of Week 64, patients receiving ixekizumab 80 mg Q4W during Period 3 may have their dose escalated to ixekizumab 80 mg Q2W if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control. However, for patients in Group B, escalation to ixekizumab 80 mg Q2W may occur only after the patient has been retreated upon flare with the ixekizumab treatment regimen received during Period 1 (ixekizumab 80 mg Q4W) for at least 12 weeks.

[e] For patients who were receiving ixekizumab in the originating study, the dose in the 24-week Lead-In Period (Period 1) will be based on the current dosing in the originating study. For patients in Study RHBX who were on placebo, patients will receive ixekizumab 80 mg Q4W.

5.2. Determination of Sample Size

It is estimated that approximately 750 patients will enter the long-term extension study (RHBY) after completion of Studies RHBV, RHBW, or RHBX. This sample size is estimated based on the 1-year retention rates from ixekizumab psoriasis studies and from 1 secukinumab radiographic (rad)-axSpA study (Baeten et al. 2015), which had a retention rate of approximately 85%. It is anticipated that approximately 30% of the 750 patients will meet the entry criteria for randomized-withdrawal (Sieper et al. 2015). Approximately 100 patients who achieved a state of sustained remission on IXE80Q4W will be randomized in a 2:1 ratio to IXE80Q4W or placebo, and approximately 100 patients who achieved a state of sustained remission on IXE80Q2W will be randomized in a 2:1 ratio to IXE80Q2W or placebo in the double-blind RWR period. This total sample size of 200 will provide over 99% power to detect a difference in the proportion of patients who do not experience a flare between the Combined Ixekizumab treatment group (including Q2W and Q4W) and placebo using a 2-sided Fisher's exact test at the 0.05 level, assuming the flare rates are 10% for ixekizumab and 70% for placebo. Sample size and power calculations are calculated using nQuery+nTerim 3.0.

5.3. Method of Assignment to Treatment

During the Lead-In Period (Period 1), patients who are previously receiving ixekizumab treatment during Studies RHBV and RHBW will, as of Week 0 in Study RHBY, continue to receive the same ixekizumab treatment regimen they are on at the end of the originating study, but now in open-label fashion.

For patients who are previously in Study RHBX, treatment during the Lead-In Period will be assigned as follows:

- patients who are rescued to open-label IXE80Q2W will remain on IXE80Q2W in open-label fashion.
- patients who are receiving blinded treatment with either IXE80Q2W or IXE80Q4W will continue on their ixekizumab dose regimen in blinded fashion.
- patients who are receiving blinded treatment with placebo will be assigned to receive blinded treatment with IXE80Q4W.

During the Extension Period, including RWR (Period 2), patients in Group A who do not meet entry criteria for RWR will continue to receive the same ixekizumab dose regimen that they are receiving during the Lead-In Period (IXE80Q2W or IXE80Q4W).

During the Extension Period, patients in Group B who have achieved a state of sustained remission, and meet the criteria for randomized withdrawal (RW) (see Section 5.1), will be assigned to treatment groups as follows by a computer-generated random sequence using an interactive web-response system (IWRS).

- Patients in the IXE80Q2W treatment group will be re-randomized to either IXE80Q2W or placebo at 2:1 ratio allocation and will be stratified by region and originating study.

- Patients in the IXE80Q4W treatment group will be re-randomized to either IXE80Q4W or placebo at 2:1 ratio allocation and will be stratified by region and originating study.

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.

During the Long-Term Extension Period (Period 3), patients will continue the same treatment that they are receiving at the end of Period 2.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter, Lilly). The statistical analyses will be performed using SAS® Version 9.4 or higher.

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

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

Change from baseline will be calculated as: observed postbaseline scores – baseline score.

For selective efficacy measures (including ASAS40 components, BASDAI score), percent improvement will be calculated as 100 × (baseline score – observed scores)/baseline score, unless otherwise specified. If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening, this measure will be negative.

Unless otherwise specified, baseline for effect in efficacy and health outcomes analyses is defined as the last available value before the first dose of study treatment in Period 2 from the originating study and, in most cases, will be the value recorded at Week 0 from the originating study. For safety analysis, baseline is defined as the last available value before the first dose at the start of each analysis period of interest in RHBY. For safety analyses using a baseline period, the baseline period is defined as the entire period, that there is no drug dispensed in, prior to the first injection of the drug in the analysis period of interest.

All confidence intervals (CIs) and statistical tests will be 2-sided with an α level of 0.05, unless otherwise specified. P-values which are ≥ 0.001, and ≤ 0.999, will be presented to 3 decimal places. All other p-values which are 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).

Section 6.1.1 describes the populations for analyses and Table RHBY.6.1 displays analysis purpose, treatment groups, and group comparisons for each analysis period and analysis population.

6.1.1. Analysis Populations

The following analysis populations will be used to address the study objectives.

Lead-In Period Safety Population: Unless otherwise specified, safety summaries for Combined Periods 1, 2, and 3 will be conducted on the Lead-In Period Safety Population, defined as all patients who receive at least 1 dose of ixekizumab in Period 1 in RHBY. Patients who do not meet entry criteria for participation in the randomized withdrawal-retreatment period (Group A) will continue to receive ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W. Patients who meet the entry criteria (Group B) may be randomized to ixekizumab or placebo at Week 24. Patients randomized to placebo may be retreated upon flare with the ixekizumab regimen that they received in Period 1. The data while on placebo is not included in the combined period analysis. For immunogenicity data analysis during the combined periods 1, 2, and 3, all data will be included regardless of being re-randomized to placebo or ixekizumab. Patients will be analyzed according to the treatment they were receiving at the start of Period 1.

Long-Term Ixekizumab Treatment Efficacy Population: Unless otherwise specified, efficacy and health outcome for Combined Periods 1, 2, and 3 will be summarized for the Long-Term Ixekizumab Treatment Efficacy Population, defined as patients who are randomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W at Week 0 of the originating studies and consistently receive the same treatment regimen through Week 64 in RHBY. Patients who were randomized to placebo or adalimumab in any of the originating studies, patients who switched from IXEQ4W to open label to IXEQ2W during the originating study of RHBX, patients who were randomized to placebo during Period 2 of RHBY, and patients who were retreated during Period 2 of RHBY are not included in this population. Patients will be analyzed according to the ixekizumab regimen they were randomized to at Week 0 of the originating study.

Ixekizumab Structure Population: The analysis of 2-year radiographic progression in spine, measured by the change in mSASSS in patients with active rad-axSpA, will be conducted on Ixekizumab Structure Population, defined as all patients who i) are from either RHBV or RHBW study; and ii) have mSASSS data at both Week 0 in the originating study and Week 56 in RHBY.

Randomized Withdrawal (RW) Intent-to-Treat (ITT) Population: Efficacy and health outcome analyses for Period 2 will be conducted on RW ITT Population, defined as all patients who achieved a state of sustained remission and were randomized to 40-week double-blind placebo-controlled RWR period (Group B), even if the patient does not receive the correct treatment or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they are assigned.

RW Safety Population: Safety analyses will be conducted on the RW Safety Population, defined as all randomized patients in Group B who have received at least 1 dose of study

treatment after randomization in the specified period. Patients will be analyzed according to the treatment to which they are assigned.

Flare Population: Defined as all randomized patients in Group B who experience a flare after randomization at Week 24. Efficacy summaries will be conducted for Period 2 and Combined Periods 2 and 3 on the Flare Population who receive at least one injection of ixekizumab retreatment after flare in the Combined Periods 2 and 3. Patients will be analyzed according to the treatment to which they are assigned at randomization and the retreatment.

Dose Escalation Population: Exploratory efficacy summaries will be conducted for Period 3 on Dose Escalation Population, defined as all patients (from Group A and Group B) who have been treated ixekizumab 80 mg Q4W for at least 12 weeks, and had their dose escalated to ixekizumab 80 mg Q2W (determined by investigator).

Follow-Up Period Population: Safety analysis for Period 4 will be conducted on the Follow-Up Period Population, defined as all patients who have completed an originating study (RHBV, RHBW, or RHBX) through Week 52 and have entered the Post-Treatment Follow-Up Period (Period 4) in RHBY. Patients will be analyzed according to the treatment they are taking before entering Period 4.

Table RHBY.6.1 displays analyses purpose and treatment groups for each analysis population and study period.

Table RHBY.6.1. Treatment Groups and Major Patient Populations for Analysis Periods for Study RHBY

Population	Period	Analyses	Treatment Groups	Group Comparisons
Lead-In Period Safety Population	Combined Periods 1 & 2 Combined Periods 1, 2, & 3	Safety	IXE80Q2W IXE80Q4W Total IXE	Descriptive No inferential statistics
Long-Term Ixekizumab Treatment Efficacy Population	Combined Periods 1 & 2 Combined Periods 1, 2, & 3	Efficacy and health outcomes	IXE80Q2W[a] IXE80Q4W[a] Total IXE	Descriptive No inferential statistics
RW Safety Population	Period 2 Period 3	Safety	IXE80Q2W IXE80Q4W Total IXE Placebo	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo
RW ITT Population	Period 2 Combined Periods 2 & 3	Efficacy and health outcomes	IXE80Q2W IXE80Q4W Total IXE Placebo	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo
Ixekizumab Structure Population	At Week 56 for a 2-year assessment	Efficacy	IXE80Q2W IXE80Q4W Total IXE	Descriptive No inferential statistics
Flare Population with retreatment	Period 2, Combined Periods 2 and 3	Efficacy	PBO/IXE80Q2W PBO/IXE80Q4W PBO/IXE IXE80Q2W/IXE80Q2W IXE80Q4W/IXE80Q4W IXE/IXE	Descriptive No inferential statistics
Dose Escalation Population	Period 3	Efficacy	PBO/IXE80Q4W, IXE80Q4W/ IXE80Q4W Total	Descriptive No inferential statistics
Follow-Up Population	Period 4	Safety	IXE80Q2W IXE80Q4W Total IXE Placebo	Descriptive No inferential statistics

Treatment Groups and Major Patient Populations for Analysis Periods for Study RHBY

Abbreviations: ITT = intent-to-treat; IXE = ixekizumab; IXE-Structure = patients from Ixekizumab Structure Population; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; PBO = placebo; RW = randomized withdrawal; Total IXE = IXE80Q2W and IXE80Q4W combined in RHBY; vs. = versus.

[a] IXEQ2W is a group of patients who have been treated consistently with ixekizumab 80 mg every 2 weeks since Week 0 in the originating studies through Week 64 of RHBY. IXEQ4W is a group of patients who have been treated consistently with ixekizumab 80 mg every 4 weeks since Week 0 in the originating studies through Week 64 of RHBY.

6.1.2. General Considerations for Analyses during the Combined Periods 1, 2, and 3

Combined Periods 1 and 2 starts at the first injection of IXE80Q2W or IXE80Q4W in RHBY, and ends on the injection date of Week 64 (Group A: Visit 10/Group B: Visit 515) or next injection date after Week 64 if injection date of Week 64 is missing which is the start date of Period 3, or at ETV prior to Week 64.

Combined Periods 1, 2, and 3 starts at the first injection of IXE80Q2W or IXE80Q4W in RHBY, and ends on the date of Week 104 visit (Group A: Visit 14/Group B: Visit 519) or at ETV prior to Week 104.

6.1.2.1. Lead-In Period Safety Population

Safety data will be summarized for Combined Periods 1 and 2 and Combined Periods 1, 2, and 3 for the Lead-In Period Safety Population by Combined Ixekizumab treatment group (Total IXE) and each of the IXE80Q2W and IXE80Q4W groups without inferential statistics.

For safety analyses, unless otherwise specified, the following baselines will be used:

- For treatment-emergent adverse events (TEAEs):
  - For patients who were not randomized to placebo at Week 24 during the Combined Periods, the baseline is the events ongoing prior to the first injection in Period 1;
  - For patients who are randomized to placebo at Week 24 and then are retreated with ixekizumab, the baseline for TEAEs during Period 1 is the events ongoing just prior to the first injection in Period 1, but the baseline for TEAEs after retreatment of ixekizumab is the events ongoing just prior to the first injection of retreatment during Periods 2 and 3 Combined.
- For change from baseline to minimum/maximum postbaseline, to last observation and to each scheduled postbaseline visit for laboratory and vital signs, and for treatment-emergent abnormal laboratory and vitals, the baseline is the last nonmissing value prior to the first injection in Period 1, regardless of changes of treatment regimen after Week 24.

The categorical safety measures will be summarized with frequency counts and incidence rates.

6.1.2.2. Long-Term Ixekizumab Treatment Efficacy Population

Efficacy and health outcome data will be summarized for the Long-Term Ixekizumab Treatment Efficacy Population (see definition in Section 6.1.1) from Week 0 in the originating study to the visit at Week 64 and Week 104, respectively, in RHBY. For patients who were escalated from ixekizumab 80 mg Q4W to ixekizumab 80 mg Q2W after Week 64, only data while on ixekizumab 80 mg Q4W will be included. If the patient early terminates the originally assigned treatment (including retreatment and escalation) prior to Week 104, then the modified nonresponder imputation (mNRI) method will be applied for categorical endpoints, and modified baseline observation carried forward (mBOCF) will be applied for continuous endpoints from the early termination visit through Week 104.

The long-term treatment effect on a categorical variable is measured by the proportion of patients who have achieved or maintained a response (see algorithm in Table RHBY.6.4) through Week 64 and Week 104, respectively, and the long-term treatment effect on a continuous variable is measured by change (or percent improvement) from baseline in the originating study.

The long-term treatment effect in categorical variables using observed cases, and continuous variables using observed cases and mBOCF will be summarized (as described in Section 6.1) by treatment group (see Table RHBY.6.1) at each scheduled visit from Week 0 in originating study. An alternative method to handle the missing data after Week 64 for the period of Week 0 in the originating study to Week 104 in RHBY, mNRI method will be applied for categorical variables and mixed model for repeated measures (MMRM) will be applied for continuous variables. Data will also be summarized graphically using the response rate for categorical variables and mean for continuous variables by group at each scheduled visit. The time points during the Extension Period (Period 2) will follow the scheduled visits for group A patients with between-visits-interval of 8 weeks.

When the MMRM is used, the model will include treatment, originating study, geographic region, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors. The covariance structure to model the within-patient errors will be unstructured. The restricted maximum likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. The least-squares (LS) means will be reported to assess the maintenance of treatment effect; the 95% CI will also 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.

6.1.3. General Considerations for Analyses during the Extension Period Including the Double-Blind RW Period (Period 2)

6.1.3.1. RW ITT and RW Safety Populations

For patients who are randomized in Period 2 (group B), comparisons between Combined Ixekizumab treatment group and placebo, as well as between each ixekizumab regimen (80 mg Q2W or 80 mg Q4W) and placebo, will be performed for all analyses at each scheduled visit in Period 2 including Visit 515 at Week 64.

Period 2 starts at the first injection of study treatment after randomization (at Week 24) and ends at the following study events:

- Prior to the first injection of study treatment at Week 64 (Visit 515) for not retreated patients who have completed visit at Week 64. If injection at Week 64 is missing, the next injection date after Week 64 is used;
- Prior to the first injection of retreatment for patients who have been retreated within Period 2;
- ETV prior to Week 64.

For patients who are in the RW ITT Population and have been retreated with the ixekizumab treatment regimen due to a flare or any other reasons, only data prior to the time of the retreatment will be included in the analysis for Period 2. Data after retreatment will be imputed using nonresponder imputation (NRI) method for categorical variables and mBOCF method for continuous variables.

The observed values after retreatment will be used for other specified analysis, for example, efficacy analysis for Flare Population with Retreatment.

For efficacy and health outcomes, baseline is defined as the last available value before the first dose of study treatment in Period 2 from the originating study and, in most cases, will be the value recorded at Week 0 from the originating study.

The primary analysis method for treatment comparisons of categorical binary efficacy and health outcome variables will be a logistic regression with treatment group, geographic region, and originating study as factors using PROC Logistic with Wald method. The odds ratio and 95% CIs will be reported; treatment difference and 95% CI will also be reported. In the case when logistic regression model does not produce statistical results due to sparse data, Fisher's exact test will be used. Same analysis will also be carried out at each of other scheduled visits in Period 2.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time (from Week 24 in RHBY) to flare. The number of patients at risk and experiencing flare by each scheduled visit during Period 2 will be presented by treatment group. The Kaplan-Meier estimate of the proportion of patients experiencing flare will be presented for each scheduled visit. Treatment group comparisons will be performed using the log-rank test with strata of geographic region and originating study. A Kaplan-Meier plot of time to the first flare by treatment group will also be provided.

Time to the first flare is defined as:

Time to the first flare (weeks) = (Date of the first flare during the analysis period

– Date of the randomization at Week 24 + 1)/7

Patients completing the treatment period without flare will be censored at the date of completion of the analysis period (eg, for Period 2, it is the date of Week 64 injection, or the last scheduled visit in the period if Week 64 injection date is missing). Patients without flare and a date of treatment period completion or a date of discontinuation will be censored at date of last dose in

the treatment period or date of last attended visit in the treatment period (scheduled or unscheduled), whichever is later.

Figures showing the proportion of patients not-experiencing flare at each scheduled visit within each treatment group will be provided. Figures showing the proportion of patients with ASAS20, ASAS40, ASAS partial remission, BASDAI50 and ASDAS inactive disease at each scheduled visit within each treatment group may also be provided.

The primary analyses for the continuous efficacy and health outcomes variables (see derivation in Sections 6.10.4 and 6.11) will be analyzed using analysis of covariance (ANCOVA) with mBOCF for missing data. The model will include treatment, Week 24 value, baseline value, geographic region, and originating study. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For variables that are not collected at each postrandomization visit due to early discontinuation visits, data may exist at visits where the variable is not scheduled to be collected. Such data will be used in shift analyses, change from baseline to mBOCF endpoint analyses and other categorical analyses for the RW ITT and Safety Populations.

For safety analysis for the RW Safety Population, baseline is defined as the last nonmissing assessment prior to the first injection of study treatment in Period 2.

Fisher's exact test will be used for all adverse event (AE), 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.

6.1.3.2. Flare Population

For patients who experienced a flare (Flare Population), a set of selected key efficacy outcomes at time of flare will be summarized.

For the Flare Population with Retreatment in Period 2, the period starts at the time of first injection of the retreatment of ixekizumab 80 mg Q2W or 80 mg Q4W following the flare and ends on the date of Period 2 defined in Section 6.1.3.1.

Summary statistics will be provided based on the Flare Population with Retreatment for a subset of efficacy outcomes: the proportion of patients who regain response in ASDAS <1.3, ASDAS <2.1, and who achieve/maintain an ASDAS<1.3, ASDAS<2.1, ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement and clinically important improvement within 16 weeks after the ixekizumab retreatment for patients who have 16 weeks of retreatment. No inferential statistics will be provided. The Kaplan-Meier estimates of the proportion of patients who first regain response on the variables of interest will be carried out at each retreatment interval (4 weeks, 8 weeks, etc.) up to 40 weeks. If an ongoing patient has not regained response by 16 weeks or Week 64, the patient will be censored at 16 weeks and Week 64, respectively. For time to response through Week 64, if a patient discontinued the study prior to Week 64, the patient will be censored at the date of their last visit during Period 2.

For counting regaining a response, once a patient has a response, the status is cumulative and carried forward. This counting process starts at the first visit when the retreatment is initiated. For counting achieving/maintaining a response, the status may change with time and the status depends on the response at each visit and does not depend on the previous visit.

6.1.4. General Consideration for Analyses at Week 56 for the 2-year Radiographic Progression in Spine

Assessment of 2-year radiographic progression in the spine from baseline in studies RHBV and RHBW to Week 56 (Group A: Visit 9/Group B: Visit 513) in RHBY will be evaluated for the Ixekizumab Structure Population (Ixe-Structure) as defined in Section 6.1.1.

Descriptive statistics will be provided for the 2-year radiographic progression in spine measured by change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), the proportion of non-progressors measured by change in Total mSASSS <2 and mSASSS <=0, respectively, and proportion of patients with no new syndesmophyte will be summarized as well.

Cumulative Probability Plot for change from baseline in mSASSS at year 2 will be provided for each ixekizumab treatment group.

Analysis will be done for Ixekizumab Structure Population who have been treated with ixekizumab for at least 24 months, namely who were initially assigned ixekizumab 80 mg Q4W or Q2W in originating studies and not re-randomized to placebo at Week 24 in RHBY. Data will also be summarized for all patients available.

Additional analysis will be repeated for Ixekizumab Structure Population, and Ixekizumab Structure Population who did not participated in the RW period.

6.1.5. General Considerations for Analyses during the Long-Term Extension Period (Period 3)

Unless otherwise specified, Period 3 starts at the first injection of study treatment at Week 64 or next injection date after Week 64 if injection date of Week 64 is missing and ends on the date of Week 104 or the ETV before the date of Week 104.

6.1.5.1. Dose Escalation Population

For the Dose Escalation Population, Period 3 starts at the time of first injection of the escalated dose of ixekizumab 80 mg Q2W and ends on the date of Week 104 or the ETV before the date of Week 104.

Summary statistics will be provided for selected efficacy outcomes (including ASDAS clinically important improvement in disease activity) at each scheduled visit after the escalated treatment. No inferential statistics will be provided.

6.1.5.2. RW Safety Population

Unless otherwise specified, for the safety analyses during Period 3, baseline is defined as the last nonmissing assessment prior to the first injection of study treatment in Period 3 (mostly at

Week 64). For TEAEs, baseline is the events ongoing just prior to the first injection of study treatment in Period 3.

Summary statistics will be provided for AEs. No inferential statistics will be provided.

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

Period 4 starts at the date of the visit (Group A: Visit 14/Group B: Visit 519) at Week 104 or at ETV and ends at study completion or at the last visit prior to study discontinuation. Safety data collected during Period 4 will be summarized by treatment that the patients are taking prior to entering Period 4.

For the safety analyses during Period 4, baseline is defined as the last nonmissing assessment prior to entering Period 4, that is, on or prior to Week 104 (Group A: Visit 14/Group B: Visit 519), or ETV.

6.2. Adjustments for Covariates

The randomization to treatment groups in Period 2 is stratified by geographic region (Table RHBY.6.2) and originating study (ie, RHBV, RHBW, and RHBX) as described in Protocol Section 6.2. The geographic regions will be collapsed into 2 levels, Europe versus Non-Europe, for statistical analysis (Table RHBY.6.3). Unless otherwise specified, all efficacy and health outcomes analysis during Period 2 for the RW ITT population will include geographic region and originating study in the analysis model. In general, when ANCOVA is used for analyses during Period 2 for the RW ITT population, baseline value and Week 24 value will be included as covariates.

The initial country allocations and geographic region classification for countries is shown in Table RHBY.6.2.

Table RHBY.6.2. Geographic Regions for Stratification

Geographic Region	Country or Countries
North America	United States, Canada
South America	Argentina, Brazil, Mexico
Eastern Europe	Finland, Hungary, Poland, Romania
Western Europe	Austria, France, Germany, Italy, Netherlands, Spain, United Kingdom
Asia	Japan, Korea, Taiwan
Rest of World	Israel, Russia

Table RHBY.6.3. Geographic Regions for Statistical Analysis

Geographic Region	Country or Countries
Europe	Czech Republic, Hungary, Poland, Germany, Netherlands, Finland, France, Italy, Spain, United Kingdom, Austria, Romania
Non-Europe	United States, Canada, Mexico, Argentina, Brazil, Japan, Korea, Taiwan, Israel, Russia

6.3. Handling of Dropouts or Missing Data

In accordance with precedent in 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 an NRI method. Patients will be considered nonresponders (eg, flare) for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at any specified analysis time point. All nonresponders at any specified time point, as well as all patients who discontinue study treatment before the specified analysis time point, for any reason, will be defined as nonresponders. Randomized patients without at least 1 observation will also be defined as nonresponders for the NRI analysis.

6.3.2. Modified Nonresponder Imputation

Analysis of categorical efficacy and health outcome variables for long-term ixekizumab treatment analysis will be assessed using an mNRI method. Patients will be considered as nonresponders if they receive retreatment due to a flare or discontinue study drug due to AE (including death) or lack of efficacy. For patients discontinuing study drug for any other reason, the data will be imputed using the multiple imputation (MI) method (as described in Section 6.3.4).

6.3.3. Modified Baseline Observation Carried Forward

An mBOCF imputation will be performed on continuous efficacy and health outcome variables. For patients discontinuing study drug due to an AE, the baseline observation at Week 0 in originating study will be carried forward to the corresponding time point for evaluation. For patients discontinuing study drug for any other reason, the last nonmissing observation before discontinuation will be carried forward to the corresponding time point for evaluation. For patients who discontinue originally assigned blinded study treatment and were retreated due to flare, or patients who are escalated from ixekizumab 80 mg Q4W to ixekizumab 80 mg Q2W, the last nonmissing observation prior to the retreatment or escalation will be carried forward to subsequent time points. For intermittent missing data before the discontinuing study drug due to any reason, the last nonmissing observation (including observation at Week 24) before the intermittent missing data will be carried forward. Randomized patients at Week 24 without at least 1 postrandomization observation will not be included for evaluation for RW ITT Population, with the exception of patients discontinuing study treatment because of an AE, including death.

6.3.4. Multiple Imputation

Analysis of continuous efficacy and health outcome variables for long-term ixekizumab treatment analysis will be assessed using the MI method. In the MI analyses, missing data will be imputed so as to estimate what the observations would have been if the patient had not discontinued. Specifically, MI is the partial imputation of non-monotone missing data using

Markov chain Monte Carlo method with the simple imputation model, followed by a sequential regression. For composite scores, the MI analysis will be done at the component level.

6.4. Multicenter Studies

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

Descriptive statistics will be provided by subgroups of geographic region: Europe or Non-Europe, and United States (US) or Non-US, for ASAS40 and BASDAI change from baseline at Week 64 for the Long-Term Ixekizumab Efficacy Population.

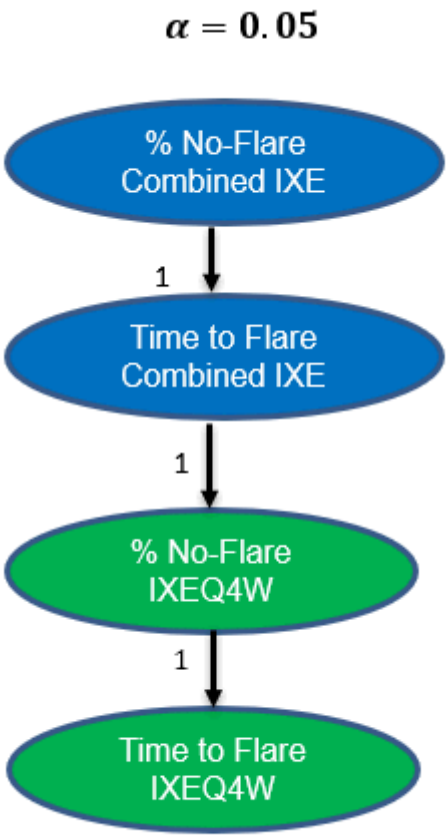
6.5. Multiple Comparisons/Multiplicity

The following is a list of primary and major secondary objectives to be tested during Period 2:

1. Primary – proportion of patients who do not experience a flare (Total IXE versus Placebo)
2. Secondary 1 – proportion of patients who do not experience a flare (IXE80Q4W versus Placebo)
3. Secondary 2 – time to the first flare (Total IXE versus Placebo)
4. Secondary 3 – time to the first flare (IXE80Q4W versus Placebo)

A multiple testing strategy using graphical multiple testing procedure (Bretz et al. 2011) 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 and major secondary endpoints will be sequentially tested in the order, as presented in Figure RHBY.6.1 using the primary statistical method described in Section 6.1.3.1 to compare ixekizumab with placebo. This is a predetermined fixed testing order; thus it is a gatekeeper method. If a test in this sequence is not significant, all the subsequent tests will be considered non-significant (Hsu and Berger 1999). The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate (Hsu and Berger 1999; Alosh et al. 2014).



Abbreviations: IXE = ixekizumab; Combined IXE = IXEQ2W + IXWQ4W; Q2W = every 2 weeks; Q4W = every 4 weeks.

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

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

6.6. Patient Disposition

The following patient disposition summaries will be provided:

- Patient flow will be summarized for all patients entered into Study RHBY Lead-in Period at Week 0 (Visit 1), being randomized (Group B), or not randomized at Week 24 (Group A), completing at Week 64, Week 104, and Follow-Up Visits 801, 802, and 803, by treatment group as assigned at the beginning of each period.
- Patient allocations by region, country, and center/site will be summarized (numbers and percentages) for patients who entered into the study, randomized at Week 24, discontinued from study treatment, and discontinued from study.

- The number and percentage of patients completing each period by treatment group and primary reason for study treatment discontinuation in:
    - Period 1 (Lead-In Period Safety Population)
    - Period 2 (RW ITT Population, Lead-In Period Safety Population – Group A, and Flare Population with Retreatment)
    - Period 3 (RW ITT Population, Lead-In Period Safety Population – Group A, and Flare Population with Retreatment)
    - Period 4 (Follow-Up Period Population).

Fisher's exact test will be used to test for treatment group differences on patient disposition for the RW ITT Population in Period 2.

Corresponding by-patient listings will also be provided for the variables summarized above.

6.7. Patient Characteristics

Patient characteristics will be listed for all entered patients and summarized by treatment assignment group for the following populations at the specified time point:

- All Entered Patients, at Week 0 in RHBY
- Long-Term Ixekizumab Treatment Efficacy Population at Week 0 from originating study
- RW ITT Population, at Week 24 in RHBY
- Ixekizumab Structure Population, at Week 0 in originating studies: for some selected characteristics
- Flare Population with Retreatment, at Week 24 in RHBY
- RW ITT Population by patients with flare and without flare, at Week 24 in RHBY

The continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, and maximum); categorical variables will be summarized using frequency counts and percentages.

Treatment group comparisons for the RW ITT Population 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.

6.7.1. Demographics and Important Characteristics

Demographics and important 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 (ie, the date when patient is first exposed to study treatment in originating study for Long-Term Ixekizumab Efficacy Population and in study RHBY for All Entered Patients in RHBY, respectively). If rfstdtc is missing, the corresponding informed consent date at the first visit in the originating study will be used.

- 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
- Country
- Weight (kg)
- Weight category: <70 kg, 70-90 kg, or ≥90 kg
- Body mass index (BMI) (kg/m^2) will be calculated as:

$$BMI\ (kg\ /\ m^2) = \frac{Weight\ (kg)}{(Height\ (m)\ at\ \text{Week 0 in originatintg studies})^2}$$

- 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 extremely obese (≥40 kg/m^2)
- Age of onset of axSpA (in years)
- Duration of symptoms since 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 onset category: <10 years, ≥10 years
- Duration of symptom since onset category: <5 years, ≥5 years
- Duration of symptom since onset category: <3 years, ≥3 years
- Duration of disease since 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) positivity: n (%)
- Current and/or history of extra-axial involvement overall and separately for: n (%)
  - inflammatory back pain
  - anterior uveitis
  - psoriasis
  - inflammatory bowel disease (including Crohn's disease or ulcerative colitis)
  - dactylitis
  - arthritis
  - enthesitis.
- Originating studies: RHBV, RHBW, or RHBX
- Initial treatment at Week 0 in originating studies: Placebo, Adalimumab, Ixekizumab

C-Reactive Protein (CRP) level:

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

Disease activity level, pain, function, and mobility:

- Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Patient global assessment of disease activity (numeric rating scale [NRS])
- Inflammation (mean of questions 5 and 6 of BASDAI)
- Total back pain (BASDAI question 2)
- Pain, NRS (on average last week): spinal pain at night due to AS
- Pain, NRS (on average last week): 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).
- Meeting entry criteria for randomized withdrawal : Yes (Group B) or No (Group A)

Concomitant therapy use:

- Disease-modifying antirheumatic drugs (DMARDs) use: n (%)
  - Overall and separately for methotrexate, sulfasalazine, and hydroxychloroquine
- Starting dosage for methotrexate, sulfasalazine, and hydroxychloroquine, see the specification of the time point for each population in the beginning of Section 6.7
- Oral corticosteroid use: n (%)

Previous therapy: axSpA: n (%)

- Biologic agent: number of tumor necrosis factor alpha (TNF-α) inhibitor used 1 or 2
- 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

Nonsteroidal Antiinflammatory Drug (NSAID) use:

- Assessment of Spondyloarthritis International Society Nonsteroidal Anti-inflammatory Drug (ASAS-NSAID) score (see Appendix 3)
- Patients with NSAIDs use: n (%)

Additional variables for Ixekizumab Structure Population only:

- Baseline mSASSS score
- Baseline mSASSS >0, n (%): >0 or = 0
- Baseline mSASSS ≥2, n (%): ≥2 or <2
- Baseline syndesmophyte, n (%): yes or no
- Magnetic resonance imaging (MRI) of spine Spondyloarthritis Research Consortium of Canada (SPARCC) score
  - SPARCC spine MRI: mean (SD)
  - SPARCC spine score ≥2: n (%)

Additional variables for RW ITT Population only:

- Residual inflammation (MRI) at Week 24: yes or no

6.7.2. Historical Illness and Preexisting Conditions

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

Historical illness/condition is defined as the condition/event recorded on the *Preexisting 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 is defined as the condition/event recorded on the *Preexisting 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 (ie, the event is ongoing) or an end date on or after the date of informed consent. Note, if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on the *Adverse Events* eCRF page from the date of worsening onwards.

The summaries as described in Section 6.1 for the following conditions will be provided for the All Entered Patients, and RW ITT Population:

- Historical illnesses by treatment group and overall, by System Organ Class (SOC) and preferred term (PT).
- Preexisting conditions by treatment group and overall, by SOC and PT.
- 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.

The comparisons among treatment groups for RW ITT Population will be conducted using Fisher's exact test.

6.8. Treatment Compliance

Throughout treatment periods, 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 is not fully administered.

Treatment compliance for each patient per period will be calculated as:

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

- The total number of injections prescribed varies by period and can be derived from the IWRS study drug dispense dataset.
- The total number of injections administered will be derived using the response to the question "Was dose administered?" on the *Exposure as Collected* eCRF page.

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

Patient treatment compliance by treatment week and overall will be summarized for the following periods and populations:

- Combined Periods 1 and 2 (Lead-In Period Safety Population)
- Combined Periods 1, 2, and 3 (Lead-In Period Safety Population)
- Period 2 (RW Safety Population) by treatment group
- Period 3 (RW Safety Population) by treatment group

The comparisons between treatment groups for RW Safety Population during Period 2 will be conducted using Fisher's exact test.

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.

6.9.1. Previous Therapy

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

Previous axial spondyloarthritis therapy will be summarized for the following populations:

- Lead-In Period Safety Population,
- Long-Term Ixekizumab Treatment Efficacy Population,
- RW ITT Population.

The following summaries will be provided by treatment assignment for each population described above:

- Previous spondyloarthritis therapy by type (biologic agent, non-biologic systemic agent, non-biologic non-systemic agent) and therapy. The previous biologic agent will be further classified as TNF-α inhibitor (includes infliximab, etanercept, adalimumab, golimumab, certolizumab pegol).
- The number and percentage of patients with each reason for discontinuation of previous spondyloarthritis therapy to be summarized by type and therapy.

The comparisons between groups for the RW ITT Population in Period 2 will be conducted using Fisher's exact test.

6.9.2. Concomitant Therapy

Concomitant therapy for each treatment period is defined as the therapy that starts before, on, or after the first day of study treatment in the defined treatment period and before the last visit date in the treatment period, and continues into the treatment period, that is, either no end date (the

therapy is ongoing) or an end date on or after the first day of study treatment in treatment period. Note that concomitant therapy will belong to a treatment period if the therapy starts and ends on the exact same day as the first day of study treatment of the treatment period.

Concomitant therapy will be summarized for the following periods and populations:

- Lead-In Period Safety Population (Combined Periods 1 and 2, Combined Periods 1, 2, and 3 in RHBY),
- RW ITT Population for Period 2 in RHBY.

and by the following concomitant therapy:

- general concomitant therapy by WHO ATC Level 4 and WHO PT,
- concomitant DMARDs, oral corticosteroids, NSAID (including cyclooxygenase- [COX-] 2) and opioids use.

The definition of above medication is provided in Appendix 10.

Comparisons between treatment groups will be conducted in Period 2 for the RW 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 RHBY.6.4 includes the description and derivation of the primary and secondary efficacy outcomes.

Section 6.10 summarizes the analyses for primary and secondary efficacy measures.

Table RHBY.6.5 provides the detailed analyses including measurement, variables, analysis method and imputation, population, treatment group comparisons, and time points for primary and secondary efficacy analyses.

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

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Ankylosing Spondylitis Disease Activity Score (ASDAS): **Criteria for the primary and major secondary outcomes**	The ASDAS is a composite index to assess disease activity in AS (Machado et al. 2011a, 2011b; Zochling 2011). The parameters used for the ASDAS (with CRP as acute phase reactant)(Sieper et al. 2009): 1) Total back pain (BASDAI Q2) 2) Patient global 3) Peripheral pain/swelling (BASDAI Q3) 4) Duration of morning stiffness (BASDAI Q6) 5) CRP in mg/L	$ASDAS_{crp}$	$ASDAS_{crp}$ (Sieper et al. 2009): 0.121× total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579× Ln(CRP+1). The higher composite score indicates the worse disease. If CRP <2 mg/L or below the limit of detection, then use 2 mg/L in the calculation (Machado et al. 2015). C-reactive protein is in mg/L, the range of other variables is from 0 to 10; Ln represents the natural logarithm. **The minimum score is 0.6361.** **Note:** IWRS will use the flare status to dispense drug. Therefore, no missing data is allowed before discontinuation. Once any intermittent component score of ASDAS is missing, the last nonmissing component score is carried forward. To keep consistent with IWRS, if a patient had intermittent missing components, last nonmissing observation before intermittent missing components will be used to impute the components. And the imputed ASDAS score will be used to code all ASDAS related categorical variables.	Observed value is missing if any component is missing. LOCF will be used for intermittent components**.**
		Sustained Remission **(randomization criterion, evaluate at both Week 16 and Week 20)**	If (ASDAS <1.3 at Week 16 and ASDAS <1.3 at Week 20) or (ASDAS <1.3 at Week 16 and ASDAS <2.1 at Week 20) or (ASDAS <2.1 at Week 16 and ASDAS <1.3 at Week 20) then Sustained Remission = 1, otherwise 0.	NA
		Flare (**Primary outcome during Period 2)**	If ASDAS ≥2.1 at 2 consecutive visits, or ASDAS >3.5 at any visit after randomization during Periods 2 and 3 then Flare = 1, otherwise 0. See Section 6.9.1 for coding regarding Week 24 (V505).	NA

		Time to the 1st flare **(major secondary outcome is during Period 2)**	Time to the 1st flare during the Period is calculated as: $\frac{Date\ of\ 1st\ flare\ in\ the\ analysis\ period - date\ of\ the\ randomization\ at\ Week\ 24 + 1}{7}$ Note: if a patient had a flare at an intermittent missing visit using the last non-missing observation carried forward, then Date of 1st flare = last visit date +28 days for Period 2, Date of 1st flare = last visit date +84 days during Period 3 for the Combined Periods 2 and 3	NA
		ASDAS inactive disease	Defined as ASDAS <1.3	NA
		$ASDAS_{crp}$ change from baseline	Calculated as: observed ASDAS – baseline ASDAS	NA
		Clinical important improvement	Defined as at least 1.1-unit change in ASDAS from baseline, calculated as above.	
		Major improvement	Defined as at least 2.0-unit change in ASDAS from baseline, calculated as above, or reached the minimum of ASDAS score (0.6361) at postbaseline visit.	
modified Stoke Ankylosing Spondylitis Spinal Score **(mSASSS)**	A spinal x-ray, plain radiograph of the lateral views of cervical and lumbar spine, measured at both baseline of the originating study and Week 56 in RHBY	Total mSASSS	Sum of the scores of 24 sites, each ranges from 0 to 3: 0 = normal; 1 = sclerosis, squaring or erosion; 2 = syndesmophyte; 3 = bony bridge. The total score ranges from 0-72.	See "mSASSS and MRI Data Programming Guidance" for data coding.
		2-year change in Total mSASSS	Change in Total mSASSS for ixekizumab patients = observed Total mSASSS at Week 56 in RHBY – baseline total mSASSS in originating study	NA (complete data).
		Non-progressor (mSASSS <2)	If change in Total mSASSS <2 then Non-progressor = 1, otherwise 0.	NA (complete data).
		Non-progressor (mSASSS ≤0) – sensitivity analysis	If change in Total mSASSS score ≤0 then Non-progressor = 1, otherwise 0.	NA (complete data).
SPARCC MRI score for Spine	All 23 disco-vertebral units (DVU) of the spine (from C2 to S1) are scored for bone	SPARCC Spine Score	The SPARCC spine score is a sum of 414 scoring units for all 23 DVUs; the sum ranges from 0 to 414.	

	marrow edema. A single DVU has 18 scoring units, and each has score of 0 or 1, bringing the maximum total score to 414, with higher scores reflecting worse disease (Maksymowych et al. 2010). Scoring will be performed by a central reader	Residual inflammation at Week 24	At Week 24, if SPARCC Spine Score >=2, residual inflammation = Yes, else = No	See "mSASSS and MRI Data Programming Guidance" for data coding.
MRI Sacroiliac Joint (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] Score)	Both left and right SIJ are scored for bone marrow edema. Each side has 6 slices and each slice has 6 scoring units, and each scoring unit has a score of 0 or 1. Total SIJ SPARCC scores 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.	
		Residual inflammation at Week 24	At Week 24, if SPARCC SIJ Score >=2, residual inflammation =Yes, else=No	See "mSASSS and MRI Data Programming Guidance" for data coding.
Assessment of Spondyloarthritis International Society 20 (ASAS20), ASAS40, ASAS Partial Remission, ASAS5/6	ASAS20, ASAS40, ASAS Partial Remission and ASAS5/6 are clinical responses derived based on the following ASAS domains (Sieper et al. 2009): 1) Patient Global 2) Spinal Pain 3) Function 4) Inflammation (mean of BASDAI Q5 and Q6) 5) CRP 6) Spinal mobility (lateral spinal flexion)	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.	See Appendix 1 for derivation of observed response.
		ASAS40	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.	
		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.	
		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.	

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 is 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 following 2 questions (on average, last week): 1. "How much pain of your spine due to ankylosing spondylitis do you have?" 2. "How much pain of your spine due to ankylosing spondylitis do you have at night?"	Spinal Pain, NRS	Range: 0 to 10 "0" (no pain) and "10" (most severe pain). This question is used to derive response for ASAS20, ASAS40, ASAS5/6 and ASAS partial remission.	Single item, missing if missing.
		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	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.

	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).	BASDAI score	BASDAI = (Q1+Q2+Q3+Q4+inflammation)/5 Range: 0 to 10 "0" (none) and "10" (very severe).	If only Q6 is missing, BASDAI is average of the other 5 questions; missing if more missing than just Q6.
		BASDAI 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 baseline or observed value is missing.
Bath Ankylosing Spondylitis Functional Index (BASFI)	The BASFI establishes a patient's functional baseline and subsequent response to treatment (Calin et al. 1995). To complete the BASFI, a patient will be asked to rate the difficulty associated with 10 individual basic functional activities. Patients respond to each question using an NRS (range 0 to 10), with a higher score indicating worse functioning (Sieper et al. 2009).	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. If ≤2 of the item scores are missing, the score is the average score of the remaining items.

<table>
<tr><td></td><td></td><td>BASFI change from baseline; % improvement from baseline</td><td>Change from baseline calculated as:
observed BASFI – baseline BASFI
% improvement from baseline calculated as:
$100 \times \frac{Baseline - Observed\ score}{Baseline}$</td><td>Missing if baseline or observed value is missing.</td></tr>
<tr><td rowspan="2">High Sensitivity CRP</td><td rowspan="2">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.</td><td>CRP value</td><td>Lab values obtained from central laboratory</td><td>Missing if missing.</td></tr>
<tr><td>CRP change from baseline and % improvement from baseline</td><td>Change from baseline calculated as:
observed CRP – baseline CRP.
% improvement from baseline calculated as:
$100 \times \frac{Baseline - Observed\ Value}{Baseline}$</td><td>Missing if baseline or observed value missing (note: if V2 CRP missing, V1 CRP will be used as baseline).</td></tr>
<tr><td>Bath Ankylosing Spondylitis Metrology Index—Spinal Mobility (BASMI)</td><td>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 5 assessments gives the BASMI linear result. The additional condition $0 \leq S \leq 10$ is always applied. A is the result of an assessment.
When 2 readings are taken for each of above measures, the better of the 2 will be used (for tragus, the smaller number is better; for the other 4 measurements, the bigger number is better).</td><td>Missing if >20% measurements (ie, >1 of the 5 clinical measure-ments) are missing. If only 1 of 5 measurements missing, then the score is the average the other 4 nonmissing ones. In some individual component (eg, lateral</td></tr>
</table>

				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.
		BASMI Linear change from baseline	Calculated as: observed BASMI Linear – baseline BASMI Linear	Missing if baseline or observed value is missing.
		5 individual component change from baseline	Calculated as: observed score – baseline score	Missing if baseline or observed value is missing.
Chest Expansion	While patients have their hands resting on or behind the head, the assessor will measure the chest encircled length by 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	Chest Expansion score	One score measured in centimeter (cm). When 2 readings are taken, the better of the two numbers (greater one) will be used.	Single item, missing if missing.
		Chest Expansion change from baseline	Calculated as: observed Chest Expansion – baseline Chest Expansion	Missing if baseline or observed value is missing.

	(larger) difference of 2 tries will be entered into the case report form (CRF).			
Occiput to Wall Distance	The patient is to make a maximum effort to touch the head against the wall when standing with heels and back against the wall. Then the distance from occiput to wall is measured. The better (smaller) measurement of 2 tries in cm (eg, 10.2 cm) is reported.	Occiput to Wall Distance score	One score measured in centimeter (cm). When 2 readings are taken, the better of the 2 numbers (smaller one) will be used.	Single item, missing if 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.
Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)	The MASES is an index used to measure the severity of enthesitis (Heuft-Dorenbosch et al. 2003). The MASES assesses 13 sites for enthesitis using a score of "0" for no activity, or "1" for activity. Sites assessed include: costochondral 1 (right/left), costochondral 7 (right/left), spinal iliaca anterior superior (right/left), crista iliaca (right/left), spina iliaca posterior (right/left), processus spinosus L5, and Achilles tendon proximal insertion (right/left).	MASES	The MASES is the sum of all site scores. Range: 0 to 13, higher scores indicate more severe enthesitis 0 = no activity and not evaluable 1 = activity	Missing if >20% (ie, ≥3) sites are missing. If ≤20% missing, then MASES score = sum of scores from nonmissing sites × 13/no. of nonmissing sites.
		MASES change from baseline	Calculated as: observed MASES – baseline MASES	Missing if baseline or observed value is missing.
		MASES = 0	Only applies to patients with baseline MASES >0 to count % of patients having MASES remission.	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 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 calcaneus (L/R), and Plantar fascia insertion into calcaneus (L/R).	SPARCC enthesitis	The SPARCC is the sum of all site scores. Range: 0–16, higher scores indicate more severe enthesitis. SPARCC enthesitis score = 0 refers to complete resolution in enthesitis.	Missing if >20% (ie, ≥4) sites are missing. If ≤20% missing, then imputed sum = sum of scores from nonmissing sites × 16/no. of nonmissing sites.
		SPARCC enthesitis change from baseline	Calculated as: observed SPARCC enthesitis – baseline SPARCC enthesitis.	Missing if baseline or observed value is missing.
		SPARCC enthesitis = 0	Only applies to patients with baseline SPARCC enthesitis >0 to count % of patients having SPARCC enthesitis remission.	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 2 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	Missing if baseline or observed

				value is missing
		TJC = 0	only applies to patients with baseline TJC > 0 to count % of patients having TJC remission.	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 2 for details.	If more than half of the joint scores are not evaluable, the total score will be missing.
		SJC change from baseline	Calculated as: observed SJC – baseline SJC	Missing if baseline or observed value is missing
		SJC=0	Only applies to patients with baseline SJC > 0 to count % of patients having SJC remission..	Missing if observed value is missing
Anterior Uveitis or Uveitis Flares	Eye pain or discomfort, eye redness, blurring of vision, or any other symptoms suggestive of anterior uveitis.	Event of anterior uveitis or uveitis flare	When a patient is diagnosed as anterior uveitis or uveitis flare by an ophthalmologist (for patients with no prior history), or a physician (for patients with prior history), then the Event =1, else=0.	If missing then missing

Abbreviations: Baseline = baseline from the originating study RHBV, RHBW or RHBX; CRP = C-reactive protein; IWRS = Interactive Web Response System; no. = number; NRS = numeric rating scale; Q = question; rad-axSpA = radiographic axial spondyloarthritis.

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

Population	Variable	Analysis Method (Section 6.1)	Comparison/Time Point
RW ITT Population (to evaluate treatment effect in maintaining response during Period 2)	**For the primary and major secondary objectives:** Not Flare (event: 0 or 1)	Logistic Regression analysis and with NRI; Fisher's exact test with NRI	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo at each scheduled visit in Period 2 including Week 64.
	For major secondary objectives: Time to the 1st Flare	Kaplan-Meier product limit method Log-Rank Test	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo within Period 2 up to Week 64.
RW ITT Population (to evaluate treatment effect in achieving/maintaining response during Period 2).	**For other secondary objectives:** • ASDAS: Clinically-important improvement Major improvement Inactive disease, ASDAS <2.1 • ASAS20; • ASAS40; • ASAS5/6; • ASAS partial remission, • BASDAI50. • Peripheral arthritis: TJC = 0 and SJC = 0 for patients with TJC >0 and SJC >0, respectively, at Baseline from originating study • Enthesitis: MASES = 0 and SPARCC = 0 for patients with Baseline MASES >0 and SPARCC >0, respectively. (See Section 6.10.4 for coding for achieving/ maintaining response for these variables derived in Table RHBY.6.4)	Logistic Regression analysis and with NRI; Fisher's exact test with NRI	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo at each scheduled visit in Period 2 including Week 64.
	Anterior uveitis or uveitis flare	Fisher's exact test and Poisson regression with total exposure adjusted	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo during Period 2

Population	Variable	Analysis Method (Section 6.1)	Comparison/Time Point
	Change from baseline in the originating study: • ASAS - 4 components: Patient global, Spinal pain, Function, Inflammation. • ASDAS • BASDAI, • BASFI, • BASMI: Linear, Chest expansion and Occiput to wall distance, • Enthesitis: MASES, SPARCC. For patients with MASES >0 and SPARCC >0, respectively, at baseline from originating study • Peripheral Arthritis Severity TJC SJC For patients with TJC >0 and SJC >0, respectively, at baseline from originating study • CRP	ANCOVA with mBOCF	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo at each scheduled visit in Period 2 including Week 64.
Ixekizumab Structure Population (2-year radiographic progression in spine: from baseline in originating study to Week 56 in RHBY)	change in Total mSASSS	Descriptive statistics	No comparisons
	• Non-progressor: change in Total mSASSS <2	Descriptive statistics	No comparisons
	• Non-progressor: change in Total mSASSS <=0 • no new syndesmophyte	Descriptive statistics	No comparisons

Population	Variable	Analysis Method (Section 6.1)	Comparison/Time Point
Long-Term Ixekizumab Treatment Efficacy Population (to evaluate long-term treatment effect through Week 104)	**For other secondary objectives:** • ASDAS: Clinically-important improvement, Major improvement, Inactive disease, ASDAS <2.1 • ASAS20, • ASAS40, • ASAS5/6, • ASAS partial remission, • BASDAI50. • Enthesitis: MASES = 0, SPARCC = 0. For patients with MASES >0 and SPARCC >0, respectively, at baseline from originating study • Peripheral arthritis: TJC = 0 SJC = 0 For patients with TJC >0 and SJC >0, respectively, at baseline from originating study • Anterior uveitis or uveitis flare: Crude and exposure-adjusted incidence rates for patients with anterior uveitis	Descriptive statistics (for categorical variables with observed and mNRI through Week 104)	IXE80Q2W [a] IXE80Q4W [a] Total IXE at each scheduled visit from Week 0 in originating study to Week 64 and Week 104, respectively.
Long-Term Ixekizumab Treatment Efficacy Population (to evaluate long-term treatment effect through Week 64 and Week 104, respectively)	**For other secondary objectives:** **Change from Baseline for:** • ASAS - 4 components: Patient global, Spinal pain, Function, Inflammation. • ASDAS • BASDAI, • BASFI,	Descriptive statistics (for continuous variables with mBOCF and MMRM through Week 104)	IXE80Q2W[a] IXE80Q4W[a] Total IXE[a] at each scheduled visit from Week 0 in originating study to Week 64 and Week 104, respectively.

Population	Variable	Analysis Method (Section 6.1)	Comparison/Time Point
	• BASMI: Linear, Chest expansion and Occiput to wall distance, • Enthesitis: MASES, SPARCC. For patients with MASES >0 and SPARCC >0, respectively, at baseline from originating study • Peripheral Arthritis Severity TJC SJC For patients with TJC >0 and SJC >0, respectively, at baseline from originating study • CRP		
	Other secondary outcomes: Treatment group by TE-ADA, NAb and Titer group on: • ASAS20, • ASAS40, • ASDAS <2.1	Descriptive statistics (observed): Number and proportion of patients achieving response of interest. No inferential statistics.	IXE80Q2W, IXE80Q4W, Total IXE by TE-ADA status, NAb status, and titer group, respectively. At Week 64 and Week 104
Flare Population with Retreatment (to assess the efficacy of retreatment)	**For other secondary objectives:** • ASAS20, • ASAS40, • ASAS5/6, • ASAS partial remission, • ASDAS: ASDAS<1.3 ASDAS<2.1 Clinically-important improvement Major improvement, Inactive disease	Descriptive statistics (for categorical variables) for within 16 weeks of ixekizumab retreatment. Kaplan-Meier estimates of the proportion of patient who regain response on the variables of interest at each post-retreatment interval up to 40 weeks.	PBO/IXE80Q2W, PBO/IXE80Q4W PBO/IXE IXE80Q2W/ IXE80Q2W IXE80Q4W/ IXE80Q4W IXE/IXE no inferential statistics within 16 weeks of Ixekizumab retreatment and at each retreatment interval (4 weeks, 8 weeks, etc.) up to 40 weeks.

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; Baseline=baseline from the originating study RHBV, RHBW or RHBX; CRP = C-reactive protein; ITT = intent-to-treat; IXE-Structure = patients from Ixekizumab Structure Population; 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 model for repeated measures; mNRI = modified nonresponder imputation; NRI = nonresponder imputation; SJC = swollen joint count; TJC = tender joint count; Total IXE = IXE80Q2W and IXE80Q4W combined; RW = randomized withdrawal.

[a]– IXEQ2W is a group of patients who have been treated consistently with ixekizumab 80 mg every 2 weeks since Week 0 in the originating studies through Week 64 of RHBY. IXEQ4W is a group of patients who have been treated consistently with ixekizumab 80 mg every 4 weeks since Week 0 in the originating studies through Week 64 of RHBY.

6.10.1. Primary Outcome and Methodology

The primary outcome to test whether the Combined Ixekizumab treatment group is superior to the placebo group in maintaining response during the RWR Period (Period 2) as measured by the proportion of patients in the RW ITT Population who do not experience a flare during the RWR Period (Period 2).

Although it is expected to be very rare that a patient, who has met the sustained remission criteria at Weeks 16 and 20 and is randomized at Week 24, will have ASDAS score >3.5 or ≥2.1 at Week 24 (V505), for purpose of retreatment, V505 will however be included for assessment of flare in the IWRS. However, for statistical analysis, V505 will not be included for assessment of flare, because it is before the randomized-withdrawal. According to ITT principle, all patients will be included for the efficacy analysis with an assumption that all patients will have no flare at Week 24 at time of initiation of the randomized-withdrawal. The potential bias caused by the violation of the assumption will be justified by the randomization and will be minimal. The general rule will be applied for the retreatment: A patient is considered as non-responder if the patient is retreated (see Section 6.1), namely, Flare=1.

The primary analysis is a logistic regression analysis with treatment group, geographic region (Europe versus Non-Europe) and originating study in the model (Section 6.1.3.1). Missing data will be imputed using the NRI method (Section 6.3.2).

6.10.2. Major Secondary Efficacy Analysis

The major secondary outcomes are:

- To evaluate in patients having achieved a state of sustained remission whether ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response as measured by the proportion of patients in the randomized-withdrawal population who do not experience a flare during the randomized withdrawal-retreatment period
- To evaluate in patients having achieved a state of sustained remission whether the Combined Ixekizumab treatment group is superior to the placebo group in maintaining response after treatment withdrawal as measured by the time to the first flare during the randomized withdrawal-retreatment period
- To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg Q4W treatment group is superior to placebo in maintaining response after treatment withdrawal as measured by the time to the first flare during the randomized withdrawal-retreatment period.

The primary analysis for categorical major secondary outcomes is a logistic regression analysis with treatment, geographic region, and originating study will be included in the model (Section 6.1.3.1). In the case when logistic regression model does not produce statistical results due to sparse data, Fisher's exact test will be used. Missing data will be imputed using the NRI method (Section 6.3.2).

Kaplan-Meier product limit method will be used to estimate the survival curves for time to the first flare for patients in RW ITT Population during Period 2. The number of patients at risk and experiencing flare by each scheduled visit during Period 2 will be presented by treatment group. The Kaplan-Meier estimate of the proportion of patients experiencing flare will be presented for each visit. Treatment group comparisons will be performed using the log-rank test with strata of geographic region and originating study. A Kaplan-Meier plot of time to the first flare by treatment group will also be provided. See Section 6.1.3 for censored data.

The variable derivations for the major secondary outcomes are described in Table RHBY.6.4.

The treatment group comparisons for the primary and major secondary outcomes will be tested based on the graphical multiple testing procedure detailed in Section 6.5.

6.10.3. Additional Analyses of the Primary Outcome

Unless otherwise specified, there will be no adjustment for multiple comparisons for additional analyses of the primary outcome, the occurrence of flare.

Figures showing the proportion of patients not experiencing a flare at each scheduled visit during Period 2 within each treatment group will be provided.

Table RHBY.6.5 provides the detailed analyses including measurement, variables, analysis method and imputation, population, treatment group comparisons, and time points for primary and secondary efficacy analyses.

6.10.4. Other Secondary Efficacy Analyses

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

Table RHBY.6.5 provides the detailed analyses including measurement, variables, analysis method and imputation method, population, treatment group comparisons, and time points for primary and secondary efficacy analyses.

6.11. Health Outcomes/Quality-of-Life Analyses

The health outcomes and quality of life (QOL) measures are ASAS HI, SF-36, EQ-5D-5L, Fatigue NRS, JSEQ, WPAI-SpA, and Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16).

The analyses of health outcomes and QOL measures will be carried out for the RW ITT Population during Period 2 and for the Long-Term Ixekizumab Treatment Population during the Combined Periods 1 and 2, and Combined Periods 1, 2, and 3. There will be no adjustment for multiple comparisons for RW ITT Population during Period 2.

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

Table RHBY.6.7 provides the detailed analyses including measurement, variables, analysis method and imputation method, population, treatment group comparisons, and time points for health outcomes and QOL analyses.

Table RHBY.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. 2015). 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 are not applicable for all patients. Item with response of 'not applicable' is considered as missing item.	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 × 17/ (17-no. of missing items). If answer to item #7 or #8 is NA, it is considered as missing (ie, if responses to both #7 and #8 are not applicable, then then patient can only have 1 more missing response for the total score to be calculated. [ASAS Health Index User Manual (WWW)].
		Change from baseline in ASAS-HI	Calculated as: observed ASAS-HI – baseline ASAS-HI	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 higher scores indicate better levels of function and/or better health. Items are	8 associated domain scores (scaled score and t-score): • Physical Functioning, • Role Physical, • Bodily Pain, • General Health, • Vitality, • Social Functioning, • Role Emotional, • Mental Health	Per copyright owner, the Quality Metric Health Outcomes™ Scoring Software will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will re-calibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (t-scores) using the 1-week recall period. The procedure to derive the SF-36 scores is described in Appendix 4. It entails exporting the patient data in a CSV or tab-delimited file for import, generation of the	If an item is missing, there will be imputation conducted by the Scoring Software.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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 (t-score): • MCS Score • PCS Score	SF-36 scores and reports, and export of the calculated scores in a CSV or tab-delimited file for integration into SDTM/ADaM datasets. .	
		change from baseline in PCS, MCS and domain scores	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
		change from baseline in Fatigue Severity NRS	Calculated as: observed score – baseline score	Missing if baseline or observed value is missing
		Fatigue Severity % improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ score\ -\ Observed\ score}{Baseline\ score}$	Missing if baseline or observed value is missing
Work Productivity and Activity Impairment Questionnaire —Spondylo-arthritis	The Work Productivity Activity Impairment—Spondyloarthritis (WPAI-SpA) consists of 6 questions to determine:1. employment status; 2. hours missed from work because of spondyloarthritis; 3. hours missed from work for other reasons; 4. hours actually worked; 5. the degree to which spondyloarthritis affected work productivity while at work; 6. the degree to which spondyloarthritis affected activities outside of work. The WPAI-SpA has been validated in the	percentage of absenteeism	% work time missed due to problem: (Q2/(Q2 + Q4))*100	if Q2 or Q4 is missing, then missing
		change from baseline in percentage of absenteeism	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
		change from baseline in percentage of presenteeism	Calculated as: observed value – baseline value	if baseline or observed value is missing, then missing
		overall work impairment (work productivity) 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

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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 in overall work impairment score	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
		change form baseline in percentage of activity impairment	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
		change from baseline and % improvement from baseline in JSEQ score	Change from baseline calculated as: observed JSEQ – baseline JSEQ $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ score\ - Observed\ score}{Baseline\ score}$	Missing if baseline or observed value is missing
Quick Inventory of Depressive Symptoma-tology-self	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
		Change from baseline in each domain	Calculated as: observed domain score – baseline domain score	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
report 16 items		16 Individual items	Range: 0 to 3.	Missing if the item is missing.
		Change from baseline in each individual item	Calculated as: observed individual item score – baseline individual item score	Missing if baseline or observed value 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
European Quality of Life – 5 Dimensions 5 Level	EQ-5D-5L: is a standardized measure of health status used to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: item 1: mobility item 2: self-care item 3: usual activities item 4: pain/discomfort item 5: anxiety/depression The respondent is asked to indicate	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	If any of the items is missing, the index score is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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.		produce a patient-level index score between -0.59 and 1.0 (continuous variable): http://www.euroqol.org/fileadmin/user_upload/Documenten/Excel/Crosswalk_5L/EQ-5D-5L_Crosswalk_Value_Sets.xls	
	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

Abbreviations: Baseline = baseline from the originating study RHBV, RHBW or RHBX; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; MCS = mental component summary; NRS = numeric rating scale; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; PCS = physical component summary; UK = United Kingdom; VAS = visual analog scale.

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

Population	Variable	Analysis Method (Section 6.1)	Comparison/Time Point
RW ITT Population (to evaluate treatment effect in achieving/maintaining response during Period 2).	**For other secondary objectives:** **Change from Baseline from originating study for:** • Fatigue NRS score • QID SR 16: Total score • SF-36: PCS MCS Associated domains • ASAS HI • EQ-5D-5L: UK index; VAS • WPAI-SpA: % absenteeism; % presenteeism; % overall work impairment score; % activity impairment • JSEQ	Analysis of covariance (ANCOVA) with mBOCF	Total IXE vs. Placebo IXE80Q2W vs. Placebo IXE80Q4W vs. Placebo at each scheduled visit in Period 2 including Week 64.
Long-Term Ixekizumab Treatment Efficacy Population (to evaluate long-term treatment effect through Week 104 and Week 104	**For other secondary objectives:** **Change from baseline of the originating study for:** • Fatigue NRS score • QID SR 16: Total score • SF-36: PCS MCS	Descriptive statistics (for continuous variables using mBOCF and MMRM for data through Week 104)	IXE80Q2W[a] IXE80Q4W[a] Total IXE at each scheduled visit from Week 0 in originating study to Week 64 and Week 104, respectively.

Population	Variable	Analysis Method (Section 6.1)	Comparison/Time Point
respectively)	Associated domains • ASAS HI • EQ-5D-5L: UK index; VAS • WPAI-SpA: % absenteeism; % presenteeism; % overall work impairment score; % activity impairment • JSEQ		

Abbreviations: ASAS HI = ASAS Health Index ; 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; JSEQ = Jenkins Sleep Evaluation Questionnaire ; mBOCF = modified baseline observation carried forward ; MCS = mental component summary; MMRM = mixed model for repeated measures; NRS = numeric rating scale; PCS = physical component summary; QIDS SR 16=Quick Inventory of Depressive Symptomatology–Self Report 16 items; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.

[a] IXEQ2W is a group of patients who have been treated consistently with ixekizumab 80 mg every 2 weeks since Week 0 in the originating studies through Week 64 of RHBY. IXEQ4W is a group of patients who have been treated consistently with ixekizumab 80 mg every 4 weeks since Week 0 in the originating studies through Week 64 of RHBY.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Observed ixekizumab serum concentrations will be summarized by treatment group, visits, and corresponding time when sampling occurred. The potential impact of immunogenicity on ixekizumab concentrations may be evaluated by graphical assessments, as appropriate, to compare drug concentration levels between anti-drug antibody (ADA) negative and ADA positive patients at corresponding visits, or before and after ADA development for patients who developed ADA. A similar approach may be taken if patients become NAb positive.

Additional exploratory analyses including the PK data may be conducted if deemed appropriate.

6.13. Safety Analyses

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

For Period 2, safety data will be summarized for the RW Safety Population. Treatment group comparisons will be performed on categorical safety data using Fisher's exact test, and continuous safety data will be analyzed by an ANCOVA model as described in Section 6.1.3.

For Combined Periods 1 and 2 (Lead-In Period Safety Population), Combined Periods 1, 2, and 3 (Lead-In Period Safety Population), Period 2 (RW Safety Population), and Period 4 (Follow-Up Period Population), the above safety variables will be summarized as described in Sections 6.1.3, 6.1.4, and 6.1.6, respectively.

For safety analyses, unless otherwise specified, the following baselines will be used:

- Treatment-emergent adverse events for RW Safety Population during Period 2:
  - The baseline is events ongoing prior to the first injection in Period 2.
- Treatment-emergent adverse events for Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3:
  - For patients who were not randomized to placebo at Week 24, the baseline is the events ongoing prior to the first injection in Period 1;
  - For patients who are randomized to placebo at Week 24 and then are retreated with ixekizumab, the baseline for TEAEs during Period 1 is the events ongoing just prior to the first injection in Period 1, but the baseline for TEAEs after retreatment of ixekizumab is the events ongoing just prior to the first injection of retreatment during Periods 2 and 3 Combined.
- Change from baseline to minimum/maximum postbaseline, to last observation and to each scheduled postbaseline visit for laboratory and vital signs, and for treatment-emergent abnormal laboratory and vitals, including shift tables (hepatic or cytopenia labs) and the elevation of hepatic labs:
  - For Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, the baseline is the last nonmissing value prior to the first injection in Period 1 regardless of changes of treatment regimen;

- For RW Safety Population during Period 2, the baseline is the last nonmissing value prior to the first injection in Period 2.

6.13.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group for RW Safety population for Period 2 and Lead-In Period Safety Population for Combined Periods 1 and 2 and Combined Periods 1, 2, and 3 using descriptive statistics.

- The duration of exposure for RW Safety Population during Period 2 will be calculated as:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ Period\ 2 \\ &\quad - Date\ of\ first\ dose\ in\ Period\ 2 + 1 \end{aligned}$$

- The duration of exposure on ixekizumab for Lead-In Period Safety Population during Combined Periods 1 and 2 or Combined Periods 1, 2, and 3:
  - For patients on uninterrupted ixekizumab treatment regimen during Combined Periods, it will be calculated as:

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

  - For patients who are randomized to placebo at Week 24, ixekizumab exposure will be calculated as:

$$Duration\ of\ exposure\ (days) = \text{Duration } 1 + \text{Duration } 2,$$

where $\text{duration } 1 = Date\ of\ last\ visit\ \ in\ Period\ 1\ - Date\ of\ first\ dose\ in\ Period\ 1 + 1$ and duration 2 =
$Date\ of\ last\ visit\ on\ retreatment\ on\ ixekizumab\ \ in$ the combined periods $-$
$Date\ of\ first\ dose\ of\ retreatment\ on\ ixekizumab\ in\ \ the\ combined\ periods + 1,$

where duration 2 is a non-zero value for patients who are retreated with ixekizumab during the combined periods, and it is 0 for patients who are on placebo from Week 24 to the end of the combined periods.

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

For Period 2:

- >0, ≥28 days, ≥56 days, ≥84 days, ≥120 days, ≥183 days. Note that patients may be included in more than 1 category.
- >0 to <28 days, ≥28 to <56 days, ≥56 to <84days, ≥84 to <120 days, ≥120 to <183 days, and ≥183 days.

For combined Periods 1 and 2:

- >0, ≥28 days, ≥56 days, ≥84 days, ≥120 days, ≥183 days, and ≥365 days. Note that patients may be included in more than 1 category.
- >0 to <28 days, ≥28 to <56 days, ≥56 to <84 days, ≥84 to <120, ≥120 to <183 days, ≥183 to <365 days, and ≥365 days.

For combined Periods 1, 2 and 3:

- >0, ≥28 days, ≥56 days, ≥84 days, ≥120 days, ≥183 days, ≥365 days, ≥548 days. Note that patients may be included in more than 1 category.
- >0 to <28 days, ≥28 to <56 days, ≥56 to <84 days, ≥84 to <120, ≥120 to <183 days, ≥183 to <365 days, ≥365 to <548 days, and ≥548 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 for each treatment group. Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose. The total dose (in mg) taken during Combined Periods 1, 2, and 3 and Periods 2 will be calculated as follows:

$$Total\ dose\ for\ a\ patient\ on\ \text{ixekizumab}\ 80\ mg\ Q2W\ or\ Q4W\ in\ a\ specific\ period = Total\ number\ of\ \text{active}\ injections\ received\ in\ that\ period \times 80$$

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

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

- The MedDRA lowest level term (LLT) will be used when classifying AEs as treatment-emergent.
- The maximum severity recorded for each LLT prior to the first dose date/time in the treatment Period will be used as the pre-treatment severity for that LLT. If an event during the baseline period has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the postbaseline level of severity. Events with a missing severity during the treatment period will be considered as treatment-emergent.
- AEs with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date/time in the treatment period (ie, a patient has no preexisting conditions with that lowest level term), or if the severity is greater than the pre-treatment severity for that lowest level term. If a partial AE start date/time is present, the date/time will be compared as far as possible to the treatment start date/time in order to determine whether the event is treatment-emergent or not. If there is any doubt, the event will be flagged as treatment-emergent.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Visit 14 (Group A) or Visit 519 (Group B) (that is, Week 104) 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 in Week 104 or ETV, the maximum severity recorded for each LLT on or prior to the date of the Visit at Week 104 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 to the corresponding study period. If a follow-up emergent event is 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 study periods by treatment groups (see Table RHBY.6.1) and analysis populations, treatment comparisons between treatment groups in Period 2 will be conducted using a Fisher's exact test:

- Combined Periods 1 and 2, Combined Periods 1, 2, and 3 (Lead-In Period Safety Population)
- Period 2 (RW Safety Population).

The following summaries/analyses will be performed:

- 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 occurring in >=5% of patients in the total ixekizumab group, SAE judged by investigator as possibly study treatment related (for combined periods only), discontinuations from the treatment due to an AE, and TEAEs of special interest.
- TEAE by SOC and PT.
- TEAE by maximum severity, SOC, and PT.

The overall summary of AEs will also be provided for the RW Safety Population during Period 3, Long-Term Ixekizumab Treatment Efficacy Population and Ixekizumab Structure Population by treatment groups.

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

- FEAE by PT.

In general, for all AE-related summaries, the number and percentage of patients experiencing the events will be presented by treatment group. In general, events will be ordered by decreasing frequency in the Combined Ixekizumab group, followed in the order of ixekizumab Q2W, ixekizumab Q4W, and placebo (when applicable) group, within SOC and/or PT for sorting.

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

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 4 after discontinuation of study drug.

An SAE is any AE that results in 1 of the following outcomes: death, life-threatening, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly or birth defect, or any other serious/important medical events.

The following summary tables (including treatment group comparison for Period 2) will be provided for the Lead-In Period Safety Population for Combined Periods 1 and 2 and Combined Periods 1, 2, and 3, and RW Safety Population for Period 2:

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

6.13.3.1. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AEs of special interest (AESI) will be presented by treatment group and by analysis period.

Table RHBY.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.

Summaries will be provided for the Lead-In Period Safety Population in the Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, and for RW Safety Population in Period 2. Fisher's exact tests will be used to compare the treatment group for the RW Safety Population during Period 2.

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

Table RHBY.6.8. Definitions and Analyses of Special Safety Topics including Adverse Events of Special Interest

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Hepatic	Hepatic AE analysis will include events that are potentially drug-related hepatic disorders by using the Medical Dictionary for Regulatory Activities (MedDRA) PTs contained in any of the following standardized MedDRA query (SMQ) or sub-SMQ as defined in MedDRA: • Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009) • Broad and narrow terms in the Hepatitis, non-infectious (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015)	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE by PT within SMQ or sub-SMQ **Listing (in Spotfire):** TEAE
	Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using Performing Lab Reference Ranges are defined as: • The baseline for RW Safety Population during Period 2 is the last non-missing value prior to the first injection in Period 2, and the baseline for the Lead-In Period during the Combined Period 1, 2, and 3 is the last value before the first injection during Period 1, regardless of interruption of ixekizumab treatment. • Include scheduled visits, unscheduled visits, and repeat measurements. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST): maximum postbaseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing Lab upper limit of normal (ULN) for all patients with a postbaseline value. o The analysis of 3× ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN, or missing. o The analysis of 5× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN, or missing. o The analysis of 10× ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN, or missing. o The analysis of 20× ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN to <20× ULN, ≥20× ULN, or missing. • Total bilirubin: maximum postbaseline measurement ≥1.5 times (1.5×), and ≥2 times (2×) the Performing Lab ULN for all patients with a postbaseline value o The analysis of 1.5× ULN will contain 4 subsets: patients whose non-missing maximum baseline	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, Combined Periods 1, 2, and 3 and Period 4 (Summary)**: Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum postbaseline category

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN, or missing. ○ 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.	
	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot: use maximum ALT measurement and maximum total bilirubin measurement with patients having at least 1 postbaseline ALT and total bilirubin, which contributes 1 point to the plot. The measurements do not need to be taken at the same blood draw.	**Period 2, Combined Periods 1 and 2, and Combined Periods 1, 2, and 3**: eDISH plot
Cytopenias	Cytopenias are defined using the PTs from the following 2 sub-SMQs of the Haematopoietic cytopenias SMQ (20000027) as specified in MedDRA: • Broad and narrow terms in the Haematopoietic leukopenia (20000030) • Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031)	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE by PT within sub-SMQ **Listing (in Spotfire):** TEAE
Infections	Infections include events in the Infections and infestations SOC and include all such events: serious infections, opportunistic and potential opportunistic infections, infections that require therapeutic intervention (antibiotics, antivirals, antifungals, etc.),	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: SAE by PT, AE leading to treatment discontinuation by PT
	Anti-infective medications are defined in Appendix 5 including antibiotics, antifungals, antivirals, or antiprotozoals. Listing of patients experiencing a TEAE of infections will be provided including the following additional information: anti-infective medications use (if treated) with medication start/end dates, indication for use, and route; minimum postbaseline value within treatment Period 1, Period 2, and Period 3 for leukocytes, platelets, lymphocytes, and absolute neutrophils.	**Listing (in Spotfire):** TEAE with anti-infective medications.

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	The list of MedDRA terms used to identify infections that are typically considered to be OIs are found in Appendix 9. This list contains PTs as contained within categories and specific PTs from the Infections and Infestations SOC and the Investigations SOC which can assist in identifying patients of interest. The narrow terms are considered 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).	**Period 2, Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE of OIs by PT TEAE of OIs by maximum severity by PT **Listing:** TEAE of OIs
Allergic Reactions/Hypersensitivities	Allergic reactions/hypersensitivity events will be categorized as either potential anaphylaxis or non-anaphylaxis events and summarized separately. Medical review will determine the final categorization of these events. 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 • 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	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE by maximum severity by PT within Category, SAE by PT within Category, AE leading to treatment discontinuation by PT within Category.

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in Appendix 6. 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 7 and excluding the anaphylactic events as defined above.	
	A by-patient listing will be provided for all patients experiencing TEAE of allergic reactions/hypersensitivities at any time, including status/criterion of anaphylaxis or non-anaphylaxis, and the associated information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page if identified by the investigator.	**Listing (in Spotfire):** TEAE including information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page
Injection Site Reactions	Injection site reaction is defined using the PTs from the MedDRA high-level term (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	**Period 2 (Fisher's exact test) Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE by maximum severity by

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	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 • [4] Clear bump 2 mm thick or more Pain (including burning) (Scored 0-3) • [0] None • [1] Mild • [2] Moderate • [3] Severe	PT within HLT, SAE by PT within HLT, AE leading to treatment discontinuation by PT within HLT TEAE identified by the investigator within HLT: by PT and maximum severity **Listing (in Spotfire):** TEAE including information collected on *Injection Site Reaction* eCRF page
Cerebro-cardiovascular Events	Cerebro-cardiovascular events will be externally adjudicated by the Central Events Committee (CEC) at the Cleveland Clinic, as outlined in the Manual of Operations. The CEC will adjudicate investigator-reported events selected for adjudication and render an assessment as to whether the event represents a confirmed event (meeting the event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE by PT within Subcategory

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	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 Block, Other, Unknown) will be displayed nested within Serious Arrhythmia.	**Listing (in Spotfire):** TEAE
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	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, Combined Periods 1, 2, and 3 (Summary)**: TEAE by maximum severity by PT within category **Listing (in Spotfire):** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	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.	
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as specified in MedDRA (SMQ: 20000091, which includes the sub-SMQs: 20000195 [Tumours of unspecified malignancy] and 20000194 [Malignant tumours]). Events will be summarize by the following categories: • Nonmelanoma Skin Cancer (NMSC) o Basal Cell Carcinoma, PTs include: ▪ Basal cell carcinoma ▪ Basosquamous carcinoma ▪ Basosquamous carcinoma of skin o Squamous Cell Carcinoma, PTs include: ▪ Squamous cell carcinoma of skin ▪ Bowen's disease ▪ Lip squamous cell carcinoma ▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)** : TEAE by PT within category **Listing (in Spotfire):** TEAE
Depression	Depression is defined using the PTs from the Depression and suicide/self-injury SMQ as specified in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excl suicide and self-injury)]).	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 (Summary)**: TEAE by PT within SMQ and sub-SMQ **Listing (in Spotfire):** TEAE
Inflammatory Bowel Disease (IBD)	IBD will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered IBD. IBD (Narrow terms)	**Period 2 (Fisher's exact test), Combined Periods 1 and 2, and Combined Periods 1, 2,**

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	• 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 8. Adjudicated IBD will also be reported.	**and 3 (Summary)**: TEAE by PT within subcategory. **Listing (in Spotfire):** TEAE
Interstitial Lung Disease (ILD)	Potential ILD is defined using the following terms: • Broad and narrow terms in the Interstitial lung disease SMQ (20000042) • Additional 6 PTs from Eosinophilic pneumonia SMQ (20000157): o Angiolymphoid hyperplasia with eosinophilia (Narrow) o Eosinophilic bronchitis (Narrow) o Hypereosinophilic syndrome (Narrow) o Loeffler's syndrome (Narrow) o Pulmonary eosinophilia (Narrow) o Pulmonary vasculitis (Narrow)	**Listing (in Spotfire**): TEAE

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; FEAE = follow-up emergent adverse event; PT = preferred term; SAE = serious adverse event; TB = tuberculosis; TEAE = treatment emergent adverse event.

6.13.4. Clinical Laboratory Evaluation

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

Continuous laboratory tests will be summarized as changes from baseline (see definition of baseline for safety in Section 6.1) to last observation for patients who have both baseline and at least 1 postbaseline result for Periods 2 (RW Safety Population) :

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- Both Système International (SI) and conventional units will be summarized when different.
- For the RW Safety Population for Period 2, the comparisons between treatment group will be conducted using an ANCOVA with treatment group and baseline value in the model.
- Data will be analyzed based on original scale.

For the RW Safety Population during Period 2, the laboratory test observed values on continuous variables at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients who have both a baseline and at least 1 postbaseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The displays with both SI and conventional units will be provided when different.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least 1 postbaseline result, mean, SD, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.
- On the box plots of the laboratory test observed values, the lines of the reference ranges/limits (by using the large clinical trial population based reference limits, that is, Lilly 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 the Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, the RW Safety Population during Period 2, and the Follow-Up Period Population during Period 4. The comparisons between treatment groups will be conducted using Fisher's exact test for the RW Safety Population during Period 2.

- All scheduled, unscheduled, and repeated measurements will be included.
- The number and percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time will be summarized by treatment group for each treatment

period. Scheduled visits, unscheduled visits, and repeat measurements will be included. Performing laboratory will be used to defined the low and high limits reference ranges

- 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. 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 neutrophils). The segmented neutrophils and absolute neutrophils will be summarized using the same categories.

Shift tables 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 Period 2, Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, respectively:

- Scheduled visits, unscheduled visits, and repeat measurements will be included.
- Baseline is defined as the minimum result during the defined baseline period or baseline.
- Use the minimum nonmissing postbaseline value within each analysis 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 Period 2.

6.13.4.2. Neutrophil Follow-Up

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

The neutrophil follow-up analysis will be conducted on the Neutrophil Follow-Up Period 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 4 and less than the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0). These patients are monitored during the Period 4 until neutrophil recovery.

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/μL (SI units: ≥1.5× 10^9/L) or greater than or equal to a patient's minimum absolute neutrophil count 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 Period Population for Period 4. The number and percentage of patients with an absolute neutrophil cell count that is at least 25%, 50%, 75%, or 100% of the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

6.13.5. 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).

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 Period 2, Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, respectively:

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

For Period 2, Combined Periods 1 and 2, and Combined periods 1, 2, and 3, the observed values on vital signs and physical characteristics at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients who have both a baseline and at least 1 postbaseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least 1 postbaseline result, mean, SD, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.

The number and percentage of patients with treatment-emergent or follow-up emergent high or low vital sign and weight at any time for Period 2, Combined Periods 1 and 2, Combined Periods 1, 2, and 3, and Period 4, respectively, will be summarized. The comparisons between and among treatment groups will be conducted using Fisher's exact test for the RW Safety Population for Period 2.

- Table RHBY.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 RHBY.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 (2015 [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 four sleep items: #1 (falling asleep), #2 (sleep during the night), #3 (waking up too early) and #4 (sleeping too much). Domain is missing if all items are missing.
2) **Sad mood:** Item #5 (feeling sad). Domain is missing if the item is missing.
3) **Decrease/increase in appetite/weight:** the highest score recorded for the appetite/weight items: #6 (decreased appetite), #7 (increased appetite), #8 (decreased weight within the last two weeks), and #9 (increased weight within the last two weeks). Domain is missing if all items are missing or not applicable.
4) **Concentration:** Item #10 (concentration / decision making). Domain is missing if the item is missing.
5) **Self-criticism:** Item #11 (view of myself). Domain is missing if the item is missing.
6) **Suicidal ideation:** Item #12 (thoughts of death or suicide). Domain is missing if the item is missing.
7) **Interest:** Item #13 (general interest). Domain is missing if the item is missing.
8) **Energy/fatigue:** Item #14 (energy level). Domain is missing if the item is missing.
9) **Psychomotor agitation/retardation:** the highest score recorded for the two psychomotor items: #15 (feeling slowed down) and #16 (feeling restless). Domain is missing if all items are missing.

The QIDS-SR16 total score is the sum of the above domain scores. The total score will be missing if any domain score is missing.

The QIDS-SR16 total scores are categorized as 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 RW Safety Population during Period 2 and the Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3.

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

In addition, the number and percentage of patients falling into the following groups based upon the maximum postbaseline QIDS-SR16 item 12 (Thoughts of Death or Suicide) score will be summarized by treatment groups for the RW Safety Population during Period 2 and the Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, respectively:

- 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 Columbia-Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. Information on the C-SSRS scale can be found through the following link: http://www.cssrs.columbia.edu.

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

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

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

Composite endpoints based on the above categories are defined below.

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

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 that 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.

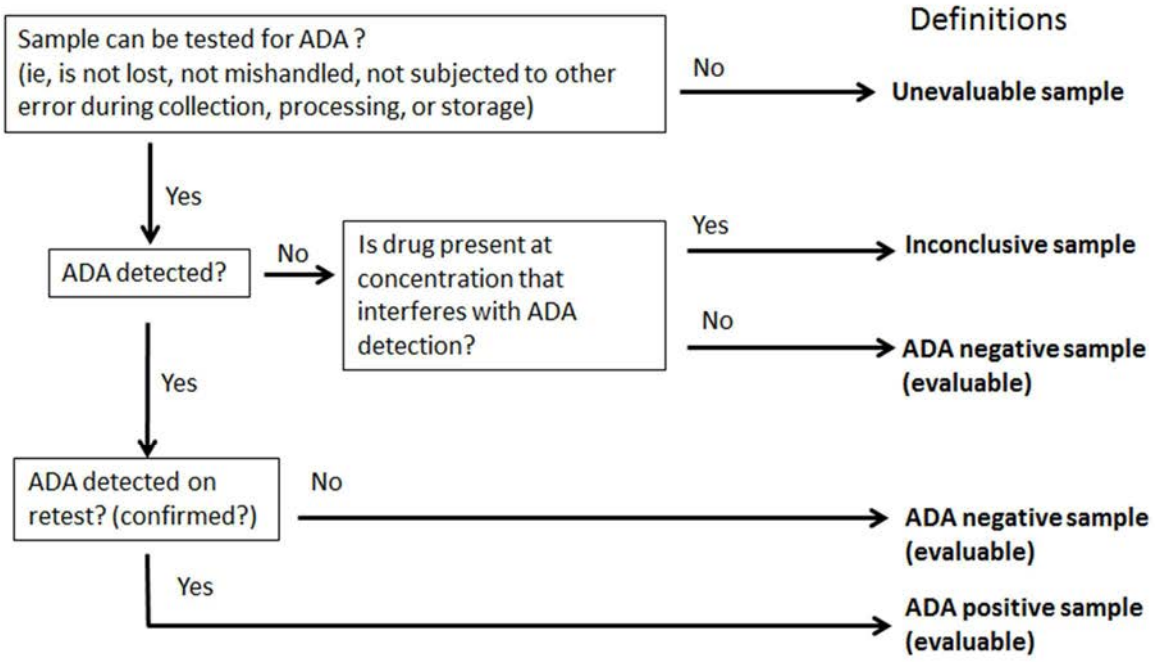
6.13.8.1.1. Sample Category Definitions

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.
- **NAb Negative sample:** The presence of NAb is not detected and the assay drug tolerance level is not exceeded.

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

Figure RHBY.6.2 illustrates the relationship of some of the above terms.



Abbreviation: ADA = anti-drug antibody.

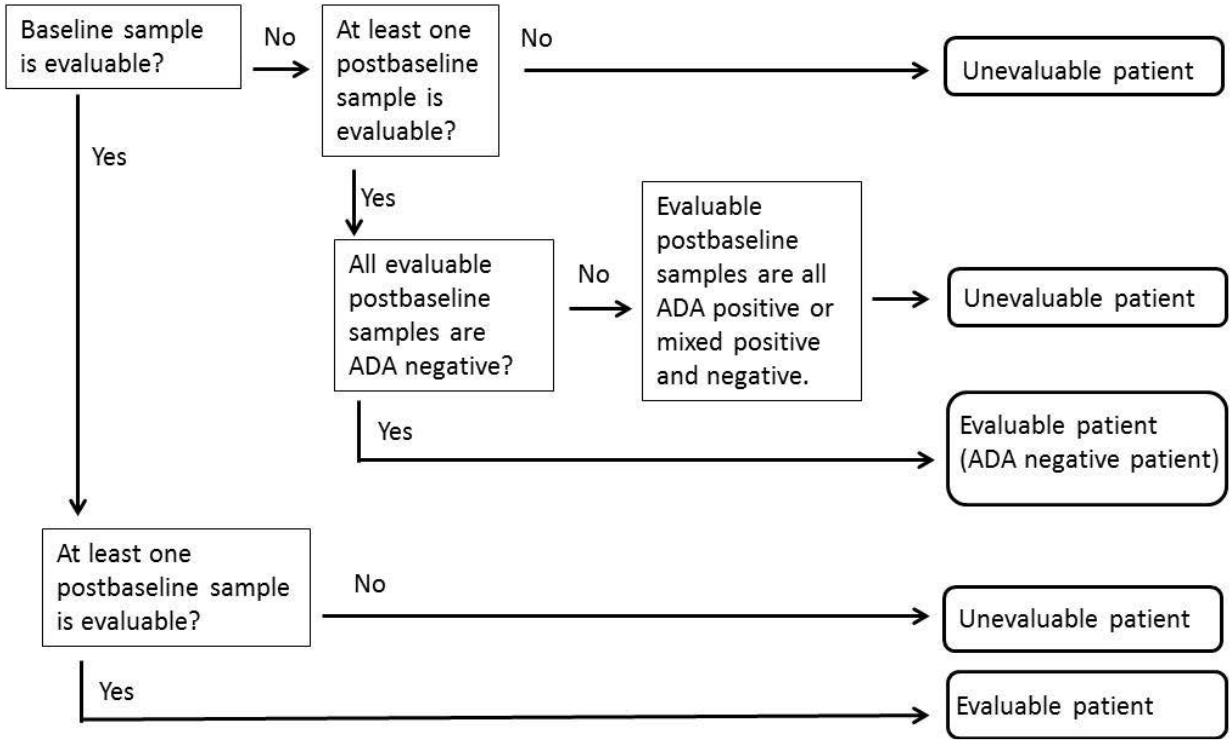
Figure RHBY.6.2. Sample definitions.

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 RHBY.6.3 illustrates the relationship of the above terms.



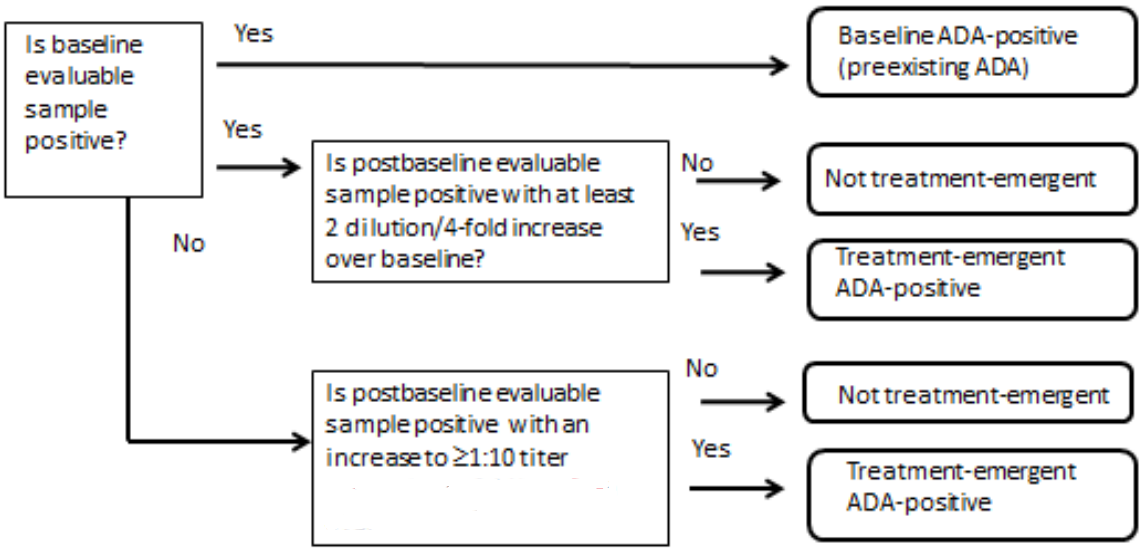
Abbreviation: ADA = anti-drug antibody.

Figure RHBY.6.3. Patient categories (evaluable/unevaluable) based on sample status at baseline and postbaseline.

6.13.8.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline**: Unless otherwise specified, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment of ixekizumab from the originating study or RHBY (that is, for patients initially randomized to ixekizumab during the originating study, the baseline will be Week 0 of the originating study; for patients randomized to placebo or adalimumab in the originating study, baseline is on or prior to the first injection of ixekizumab).
- **Baseline ADA positive (preexisting antibody):** ADA detected in a sample collected at baseline.
- **Baseline ADA-negative:** ADA is not detected in a sample collected at baseline.
- 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.
- **TE-ADA inconclusive patient:** A patient without a TE-ADA positive sample and with at least 1 sample for which drug levels may interfere with the ADA assay.
- **TE-ADA negative patient:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.

Figure RHBY.6.4 illustrates the relationship of some of these terms.



Abbreviation: ADA = anti-drug antibody.

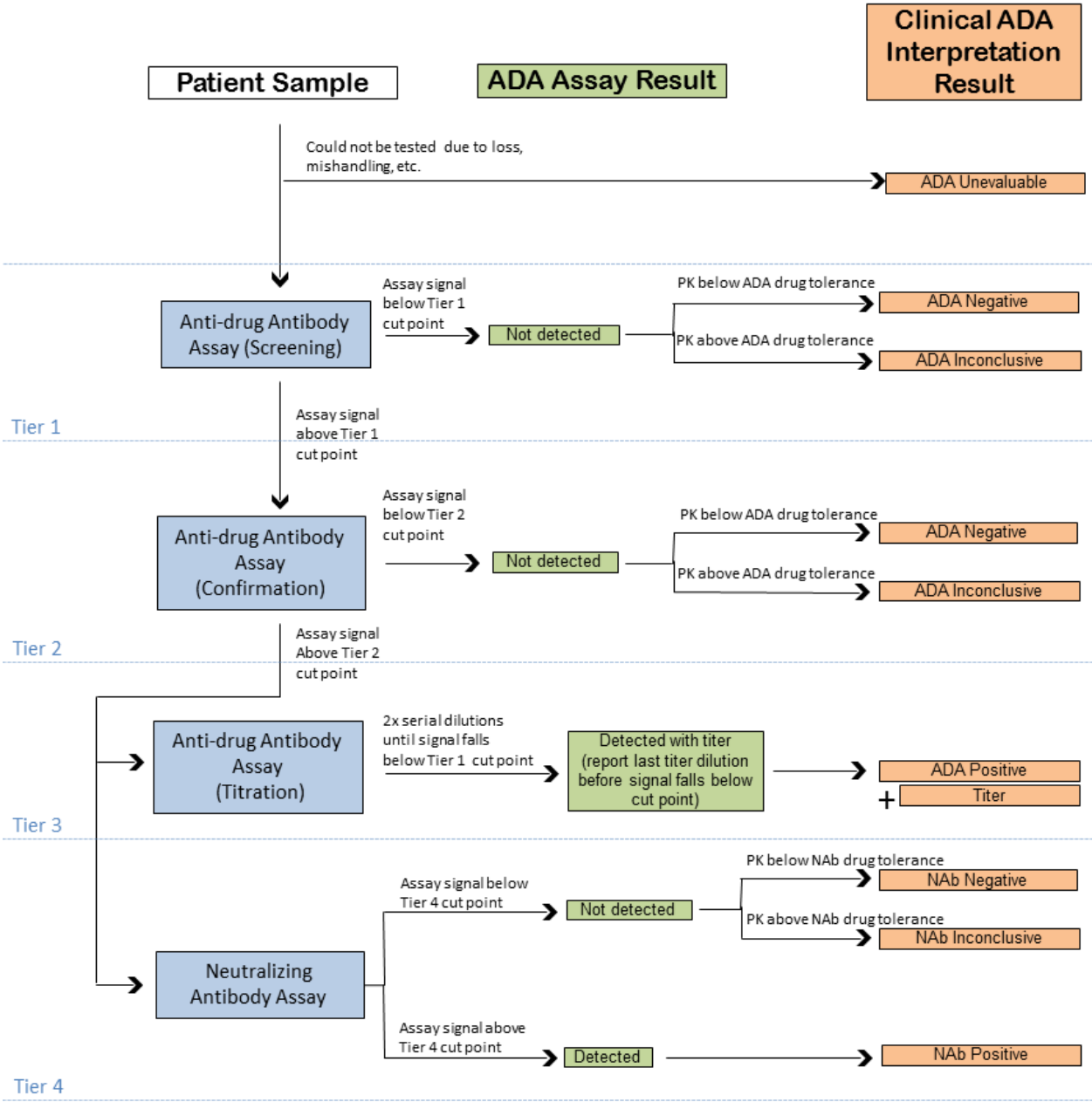
Figure RHBY.6.4. Relationship of terms for clinical interpretation of assay results for evaluable patients.

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

A flow chart that reflects the connection between the analytical test results and the clinical interpretation based on the definitions is shown in Figure RHBY.6.5.



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

Figure RHBY.6.5. 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; and
- TE-ADA titer groups for TE-ADA positive patients:
  - Low Titer: TE-ADA titer value (LOCF) <1:160;
  - Moderate Titer: TE-ADA titer value (LOCF) ≥1:160 and <1:1,280; and
  - High Titer: TE-ADA titer value (LOCF) ≥1:1,280.

Time-Varying TE-ADA Status Groups:

Individual ADA samples will be ascribed into 3 different dichotomous variables as explained in Table RHBY.6.10. Each variable has possible values of a "greater-TE-ADA status" or a "lesser-TE-ADA status," in the sense that the level of TE-ADA detected in the greater-TE-ADA category is higher than in the lesser-TE-ADA category.

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

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

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. For those time points when there is no TE-ADA sample is collected, the TE-ADA status will be derived as: 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 RHBY.6.10. If there is no value satisfying criterion (a), then the value (b) is used. Similarly, if there is no value (b), then the value (a) is used.

For each analysis period and 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 least once in the greater-TE-ADA status postbaseline.

6.13.8.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of ADA effects will be conducted on all evaluable patients within the Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3 and with RW Safety Population during Period 2.

Evaluable patients will be identified as positive, negative, or inconclusive for ADA, according to the definitions provided in Section 6.13.8.1.2.

The frequency and percentage (incidence) of patients will be summarized by treatment group for the TE-ADA status groups and the time-varying TE-ADA status groups. Scheduled visits, unscheduled visits, and repeat measurements will be included. This analysis will also be done for Group A and Group B Patients separately during Period 1.

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.

For each TE-ADA status dichotomous variable (as defined in Table RHBY.6.10), summaries will be provided of the total postbaseline time in the greater-TE-ADA status for patients who were at some point postbaseline in the greater-TE-ADA status group. Postbaseline time in the greater-TE-ADA status for each patient will be aggregated.

A by-patient listing to include treatment, visit date, visit, ADA result, TE-ADA result, NAb result, ADA titer value, ixekizumab concentration, ADA and NAb inconclusive results will also be provided, for patients with any 1 sample of ADA (or NAb) positive or inconclusive.

6.13.8.2.2. Analyses of ADA Effects on Efficacy

The impact of ADA effect on efficacy will be done for Long-Term Ixekizumab Efficacy Population. The proportion of patients achieving ASAS 20, ASAS 40 and ASDAS <2.1 will be summarized by TE-ADA status at Week 64 and Week 104. Similarly, summary statistics will be provided by NAb status and TE-ADA titer group, respectively.

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

The analyses of TE-ADA on specific adverse events will be conducted on all evaluable patients within the Lead-In Period Safety Population during Combined Periods 1 and 2, and Combined Periods 1, 2, and 3, and for RW Safety Population during Period 2. For Lead-In Period Safety Population during the combined periods, all data are included regardless of treatment changes.

Adverse events of special interest, 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 RHBY.6.10), patients will be categorized according to whether they were (i) always in lesser-TE-ADA status postbaseline or (ii) at least once in greater-TE-ADA status postbaseline. 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. Subgroup Analyses

6.14.1. Efficacy Subgroup Analyses

Unless otherwise specified, subgroup analysis will be conducted for Long-Term Ixekizumab Efficacy Population, RW ITT Population and Ixekizumab Structure Population for selected outcomes.

For the RW ITT Population during Period 2 to compare the Combined Ixekizumab group to the placebo group on proportion of patients who do not experience a flare, a logistic regression analysis, including variables of treatment, subgroup, and treatment-by-subgroup interaction, will be used. The treatment-by-subgroup interaction will be tested at the 10% significance level. If any group within the subgroup is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

The following subgroups will be analyzed for the Long-Term Ixekizumab Efficacy Population on ASAS40 and change from baseline in BASDAI at Week 64 in RHBY, unless otherwise specified. All subgroups are based on records at Week 0 in originating studies. Descriptive statistics will be provided for the observed cases.

- Patient Demographics Subgroups:
  - Sex;
  - Age category: <40 years, ≥40 years;
  - Age category: <50 years, ≥50 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 and Study Subgroups:
  - Geographic region: Europe or Non-Europe;
  - Geographic region: US (including Puerto Rico sites if any) or Non-US;
  - Originating Study: RHBV, RHBW or RHBX;
  - Originating Study: r-axSpA (RHBV and RHBW) vs nr-axSpA (RHBX).
- Other Patient Characteristics Subgroups:
  - Baseline CRP categories:
    - ≤5.00 mg/L or >5.00 mg/L;
    - ≤10.00 mg/L or >10.00 mg/L;
  - Duration of symptom of onset category: <5 years or ≥5 years;
  - Duration of symptom of onset category: <10 years or ≥10 years;
  - HLA-B27 status: positive or negative;
  - Smoking status: current or former/never;
  - Concomitant conventional disease-modifying antirheumatic drug (cDMARDs) (methotrexate, sulfasalazine, hydroxychloroquine) at baseline: yes or no;
  - History of arthritis/ dactylitis (peripheral): yes (historical /current) or no;
  - History of uveitis/ inflammatory bowel disease / psoriasis (extra-axial): yes or no;
  - History of enthesitis: yes or no.

The following subgroups will be analyzed for the RW ITT Population on proportion of patients who do not experience a flare in Period 2:

- Originating Study: RHBV, RHBW, RHBX;
- Originating Study: r-axSpA (RHBV, RHBW) vs. nr-axSpA (RHBX);
- TNFi experience: bDMARD-naïve (RHBV and RHBX) vs. TNFi-experience (RHBW);
- Length of treatment on ixekizumab for RHBX patients: 24-44 weeks, 52-60 weeks, 76 weeks;
- Length of treatment on ixekizumab for RHBV and RHBW patients: 56-60 weeks, 76 weeks.

The following subgroups will be analyzed for the Ixekizumab Structure Population on change from baseline in mSASSS, non-progression rate and no-new-syndesmophyte, respectively:

- cDMARD Experience: Yes or No;
- Baseline NSAID Use: Yes or No;
- TNFi Experience: Yes or No;
- Sex: Female or Male;
- Smoking Status: current or former/never;
- Baseline CRP Status: ≤5.00 mg/L or >5.00 mg/L;
- Baseline mSASSS>=2: Yes or No;
- Baseline MRI spine SPARCC score >=2: Yes or No;
- Group: A or B.

Additional subgroup analyses on efficacy may be performed as exploratory analyses.

6.14.2. Safety Subgroup Analyses

No safety subgroup analysis will be performed.

6.15. 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 RHBY.6.11 includes the categories and subcategories of important protocol deviations, the source of identification for the deviations, and the statistical programming guidance for the CSR.

The number and percentage of patients having important protocol deviations will be summarized within category and subcategory of deviations for all patients entered into RHBY regardless of treatment group during:

- The Combined Periods 1 and 2;
- The Combined Periods 1, 2 and 3.

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

Table RHBY.6.11. Identification and Action of Important Protocol Deviations

Important Protocol Deviation Category/Subcategory/Study Specific	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
Category: Eligibility		
Subcategory: Inclusion/Exclusion		
[1] Not complete the final study visit in the originating study. Or if patients from RHBX permanently discontinued ixekizumab and were receiving a TNF-inhibitor	Monitor	From monitor's list
[2] Female patient of childbearing potential did not agree to use a reliable method of birth control, or had a positive pregnancy test.	Monitor	From monitor's list,
[3] Didn't give written informed consent approved by Lilly or its designee, and the Investigational Review Board (IRB)/Ethical Review Board (ERB) governing the site	Monitor	From monitor's list
[4] Presence of significant uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during the originating study	Monitor	From monitor's list.
[5] Have a known hypersensitivity to ixekizumab or any component of this investigational product	Monitor	From monitor's list.
[6] Permanently discontinued ixekizumab during the originating study	Monitor	From monitor's list
[7] Had temporary ixekizumab interruption at any time of the originating study and, in PI's opinion, restarting ixekizumab poses an unacceptable risk for the patient's participation in the study	Monitor	From monitor's list,
[8] Have any other condition that in PI's opinion precludes the patient from following and completing the protocol	Monitor	From monitor's list
[9] 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	Monitor	From monitor's list
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, UK sites, not discontinued IP for abnormal liver tests.	Monitor	From monitor's list

Important Protocol Deviation Category/Subcategory/Study Specific	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[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 (see Protocol Section 9.4.10.1) and a concurrent infection	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed segmented neutrophil counts <0.50 GI/L (defined as a test of <0.50 GI/L and a retest within 10 days still <0.50 GI/L; if no retest, use the test as the confirmed)
[D2-W] Total WBC count <2.00 GI/L	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed total WBC count <2.00 GI/L (defined as a test of <2.00 GI/L and a retest within 10 days still <2.00 GI/L; if no retest, use the test as the confirmed)
[D2-L] Lymphocyte count <0.50 GI/L	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed lymphocyte count <0.50 GI/L (defined as a test of <0.50 GI/L and a retest within 10 days still <0.50 GI/L; if no retest, use the test as the confirmed)
[D2-P] Platelet count <50 GI/L	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed platelet count <50 GI/L (defined as a test of <50 GI/L and a retest within 10 days still <50 GI/L; if no retest, use the test as the confirmed)
[D3] In the opinion of investigator, if a 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.	Monitor	From monitor's list
[D4] Any positive TB test and the patient does not receive appropriate treatment for latent TB; or there is evidence of active TB infection at any time	Monitor	From monitor's list.
[D5] Clinically significant systemic hypersensitivity reaction that does not respond to treatment	Monitor	From monitor's list
[D6] Patient became pregnant	Monitor	From monitor's list
[D7] Patient developed a malignancy (Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers during the study)	Monitor	From monitor's list

Important Protocol Deviation Category/Subcategory/Study Specific	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[D8] Enrolled in prohibited medical research	Monitor	From monitor's list
[D12] Lilly stopped the patient participation	Monitor	From monitor's list
[D13] Patient became HBV DNA positive	Monitor/stats	From monitor's list, or stats program based on HBV DNA records.
[D14] Patient has a confirmed diagnosis of PCP during the study for patients from Japan sites	Monitor	From monitor's list
Category: Study Procedures		
Subcategory: Excluded Con-meds	Monitor	Either from monitor's list .
Subcategory: Lab/Imaging Criteria		
Missing lab chemistry and hematology: missing at Week 0, or not having at least 1 visit after Week 0.	Stats	If missing at Week 0 from RHBY, or not having at least 1 visit after Week 0 from RHBY.
Subcategory: Other		
Missing QIDS total score: missing at Week 0 or not having at least one scheduled visit in each period.	Stats	If missing QIDS total score at Week 0 or not having at least one scheduled visit in each period
Missing Columbia scale score at any visit	Monitor and Stats	From monitor's list; if missing Columbia scale at any visit
Incorrect IWRS entries of partial ASDAS scores or CRP resulting in errors to define sustained remission status during Period 1 or the 1st flare at the post-randomization visits during Period 2 and Periods 2 and 3 combined	Monitor	From monitor's list, Stats will use program to support for data checking
Had unqualified site personnel perform clinical safety and/or efficacy assessments	Monitor	From monitor's list

Important Protocol Deviation Category/Subcategory/Study Specific	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
Category: Investigational Product		
Subcategory: Treatment Assignment/Randomization Error		
Took incorrect study medication	Stats and monitor	If IWRS study drug dispense data not match with the treatment label identifier on the *Exposure as Collected* eCRF page From monitor's list: Randomized patients should consistently take the assigned medication during Period 2
Not meet sustained remission at randomization, but randomized in Group B	Stats	Stats will program based on ASDAS score using remission criteria: ASDAS <1.3 at Week 16 and Week 20, or ASDAS <1.3 at Week 16 or Week 20, and ASDAS <2.1 at the other visit.
Subcategory: Compliance	Stats	If non-compliant with study medication regimen or over-dose during the treatment period. Note: Non-compliance with therapy is defined to be missing more than 20% of expected doses or missing 2 or more consecutive doses; over-dose is defined as to take more injections at the same time point than specified in the protocol. Note: For non-compliance programming, Week 64 is included in Period 3 not Period 2.
Subcategory: Patient took medication not fit for use	Monitor	From monitor's list
Subcategory: Other		
Randomized but did not take any study medication	Stats	If a patient is randomized but does not take any study medication
Category: Safety		
Subcategory: SAEs		
Not reported in 24 hours	Monitor	From monitor's list
Category: Informed Consent		
Subcategory: Informed Consent not Obtained		
Procedure done prior to or without consent	Monitor and Stats	Either from monitor's list, or, If patient informed consent date is after Visit 1 date or missing informed consent

Important Protocol Deviation Category/Subcategory/Study Specific	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
Category: administrative/oversight		
Subcategory: Regulatory/Ethic Approvals	Monitor	From monitor's list
Subcategory: Other	Monitor	From monitor's list
Enrolled in a site with significant GCP non-compliance issue	Monitor	From monitor's list

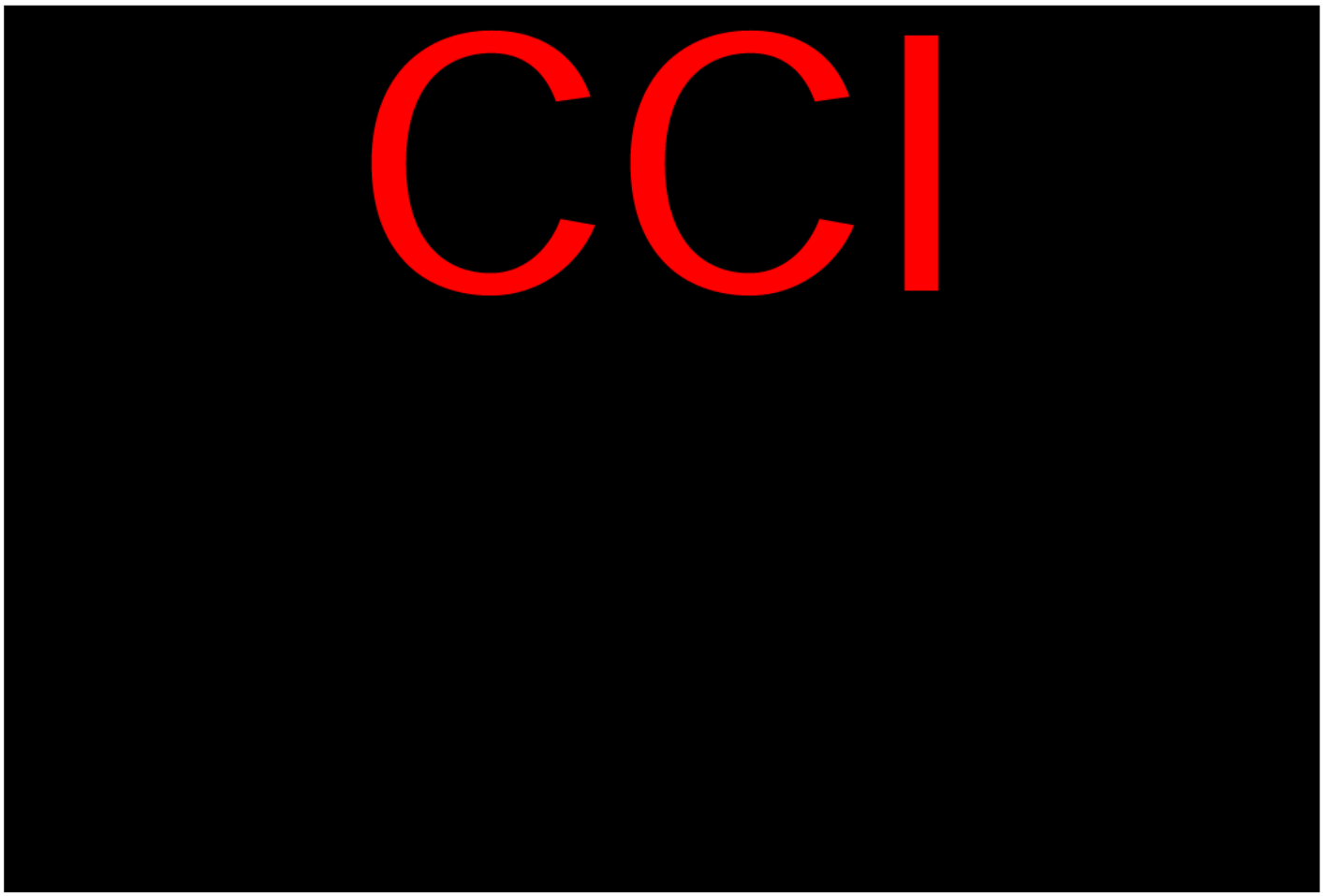
Abbreviations: ASDAS= Ankylosing Spondylitis Disease Activity Score; eCRF = electronic case report form; GCP = good clinical practice; HBV = hepatitis B virus; ICF= informed consent form; ITT = intent-to-treat; IWRS = interactive web-response system; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self-Report 16 items; RW=randomized withdraw; TB = tuberculosis.

[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.

6.16. Interim Analyses and Data Monitoring

The study will have approximately 1 interim database lock and 1 final database lock. The interim database lock and the unblinding will occur and the analysis will be performed at the time when all patients have completed through Week 64 or have discontinued at or prior to Week 64. The final database lock and the analysis will occur when all patients have completed or discontinued the study. The interim database lock will include all data collected by the cutoff date, including the data from the Long-Term Extension Period (Period 3), and follow-up data from patients that have begun the Post-Treatment Follow-Up Period (Period 4). The analyses from the Week 64 database lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

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



6.18. Annual Report Analyses

Annual report analyses will be documented in a separate document.

6.19. 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).
- AE reporting is consistent with other document disclosures such as the CSR.

7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

8. References

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

Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum.* 2001;44(8):1876-1886.

[APA] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: APA; 1994.

Appel H, Heydrich R, Loddenkemper C, Hempfing A, Sieper J. In situ detection of IL-17 secreting cells in the bone marrow of facet joints obtained from patients with ankylosing spondylitis. *Arthritis Rheum.* 2008;58(suppl):S351.

Baeten D, Sieper J, Emery P, Braun J, Heijde D, McInnes I, van Laar JM, Landewe R, Wordsworth P, Wollenhaupt J, Kellner H, Paramarta J, Berolino AP, Wright AM, Hueber W. The anti-IL-17A monoclonal antibody secukinumab (AIN457) showed good safety and efficacy in the treatment of active ankylosing spondylitis [poster]. Presented at: Annual Meeting of the American College of Rheumatology; 10 November 2010; Atlanta, GA. Available at: http://www.abstracts2view.com/acr/view.php?nu=4350&type=abstract&sesId=541&num=APS&trk=). Accessed February 21, 2011.

Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, McInnes I, van Laar JM, Landewé R, Wordsworth P, Wollenhaupt J, Kellner H, Paramarta J, Wei J, Brachat A, Bek S, Laurent D, Li Y, Wang YA, Bertolino AP, Gsteiger S, Wright AM, Hueber W. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382(9906):1705-1713.

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

Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, Deodhar A, Porter B, Martin R, Andersson M, Mpofu S, Richards HB; MEASURE 1 Study Group; MEASURE 2 Study Group. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med.* 2015;373(26):2534-2548.

Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, Gromnica-Ihle E, Kellner H, Schneider M, Sörensen H, Zeidler H, Rudwaleit M, Sieper J, Braun J. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res Ther*. 2005;7(3):R439-444.

Baraliakos X, Listing J, Rudwaleit M, Brandt J, Alten R, Burmester G, Gromnica-Ihle E, Haibel H, Schewe S, Schneider M, Sörensen H, Zeidler H, Visvanathan S, Sieper J, Braun J. Safety and Efficacy of readministration of infliximab after longterm continuous therapy and withdrawal in patients with ankylosing spondylitis. *J Rheumatol*. 2007;34(3):510-515.

Baraliakos X, Braun J, Laurent DD, Baeten D, van der Heijde D, Sieper J, Emery P, McInnes I, van Laar J, Landewe R, Wordsworth P, Wollenhaupt J, Kellner H, Wright AM, Gsteiger S, Hueber W. Interleukin-17A blockade with secukinumab reduces spinal inflammation in patients with ankylosing spondylitis as early as week 6, as detected by magnetic resonance imaging. *Arthritis Rheum.* 2011;63(suppl 10):2486D.

Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, Cawkwell LS, McGonagle D, Emery P. Clinical response and time to active disease following infliximab therapy in patients with HLA-B27 positive very early ankylosing spondylitis [abstract]. *Ann Rheum Dis* 2009;68(supp13):72. Abstract OP-0016.

Boonen A, van der Linden SM. The burden of ankylosing spondylitis. *J Rheumatol Suppl*. 2006;78:4-11.

Brandt J, Khariouzov A, Listing J, Haibel H, Sörensen H, Grassnickel L, Rudwaleit M, Sieper J, Braun J. Six-month results of a double-blind placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum*. 2003;48(6):1667-1675.

Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. *Ann Rheum Dis.* 2004;63(11):1438-1444.

Brandt J, Listing J, Haibel H, Sörensen H, Schwebig A, Rudwaleit M, Sieper J, Braun J. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. *Rheumatology (Oxford)*. 2005;44(3):342-348.

Braun J, Sieper J. Ankylosing spondylitis. *Lancet.* 2007;369(9570):1379-1390.

Braun J, Sieper J. Treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol*. 2009;27(4 suppl 55):S146-S147.

Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, Dagfinrud H, Dijkmans B, Dougados M, Emery P, Geher P, Hammoudeh M, Inman RD, Jongkees M, Khan MA, Kiltz U, Kvien TK, Leirisalo-Repo M, Maksymowych WP, Olivieri I, Pavelka K, Sieper J, Stanislawska-Biernat E, Wendling D, Ozgocmen S, van Drogen C, van Royen BJ, van der Heijde D. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis*. 2011;70(6):896-904.

Braun J, Baraliakos X, Heldmann F, Kiltz U. Tumor necrosis factor alpha antagonists in the treatment of axial spondyloarthritis. *Expert Opin Investig Drugs.* 2014;23(5):647-659.

Braun J, Deodhar AA, Sieper J, Dougados M, Porter B, Andersson M, Richards H. Secukinumab Significantly improves signs and symptoms of active ankylosing spondylitis: 52-week results from a randomized, double-blind, placebo-controlled phase 3 trial with subcutaneous loading and maintenance dosing [abstract]. *Arthritis Rheumatol*. 2015;67(suppl 10). Abstract 974.

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

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

CIMZIA [package insert]. Smyrna, Georgia: UCB; 2016. Available at: http://www.cimzia.com/assets/pdf/Prescribing_Information.pdf. Accessed August 14, 2016.

Columbia Suicide-Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed August 14, 2016.

COSENTYX [package insert]. East Hanover, New Jersey: Novartis; 2016. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/cosentyx.pdf. Accessed August 14, 2016.

Deodhar A, Braun J, Inman RD, Mack M, Parasuraman S, Buchanan J, Hsu B, Gathany T, van der Heijde D. Golimumab reduces sleep disturbance in patients with active ankylosing spondylitis: results from a randomized, placebo-controlled trial. *Arthritis Care Res (Hoboken)*. 2010;62(9):1266-1271.

Deodhar A, Reveille JD, van den Bosch F, Braun J, Burgos-Vargas R, Caplan L, Clegg DO, Colbert RA, Gensler LS, van der Heijde D, van der Horst-Bruinsma IE, Inman RD, Maksymowych WP, Mease PJ, Raychaudhuri S, Reimold A, Rudwaleit M, Sieper J, Weisman MH, Landewé RB. The concept of axial spondyloarthritis: joint statement of the Spondyloarthritis Research and Treatment Network and the Assessment of SpondyloArthritis International Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol.* 2014;66(10):2649-2656.

Dougados M, Baeten D. Spondyloarthritis. *Lancet*. 2011;377(9783):2127-2137.

Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, Miceli-Richard C, Wei JC, Pederson R, Bonin R, Rahman MU, Logeart I, Wajdula J, Koenig AS, Vlahos B, Alvarwz D, Bukowski JF. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2014;66(8):2091-2102.

ENBREL [package insert]. Thousand Oaks, California: Amgen Inc; 2015. Available at: http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf. Accessed August 14, 2016.

EuroQol Group. EQ-5D-5L User Guide. Version 1.0. April 2011. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L. Accessed August 14, 2016.

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

Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis*. 2010;69(11):2002-2008.

Gottlieb AB, Mease PJ, Cuchacovich RS, Shuler CL, Lin CY, Burge RT, Samanta S, Lee CH, Gladman DD. Ixekizumab improves physical function, quality of life, and work productivity in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis [abstract]. *Arthritis Rheumatol*. 2015;67(suppl 10).

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015;386(9993):541-551.

Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, Braun J, Sieper J. Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum.* 2008;58(7):1981-1991.

Haibel H, Specker C. Disease-modifying anti-rheumatic drugs in rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol*. 2009:27(4 suppl 55):S159-S163.

Haibel H, Heldmann F, Rudwaleit M, Listing J, Kupper H, Braun J, Sieper J. Long-term efficacy of adalimumab for patients with active non-radiographic, axial spondyloarthritis (SPA) who relapsed following adalimumab withdrawal [abstract]. *Ann Rheum Dis* 2010;69(SuppI3):59. Abstract OP0027.

Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, Kvien TK. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis Rheum.* 2008;59(2):234-240.

Hsu J, Berger RL. Stepwise confidence intervals without multiplicity adjustment for dose response and toxicity studies. *J Am Stat Assoc*. 1999;94:468–482.

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

HUMIRA [package insert]. North Chicago, IL: AbbVie Inc; 2016. Available at: http://www.rxabbvie.com/pdf/humira.pdf. Accessed August 14, 2016.

IDS/QIDS home page. IDS/QIDS web site. Available at: http://www.ids-qids.org/. Accessed August 14, 2016.

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

Jandus C, Bioley G, Rivals JP, Dudler J, Speiser D, Romero P. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondyloarthritides. *Arthritis Rheum*. 2008;58(8):2307-2317.

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

Kiltz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, Maksymowych WP, Marzo-Ortega H, Reveille J, Stebbings S, Bostan C, Braun J. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis.* 2015;74(5)830-835.

Landewé R, Rudwaleit M, van der Heijde D, Dougados M, Maksymowych WP, Braun J, Deodhar AA. Effect of certolizumab pegol on signs and symptoms of ankylosing spondylitis and non-radiographic axial spondyloarthritis: 24 week results of a double blind randomized placebo-controlled phase 3 axial spondyloarthritis study [abstract]. *Arthritis Rheum.* 2012;64(Suppl 10):777.

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

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

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

Machado PM, Navarro-Compán V, Landewé R, Floris A, van Gaalen A, Roux C, van der Heijde D. Calculating the Ankylosing Spondylitis Disease Activity Score if the conventional c-reactive protein level is below the limit of detection or if high-sensitivity c-reactive protein is used: an analysis in the DESIR cohort. *Arthritis Rheum*. 2015;67(2):408-413.

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

Maksymowych WP. Disease modification in ankylosing spondylitis. *Nat Rev Rheumatol*. 2010:6(2):7581.

Mease PJ, van der Heijde D, Ritchlin CT, Cuchacovich R, Shuler CL, Lee CH, Samanta S, Lin CY, Gladman DD, Vangerow H. A randomized, double-blind, active- and placebo-controlled phase 3 study of efficacy and safety of ixekizumab, adalimumab, and placebo therapy in patients naive to biologic disease modifying anti-rheumatic drugs with active psoriatic arthritis [abstract]. *Arthritis Rheumatol*. 2015;67(suppl 10).

Mei Y, Pan F, Gao J, Ge R, Duan Z, Zeng Z, Liao F, Xia G, Wang S, Xu S, Xu J, Zhang L, Ye D. Increased serum IL-17 and IL-23 in the patient with ankylosing spondylitis. *Clin Rheumatol.* 2011;30(2):269-273.

Naegeli AN, Flood E, Tucker J, Devlen J, Edson-Heredia E. The patient experience with fatigue and content validity of a measure to assess fatigue severity: qualitative research in patients with ankylosing spondylitis (AS). *Health Qual Life Outcomes.* 2013;11:192.

Poddubnyy D, Brandt H, Vahldiek J, Spiller I, Song IH, Rudwaleit M, Sieper J. The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic. *Ann Rheum Dis.* 2012;71(12):1998-2001.

Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? *Ther Adv Musculoskelet Dis*. 2013;5(1):45-54.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035-1043.

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

Reilly Associates Health Outcomes Research web site. Available at: http://www.reillyassociates.net/. Accessed August 14, 2016.

Reveille JD. The genetic basis of spondyloarthritis. *Ann Rheum Dis*. 2011:70(suppl 1):i44-i50.

Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondyloarthritis in the United States: estimates from a cross-sectional survey. *Arthritis Care Res*. 2012;64(6): 905–910.

Robinson PC, Bird P, Lim I, Saad N, Schachna L, Taylor AL, Whittle SL, Brown MA. Consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA). *Int J Rheum Dis.* 2014;17(5):548-556.

Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis.* 2004;63(5):535–543.

Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum.* 2005;52(4):1000–1008.

Rudwaleit M, Landewé R, van der Heijde D, Listing J, Braun J, Burgos-Vargas R, Collantes-Estevez E, Davis J, Dijkmans B, Dougados M, Emery P, van der Horst-Bruinsma E, Inman R, Khan MA, Leirisalo-Repo M, van der Linden S, Maksymowych WP, Mielants H, Olivieri I, Sturrock R, de Vlam K, Sieper J. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis.* 2009a;68(6):770–776.

Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, Braun J, Chou CT, Collantes-Estevez E, Dougados M, Huang F, Gu J, Khan MA, Kirazli Y, Maksymowych WP, Mielants H, Sørensen IJ, Ozgocmen S, Roussou E, Valle-Oñate R, Weber U, Wei J, Sieper J. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009b;68(6):777-783.

Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H, Braun J, Sieper J. The early disease stage in axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum.* 2009c;60(3):717–727.

Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. *Nat Rev Rheumatol.* 2012;8(5):262–268.

Sanford M, McKeage K. Secukinumab: first global approval. *Drugs.* 2015;75(3):329-328.

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

Sieper J, van der Heijde, Dougados M, Brown LS, Lavie F, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2012;71(5):700-706.

Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, Arora V, Pangan AL. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis*. 2013;72(6):815-822.

Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, Park S, Song Y, Yao R, Chitkara D, Vastesaeger N; All INFAST Investigators. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. *Ann Rheum Dis*. 2014;73(1):101-107.

Sieper J, Landewé R, Rudwaleit M, van der Heijde D, Dougados M, Mease PJ, Braun J, Deodhar A, Kivitz A, Walsh J, Hoepken B, Nurminen T, Maksymowych WP. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. *Arthritis Rheumatol*. 2015; 67(3):668-677.

SIMPONI [package insert]. Horsham, PA: Janssen Biotech; 2016 Available at: http://www.simponi.com/shared/product/simponi/prescribing-information.pdf. Accessed August 14, 2016.

Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, Guérette B, Kupper H, Redden L, Arora V, Kavanaugh A. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet*. 2014;383(9914):321-332.

Strand V, Rao SA, Shillington AC, Cifaldi MA, McGuire M, Ruderman EM. Prevalence of Axial Spondyloarthritis in United States Rheumatology Practices: Assessment of SpondyloArthritis International Society Criteria versus Rheumatology Expert Clinical Diagnosis. *Arthritis Care Res.* 2013;65(8):1299-1306.

van den Berg R, de Hooge M, Rudwaleit M, Sieper J, van Gaalen F, Reijnierse M, Landewé R, Huizinga T, van der Heijde D. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis.* 2013;72(10):1646–1653.

van der Heijde D, Landewé R, van der Linden S. How should treatment effect on spinal radiographic progression in patients with ankylosing spondylitis be measured? *Arthritis Rheum*. 2005;52(7):1979-1985.

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

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

Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, Smith JA, Borenstein D, Hiratzka J, Weiss PF, Inman RD, Majithia V, Haroon N, Maksymowych WP, Joyce J, Clark BM, Colbert RA, Figgie MP, Hallegua DS, Prete PE, Rosenbaum JT, Stebulis JA, van den Bosch F, Yu DT, Miller AS, Reveille JD, Caplan L. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2016;68(2):282-298.

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

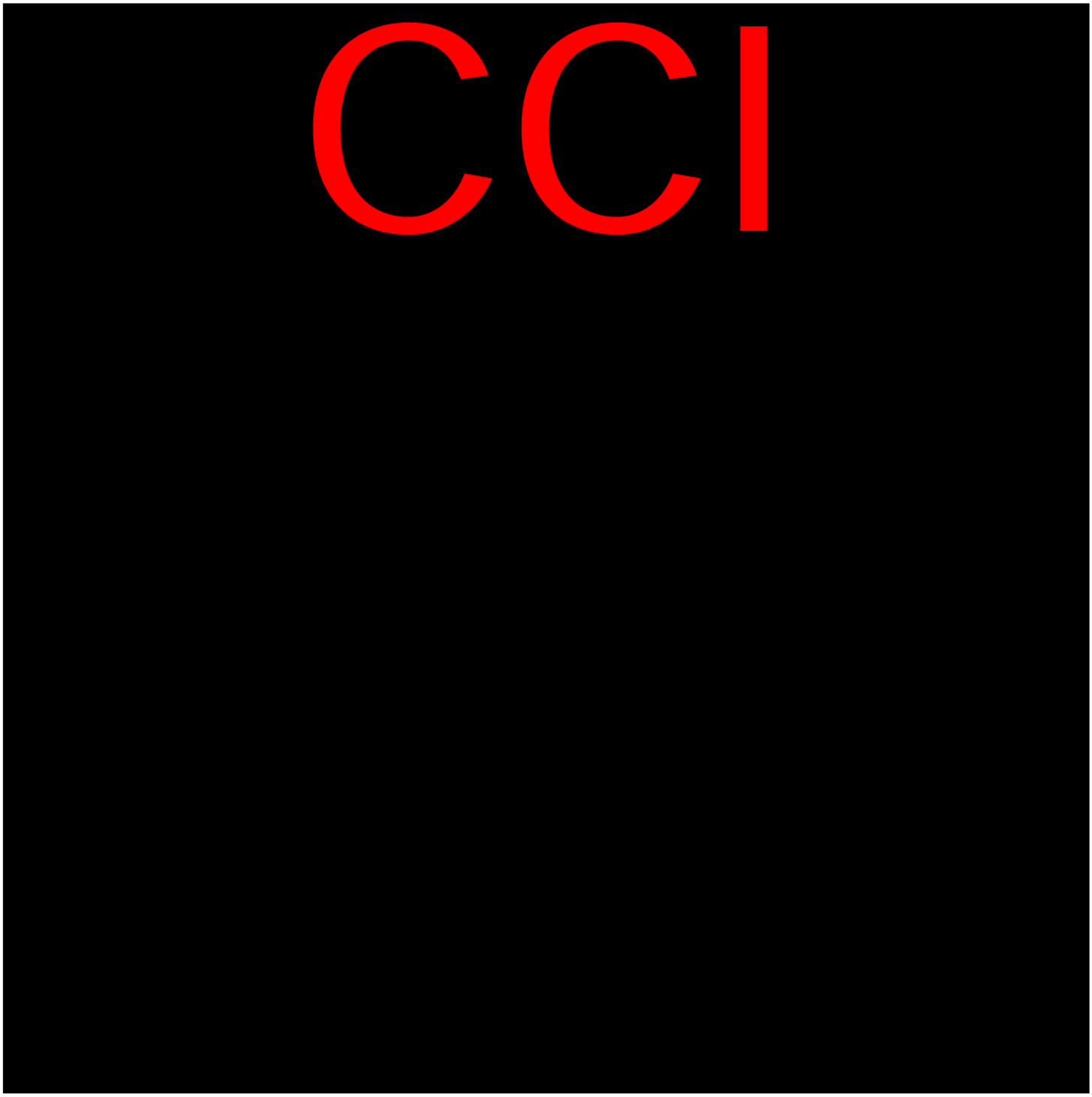
Wendling D, Cedoz JP, Racadot E, Dumoulin G. Serum IL-17, BMP-7, and bone turnover markers in patients with ankylosing spondylitis. *Joint Bone Spine.* 2007;74(3):304-305.

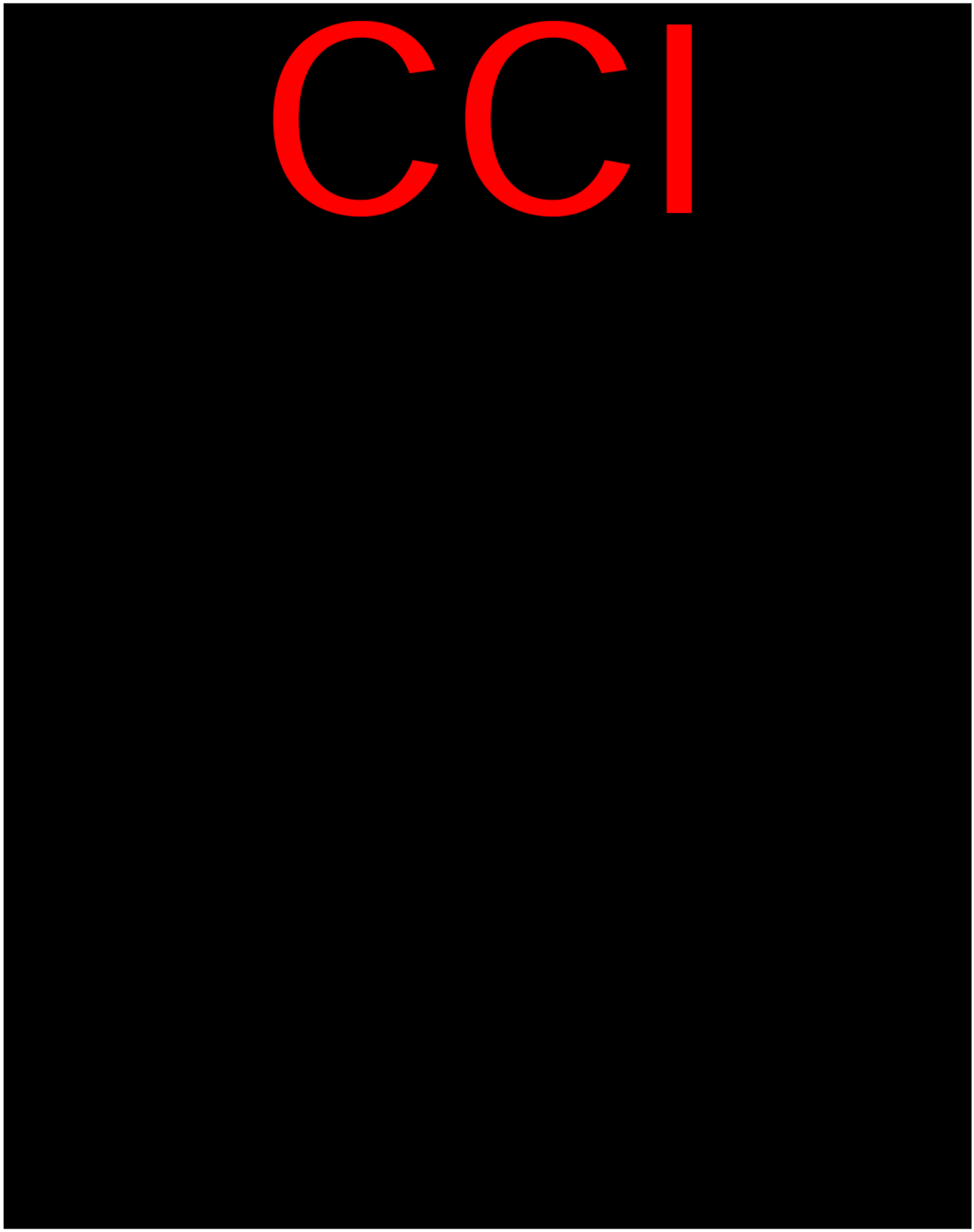
Yeremenko N, Paramarta JE, Baeten D. The interleukin-23/interleukin-17 immune axis as a promising new target in the treatment of spondyloarthritis. *Curr Opin Rheumatol*. 2014;26(4):361-370.

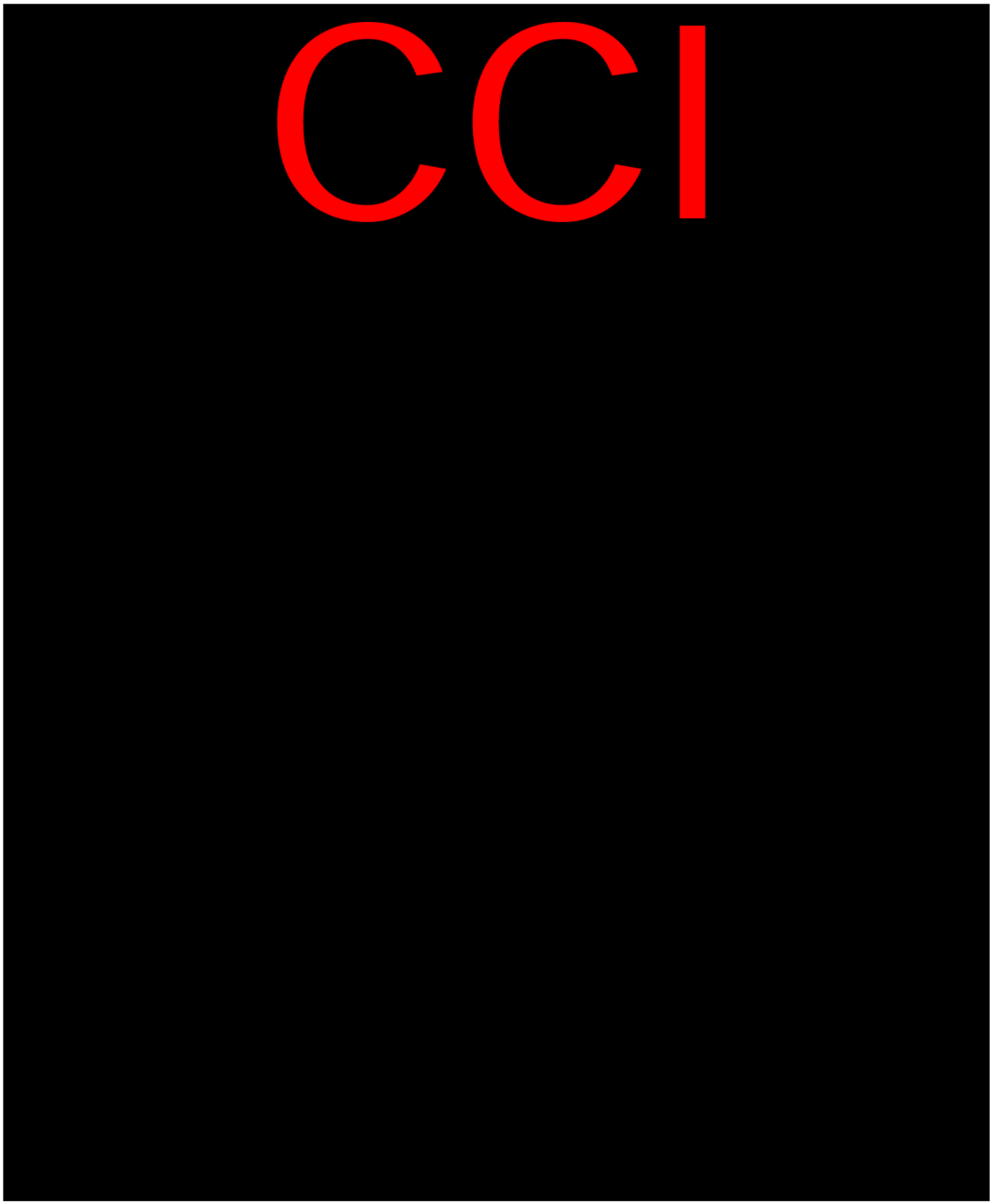
Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI),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

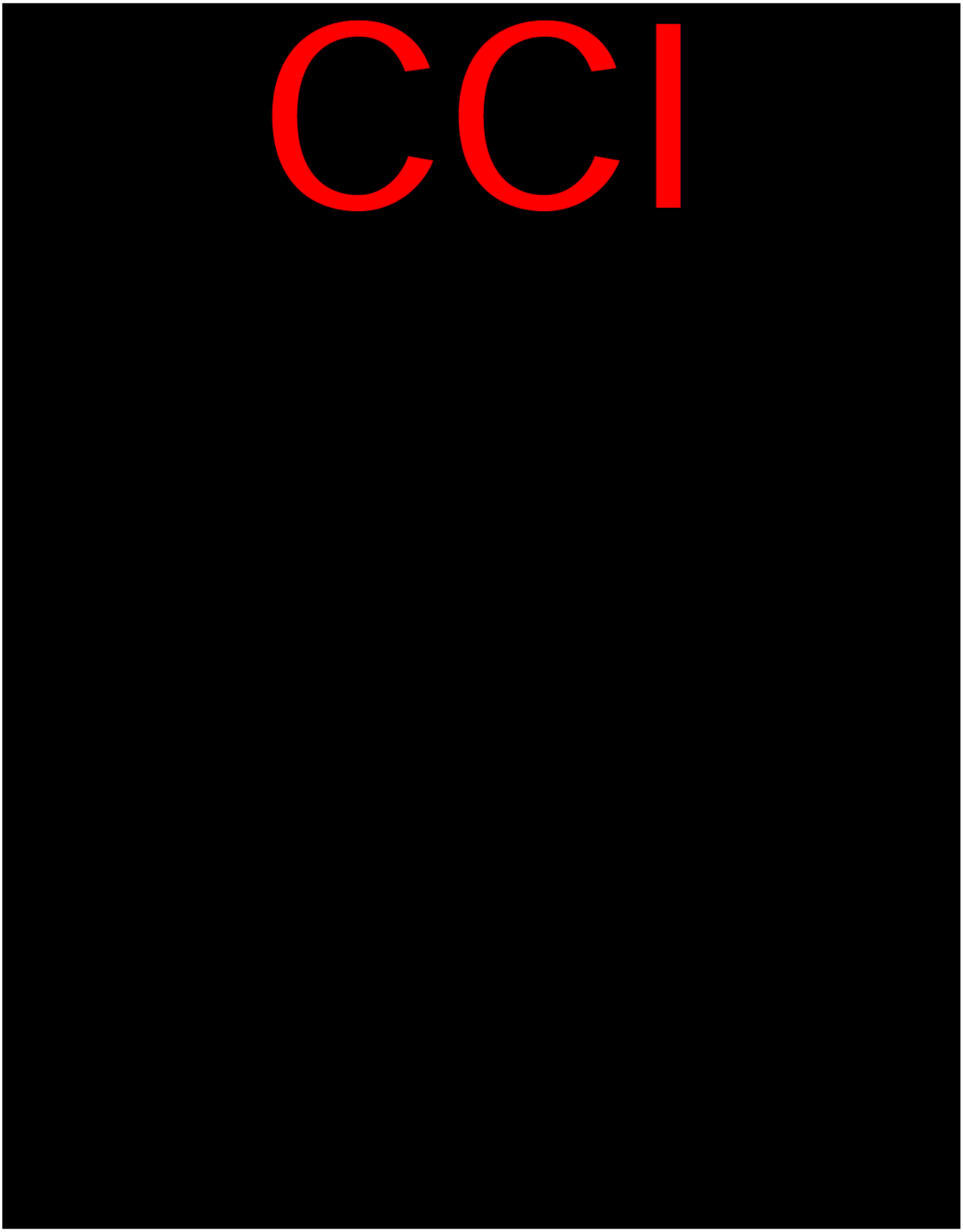
9. Appendices

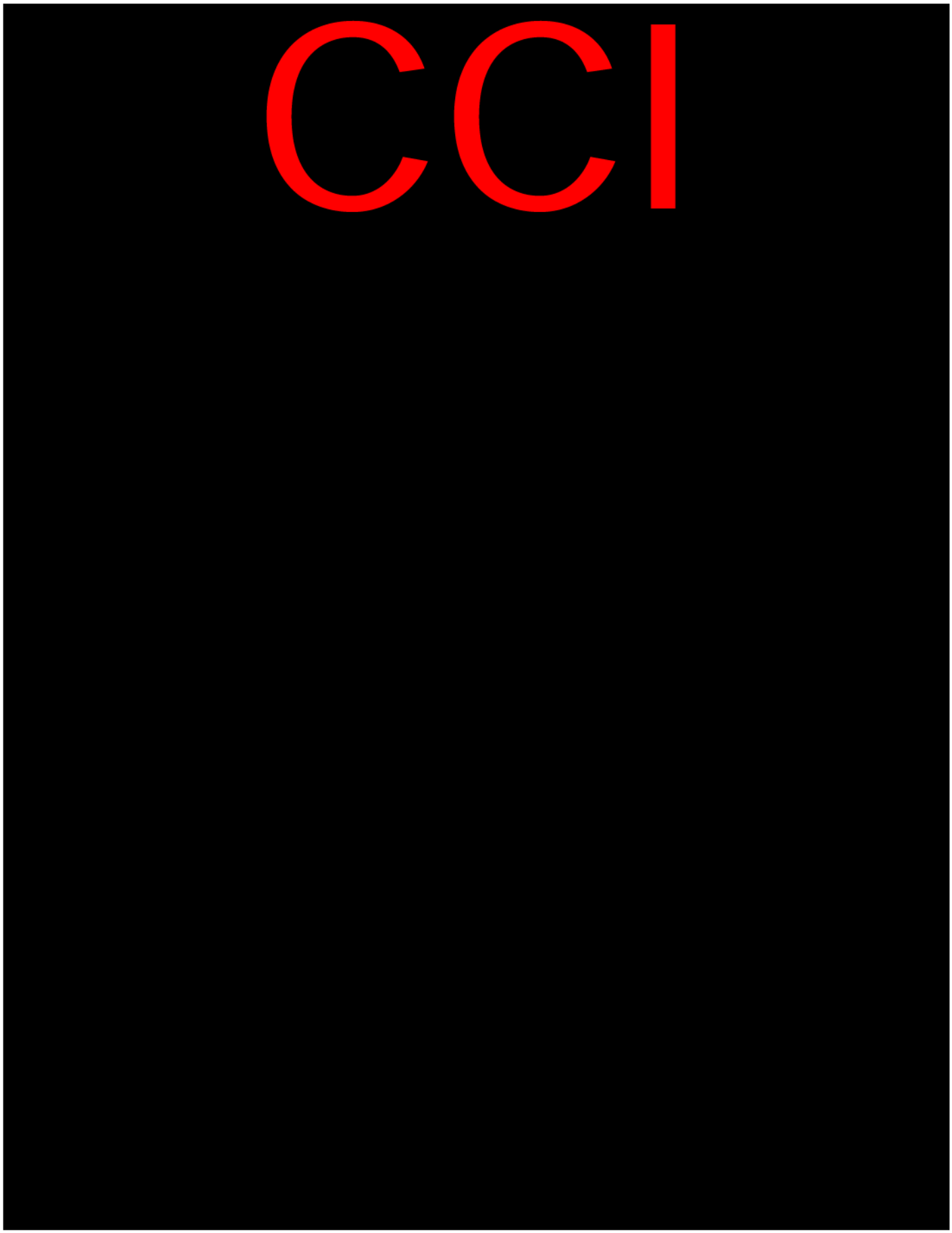
CCI

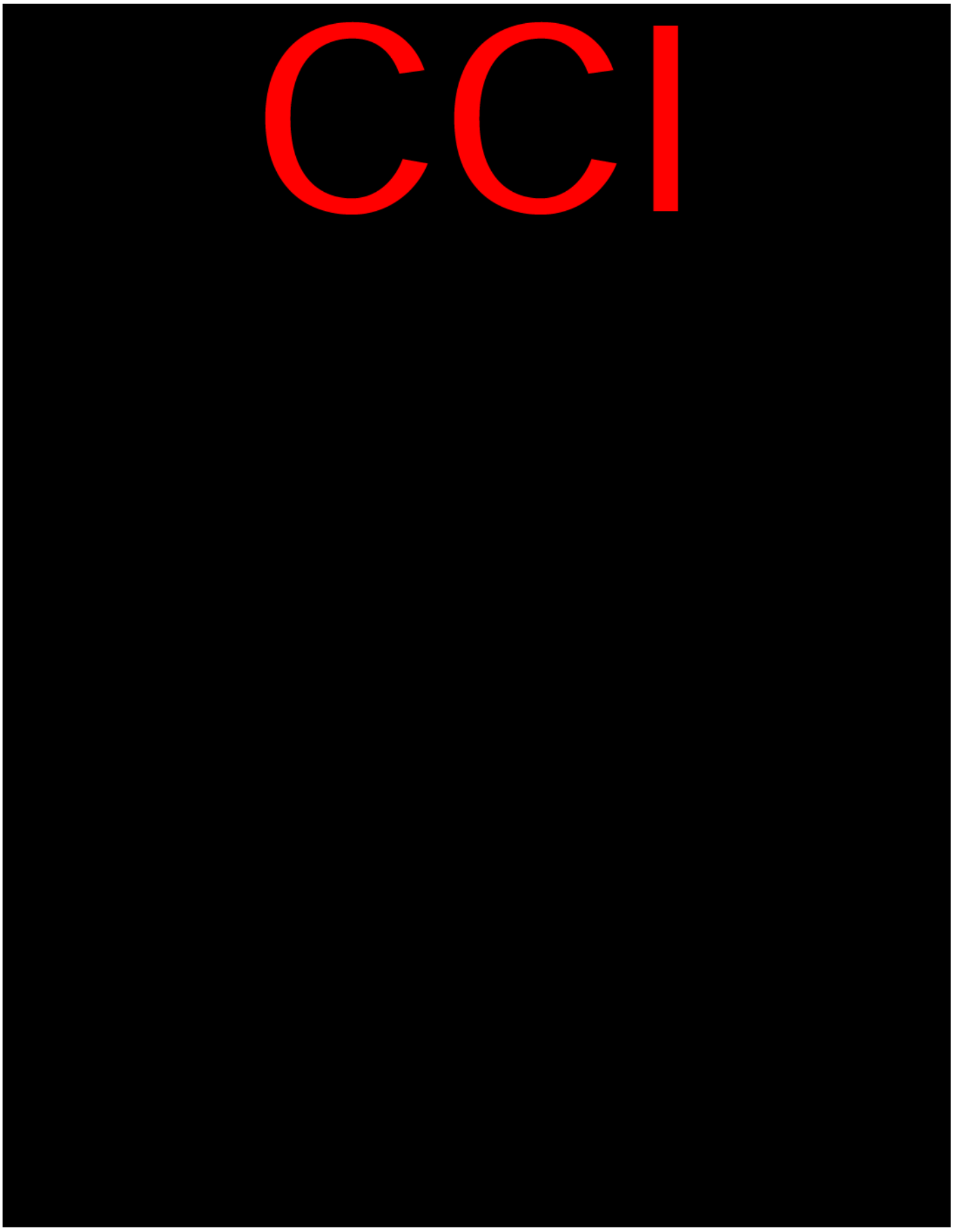

CCI

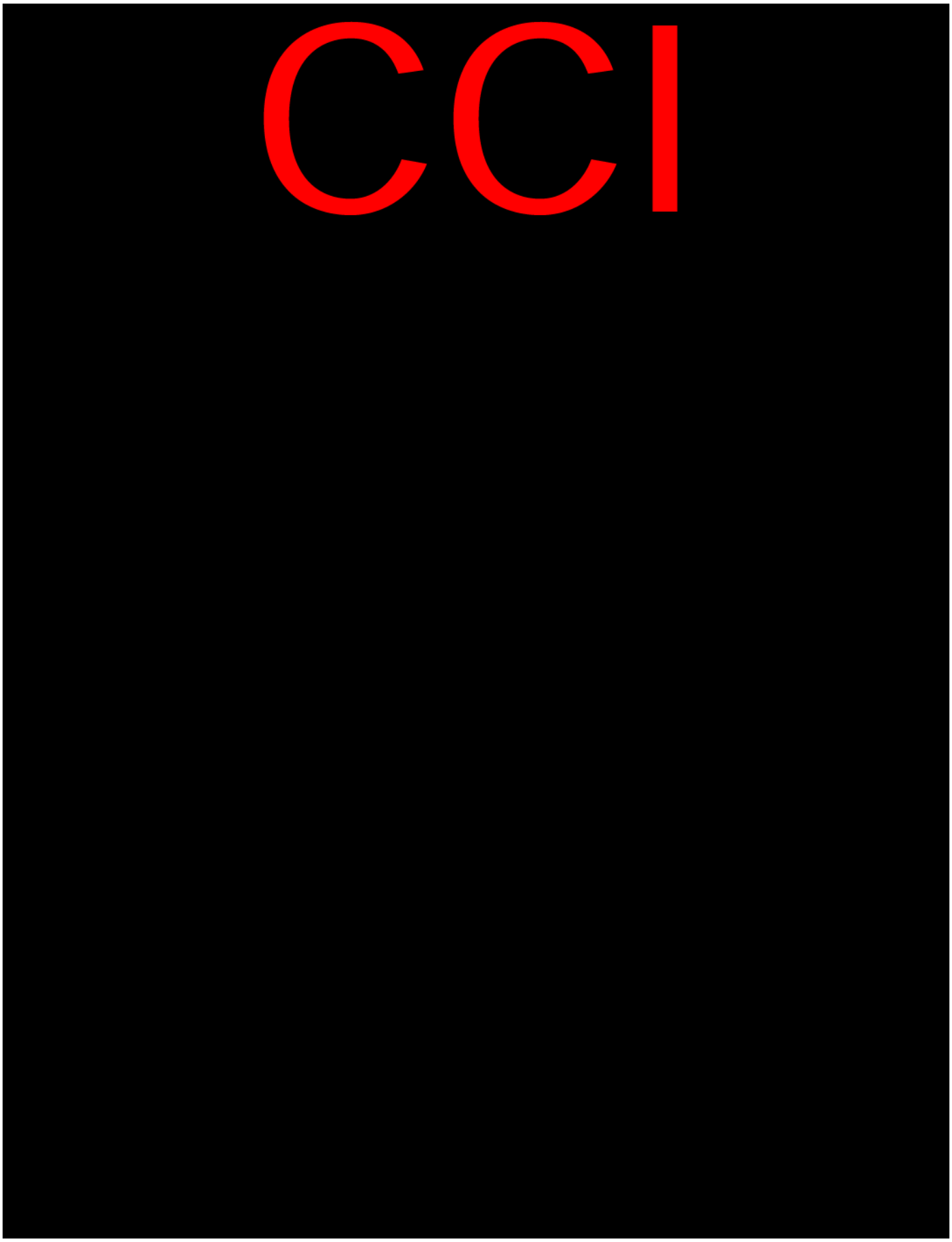

CCI

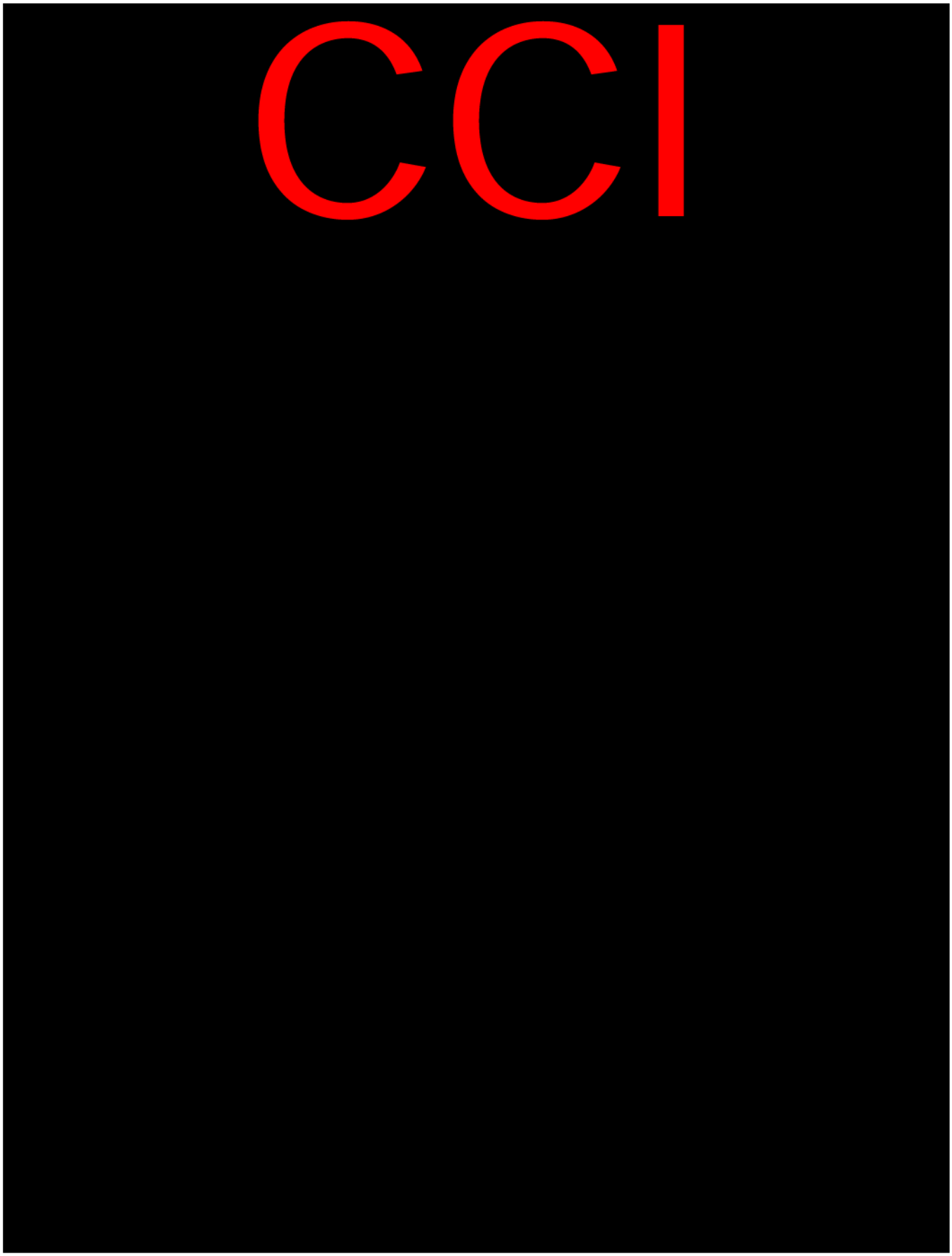

CCI


CCI

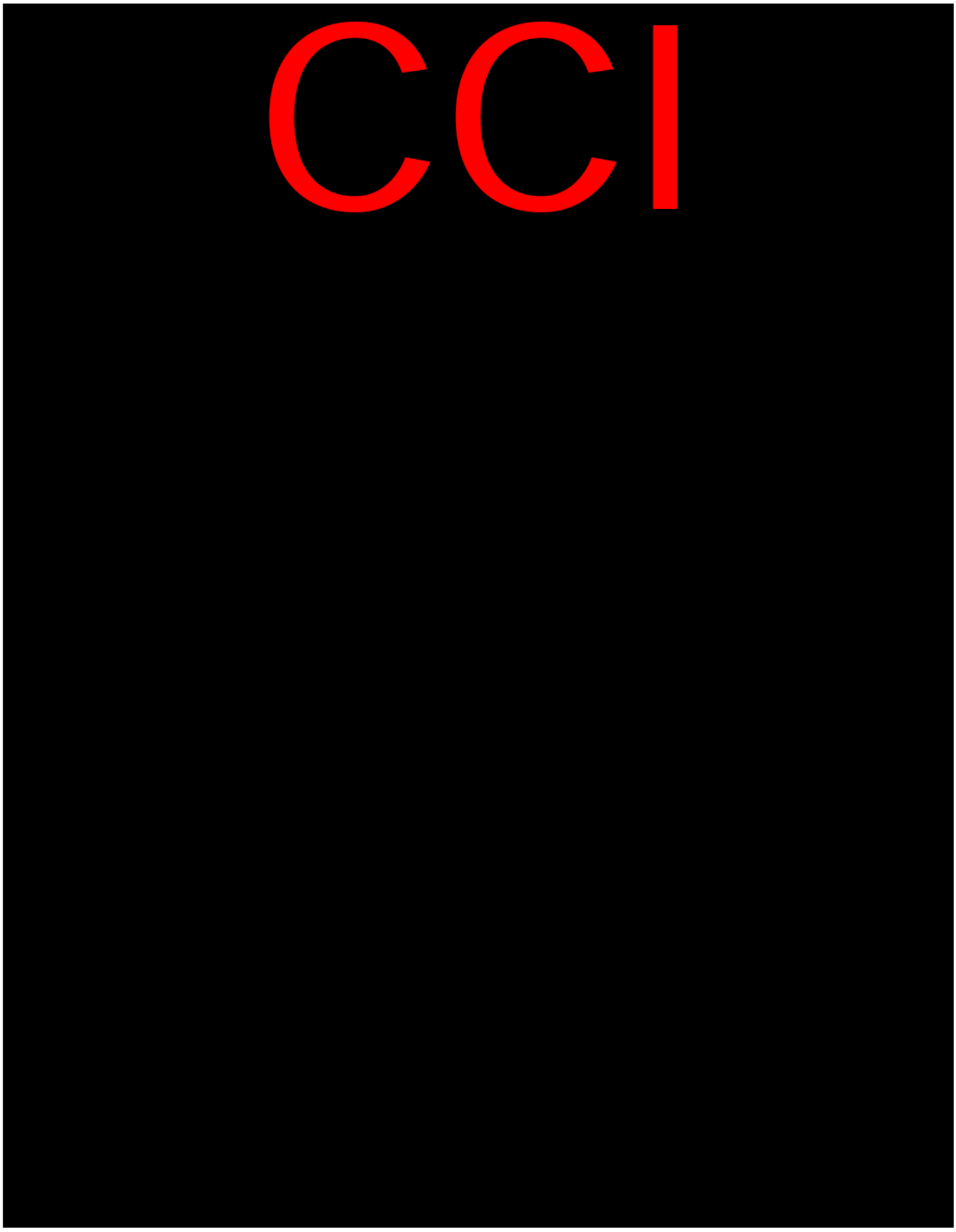

CCI

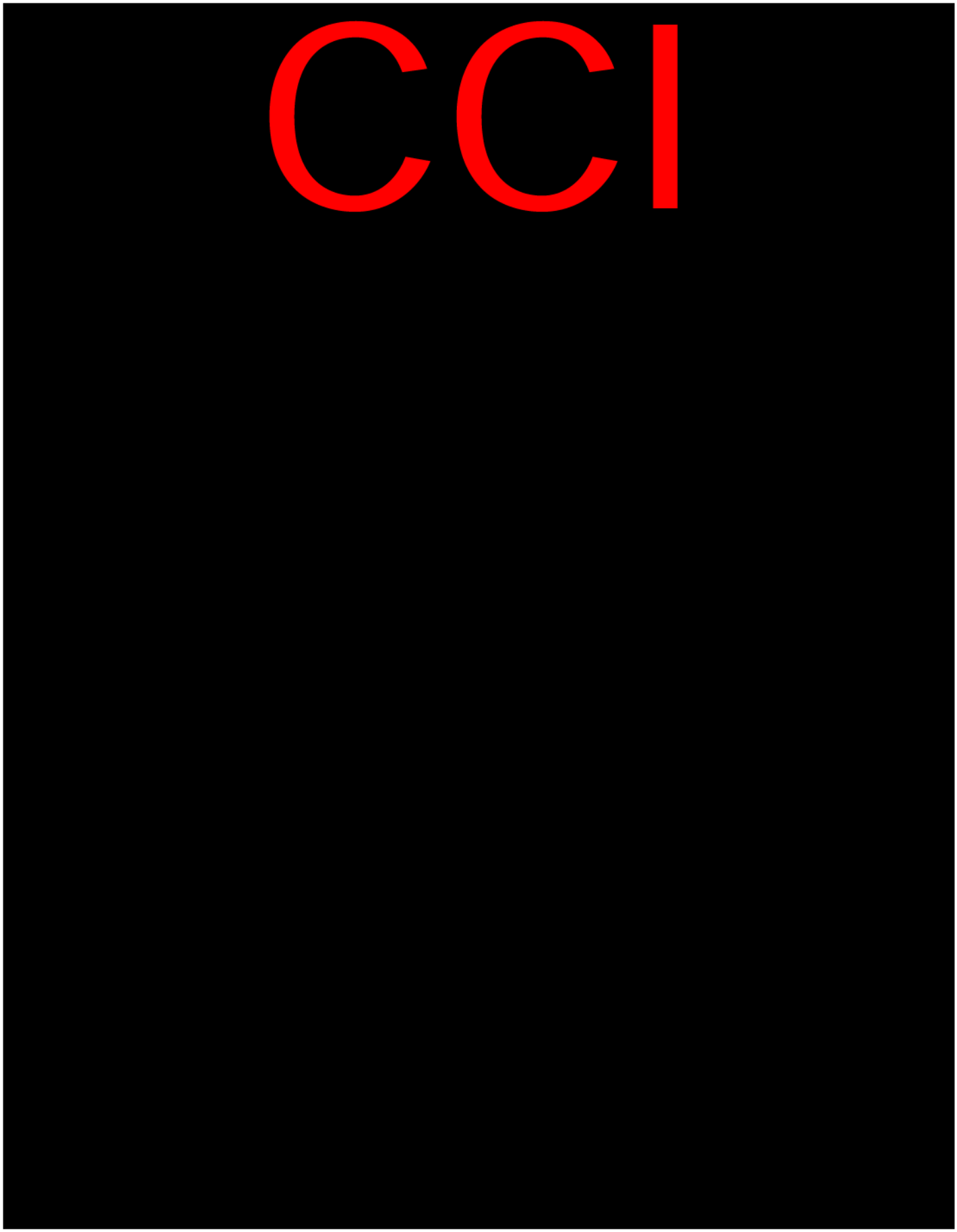

CCI


CCI

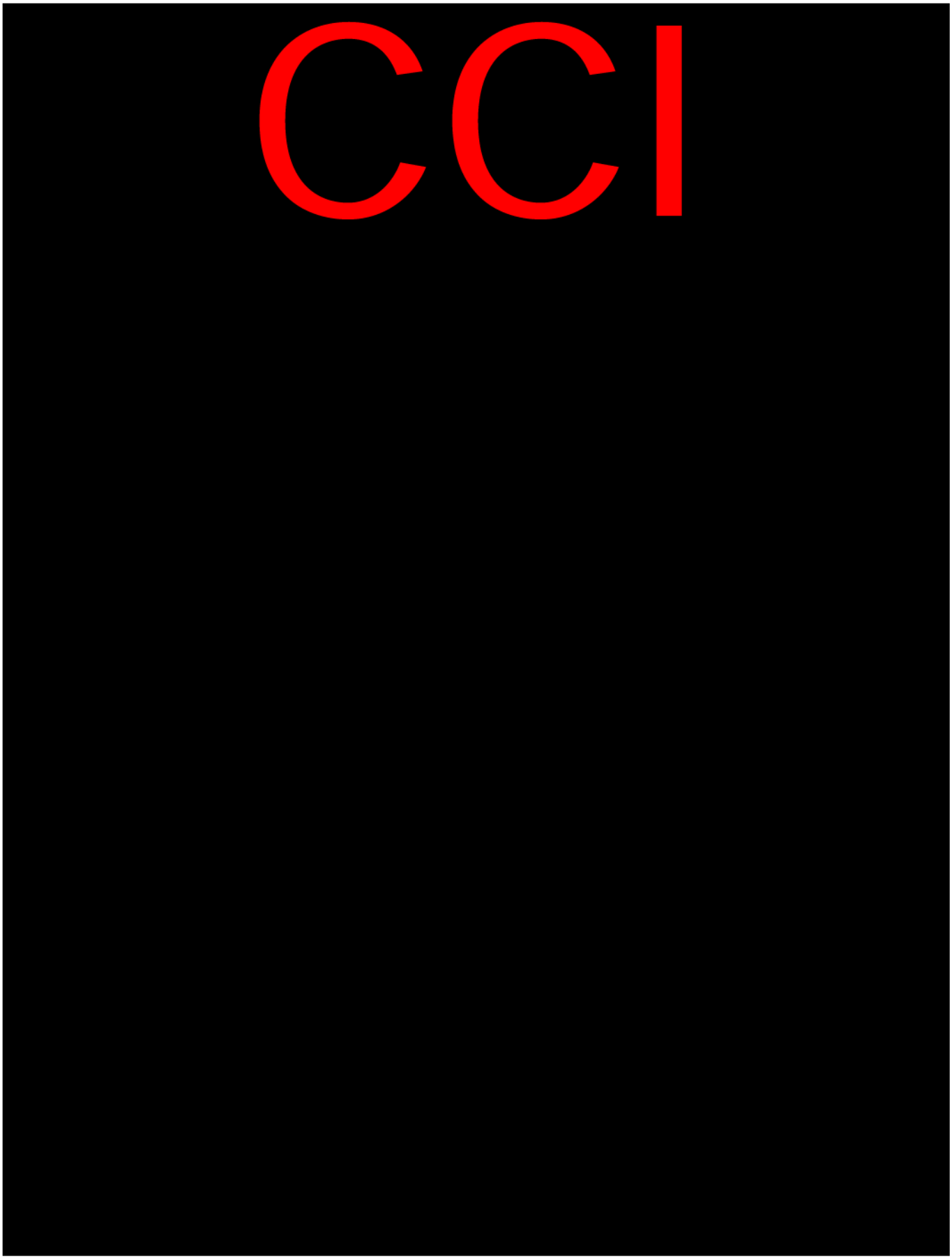

CCI

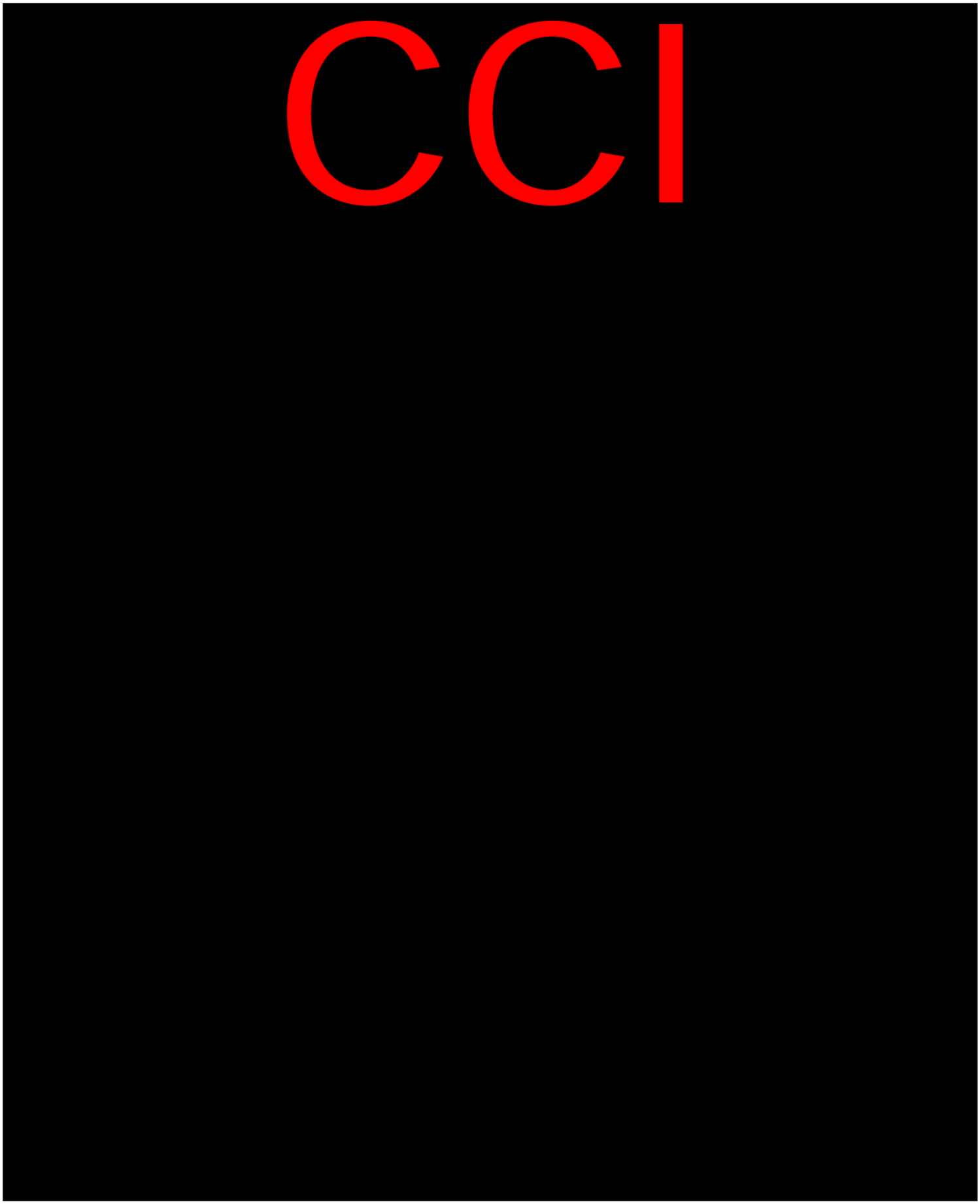

CCI

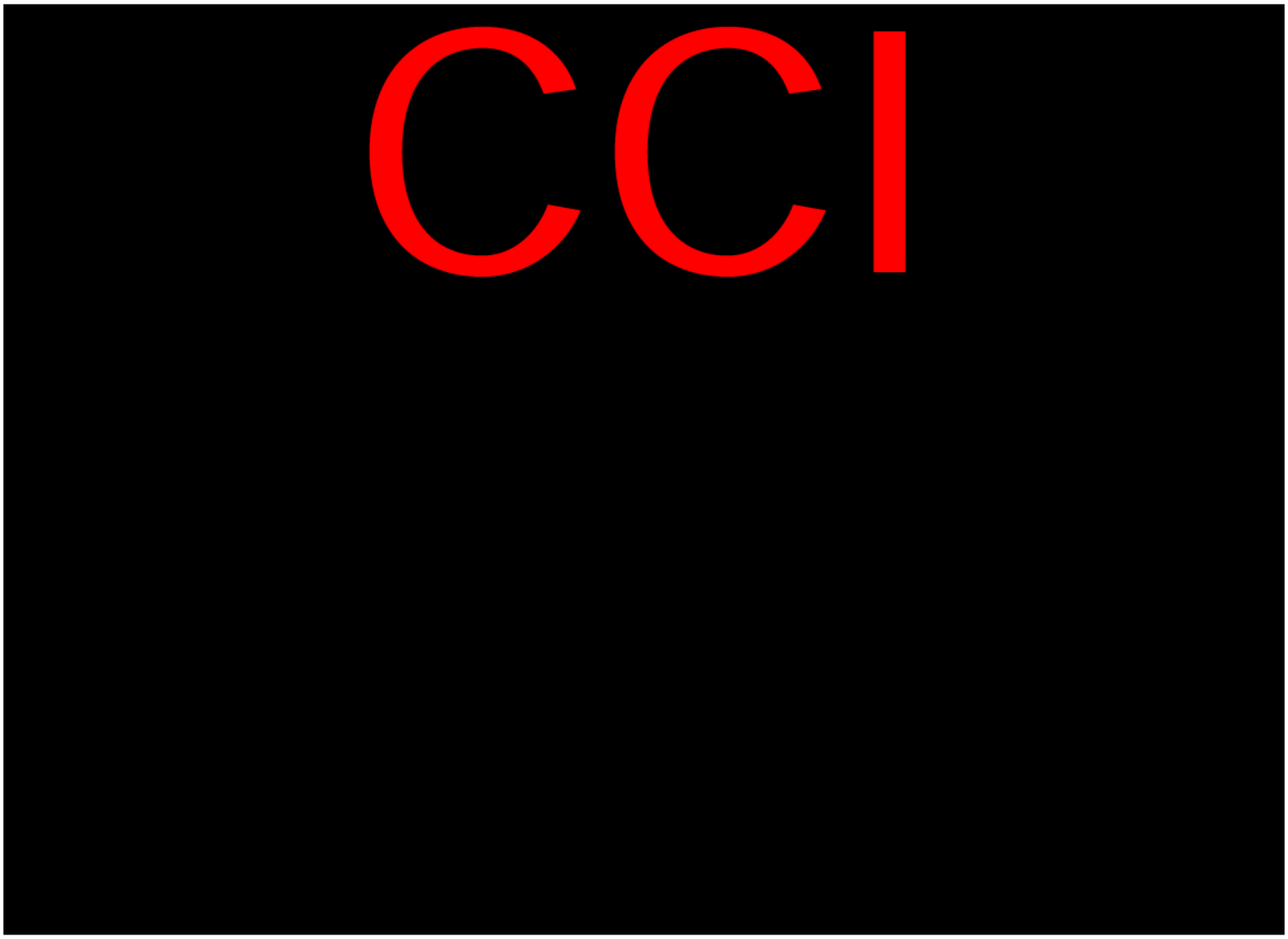

CCI

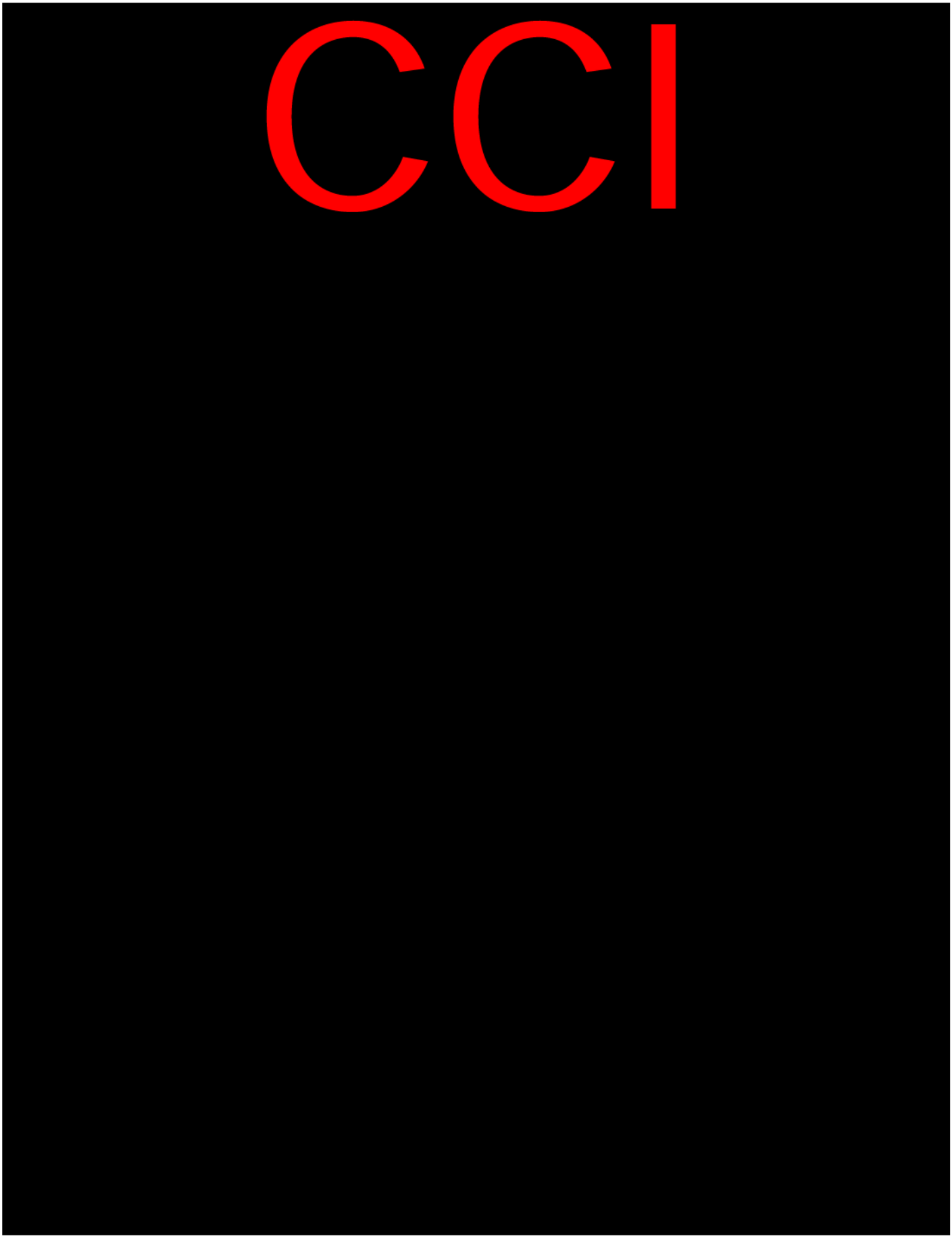

CCI

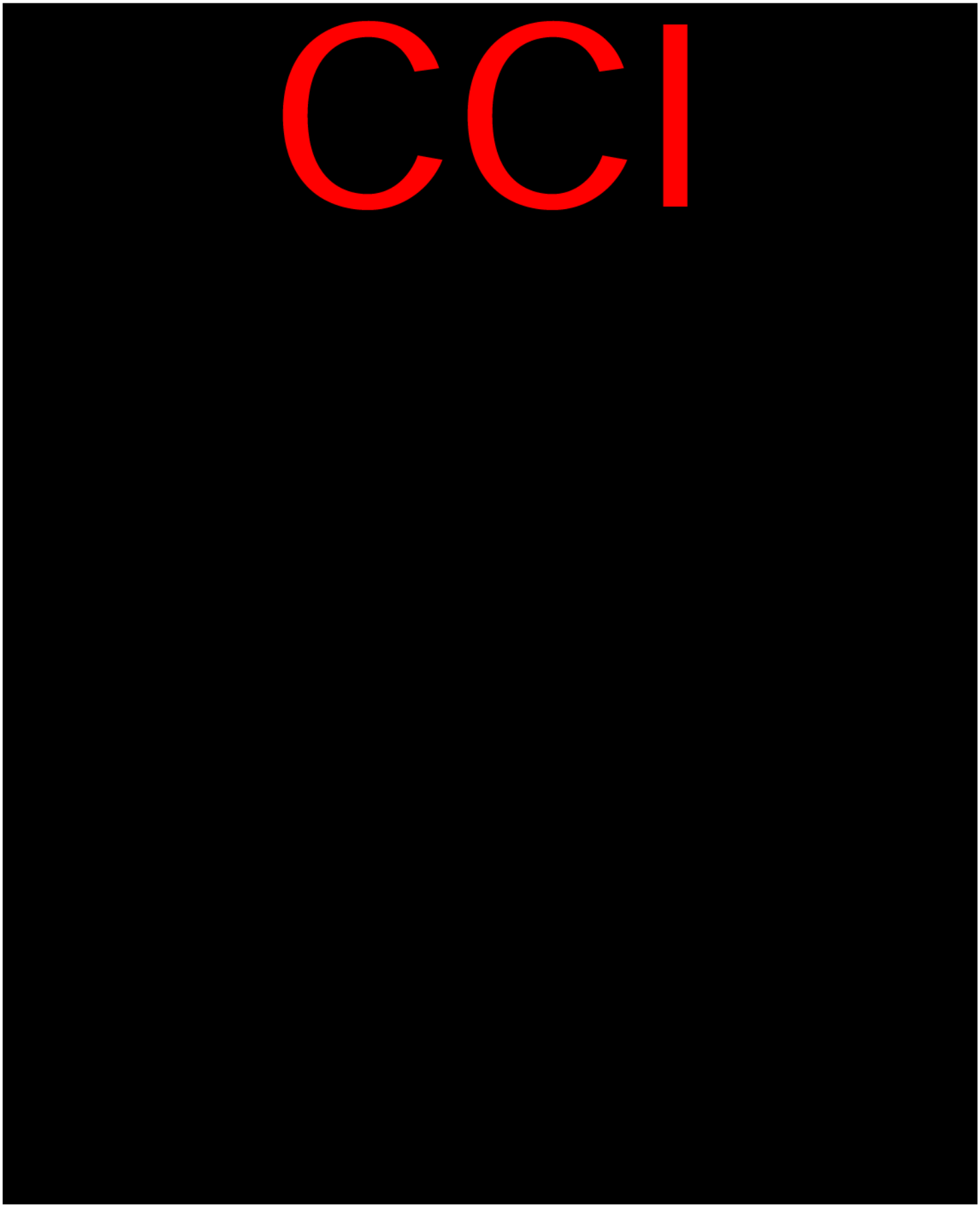
CCI


CCI

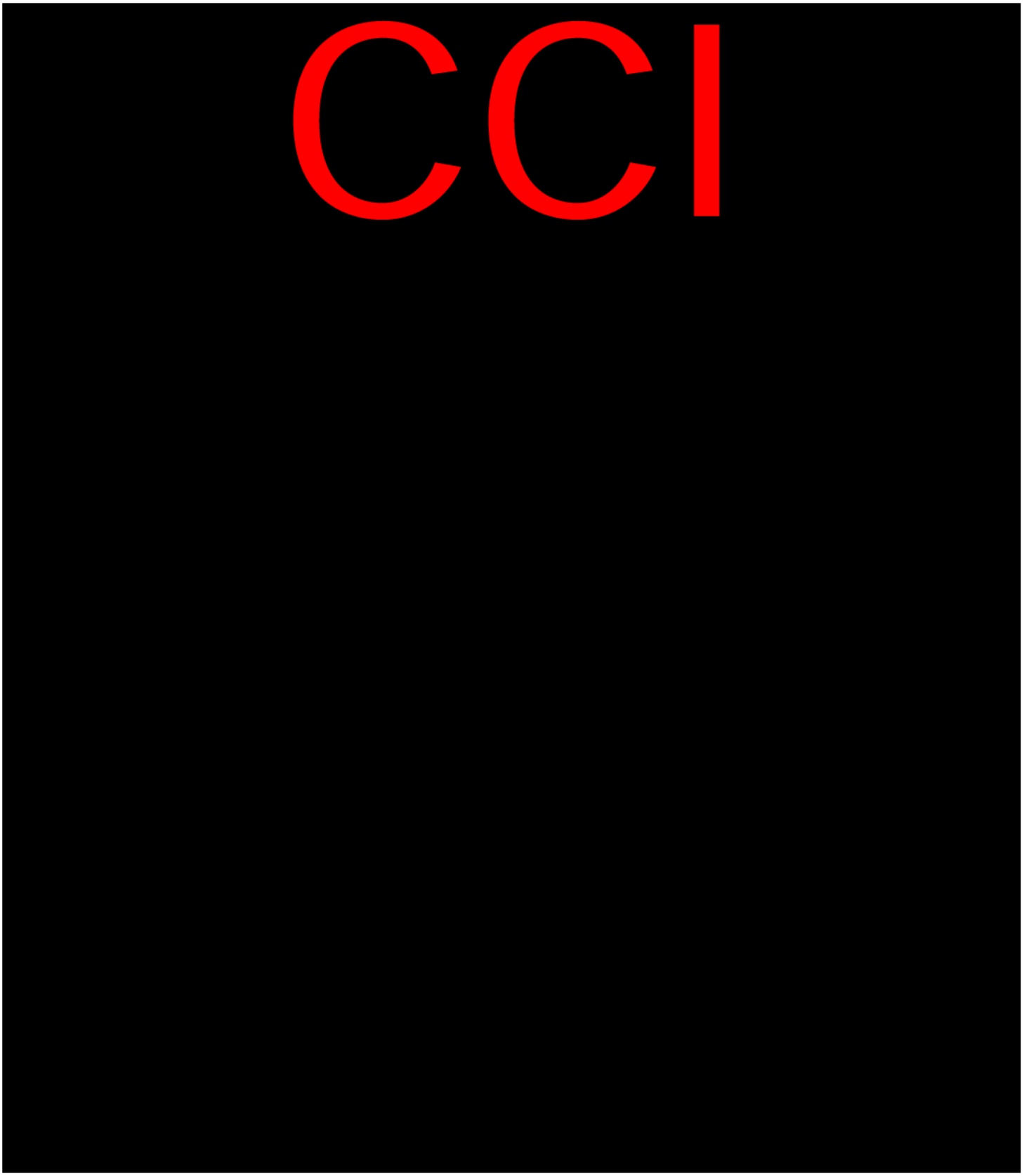

CCI

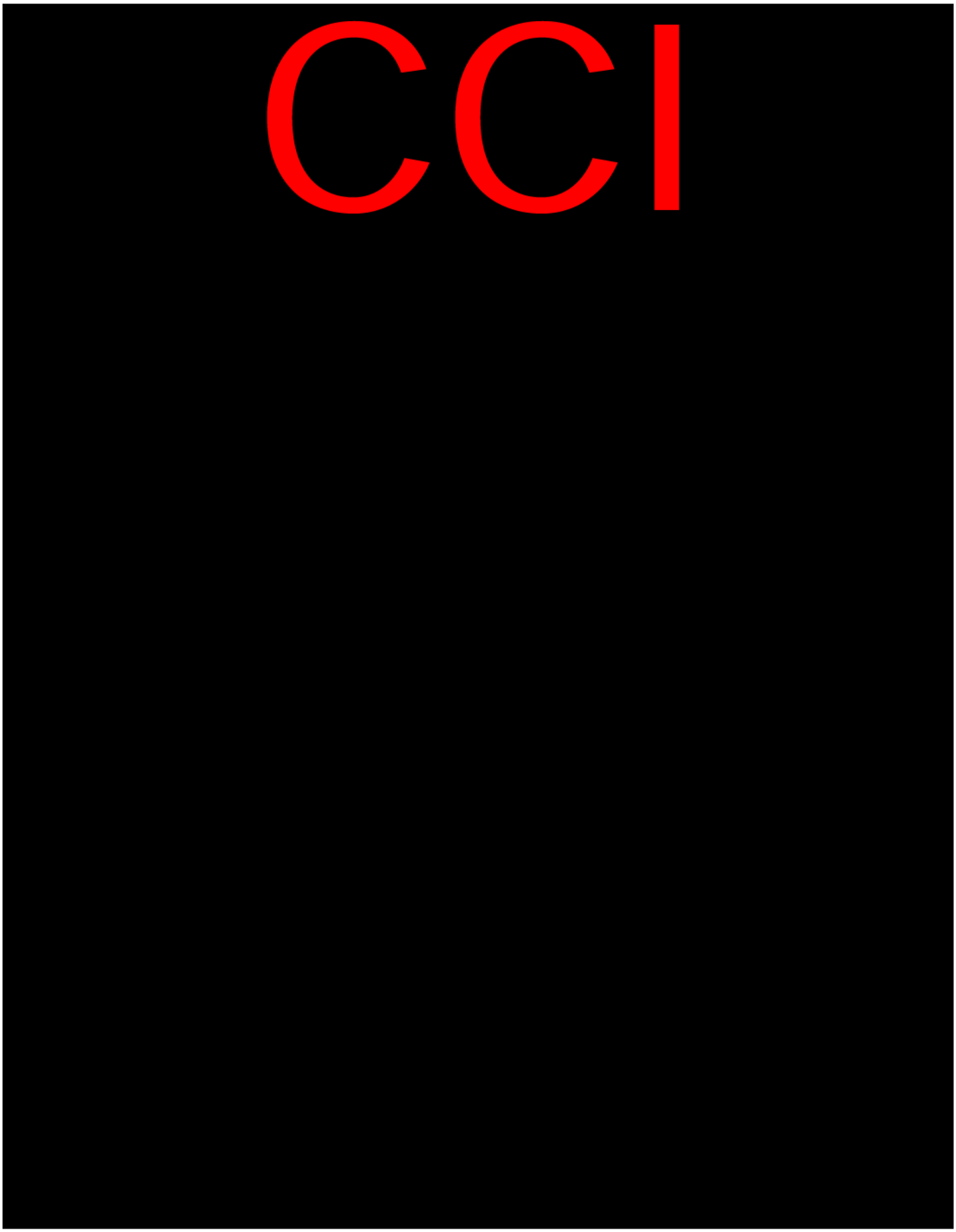

CCI


CCI

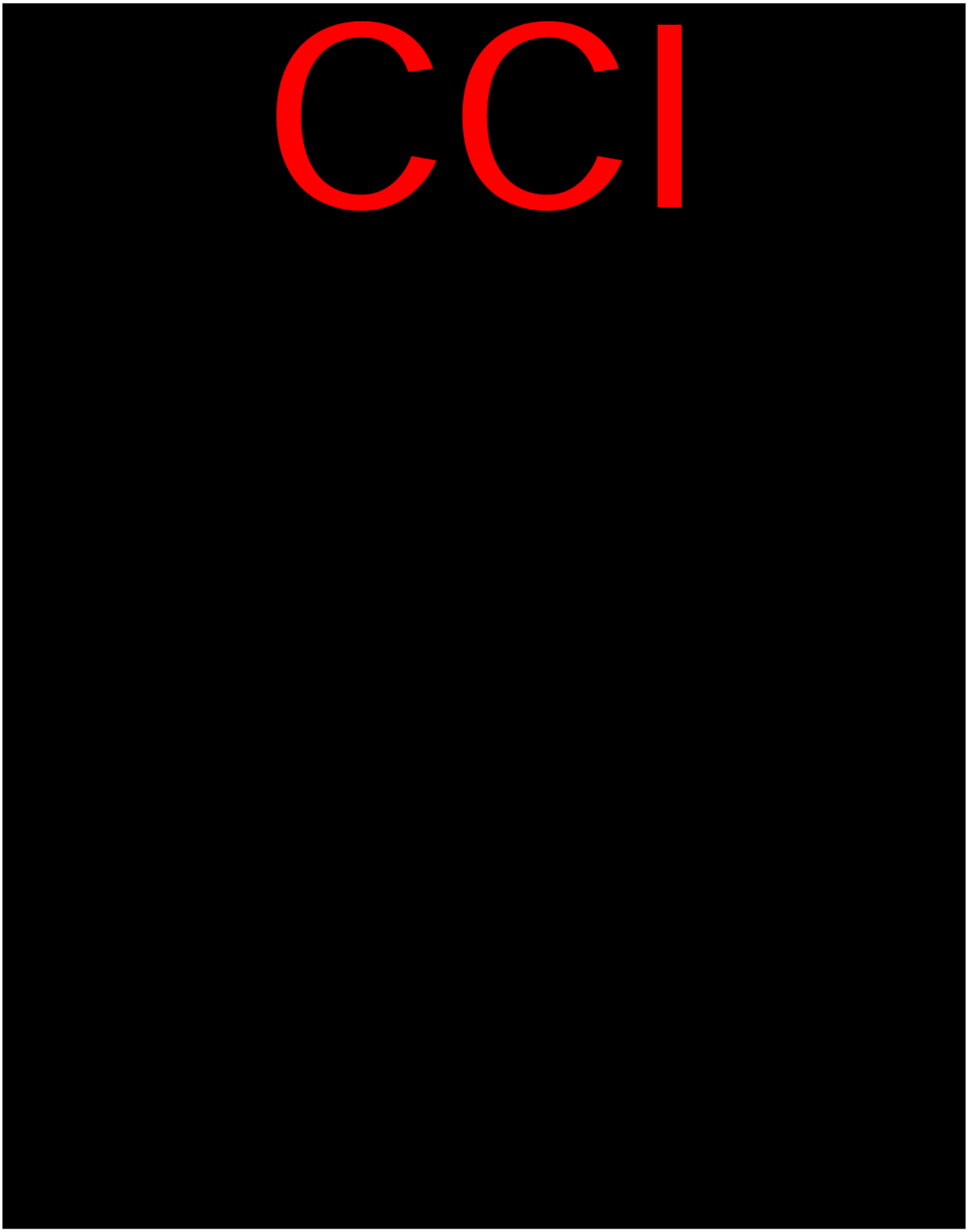

CCI

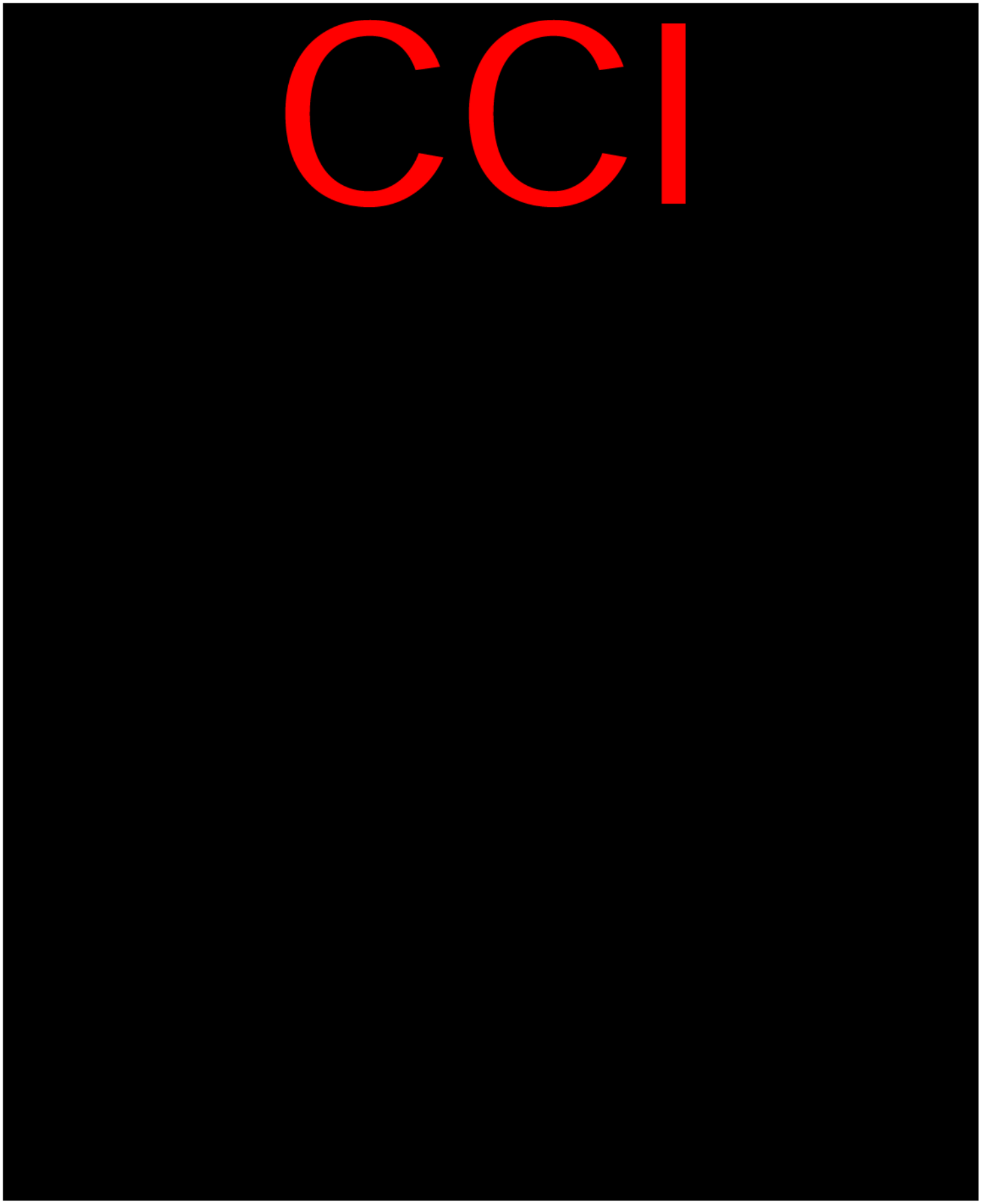
CCI

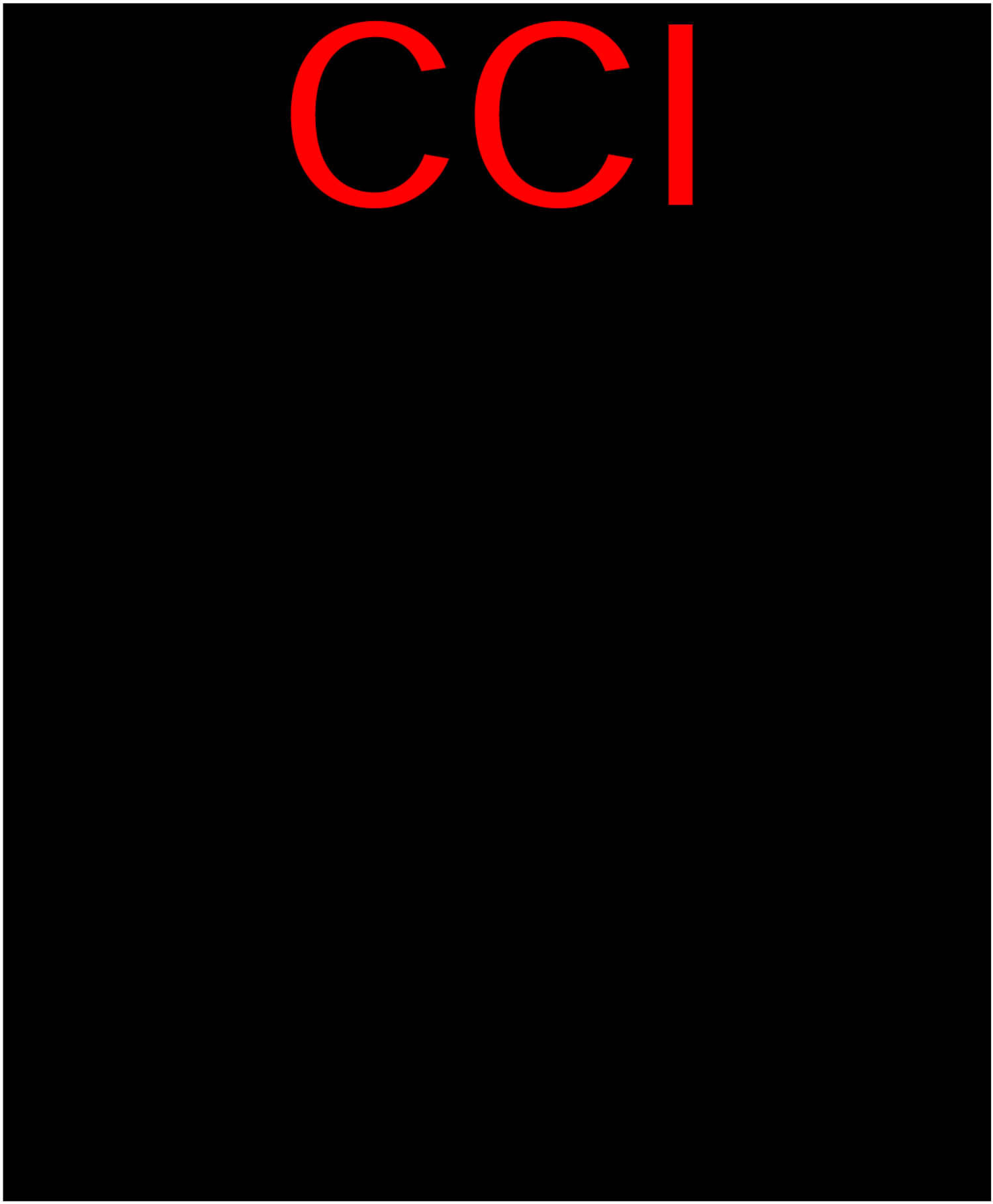

CCI


CCI

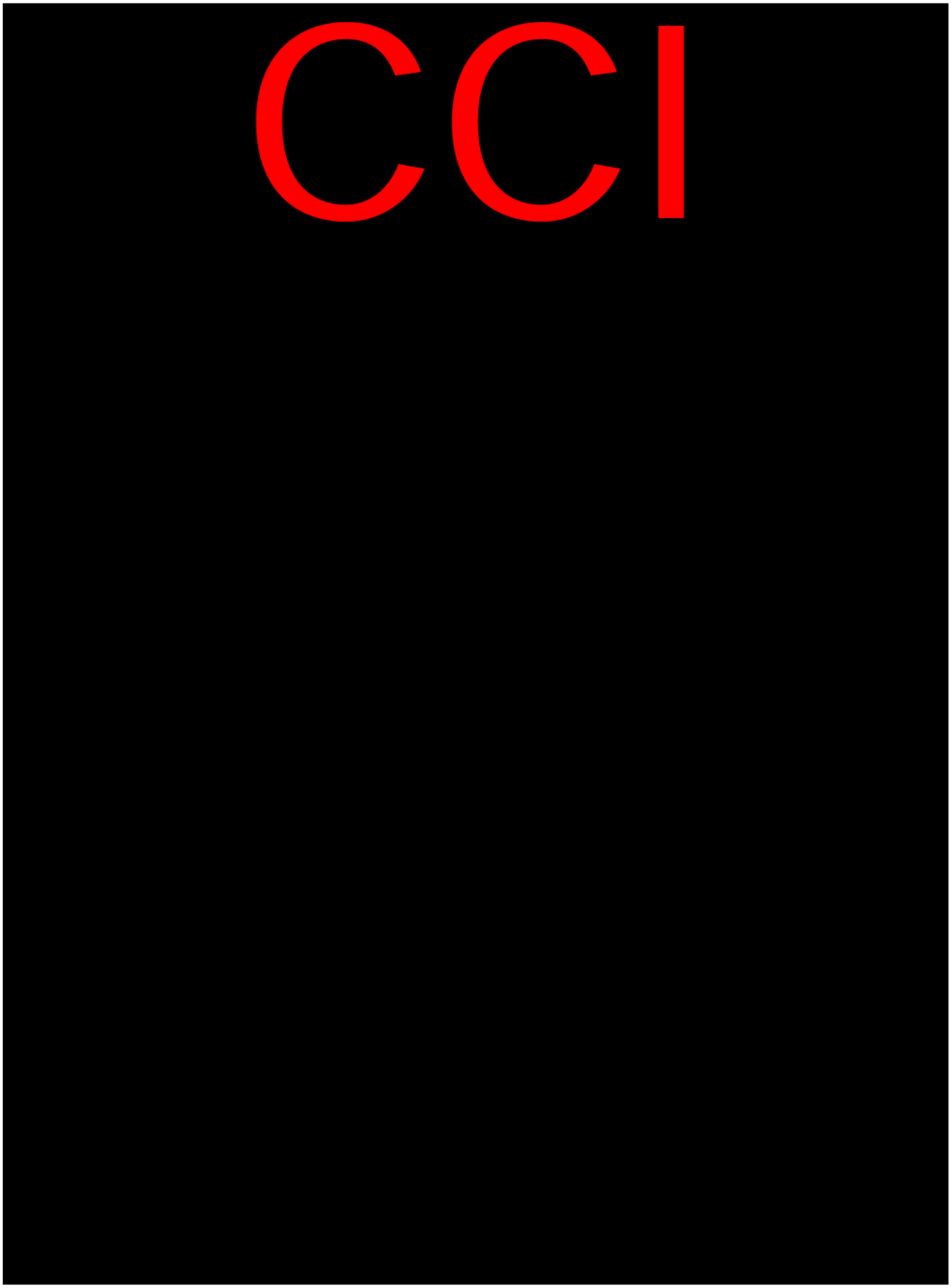
CCI


CCI


CCI

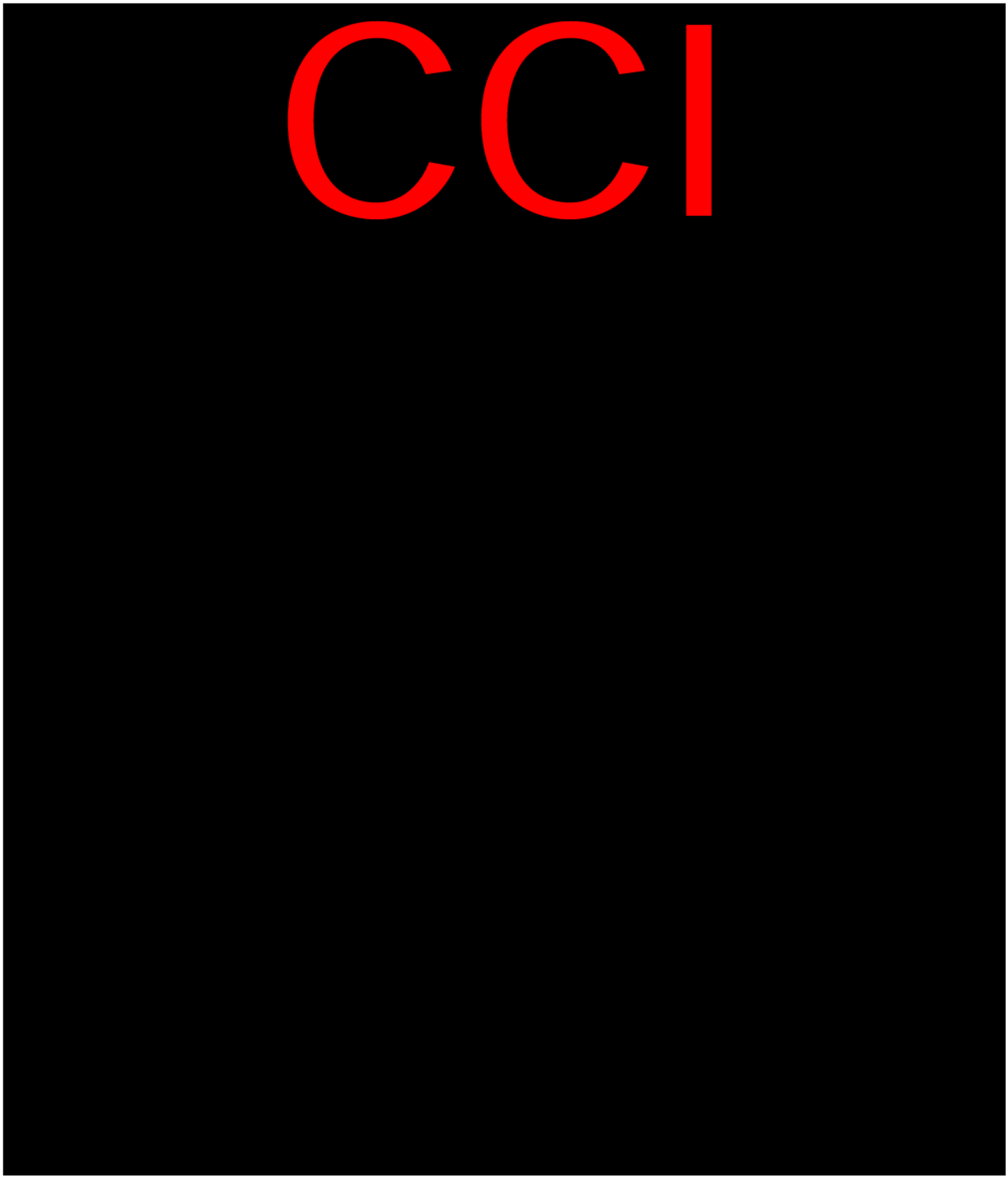

CCI


CCI

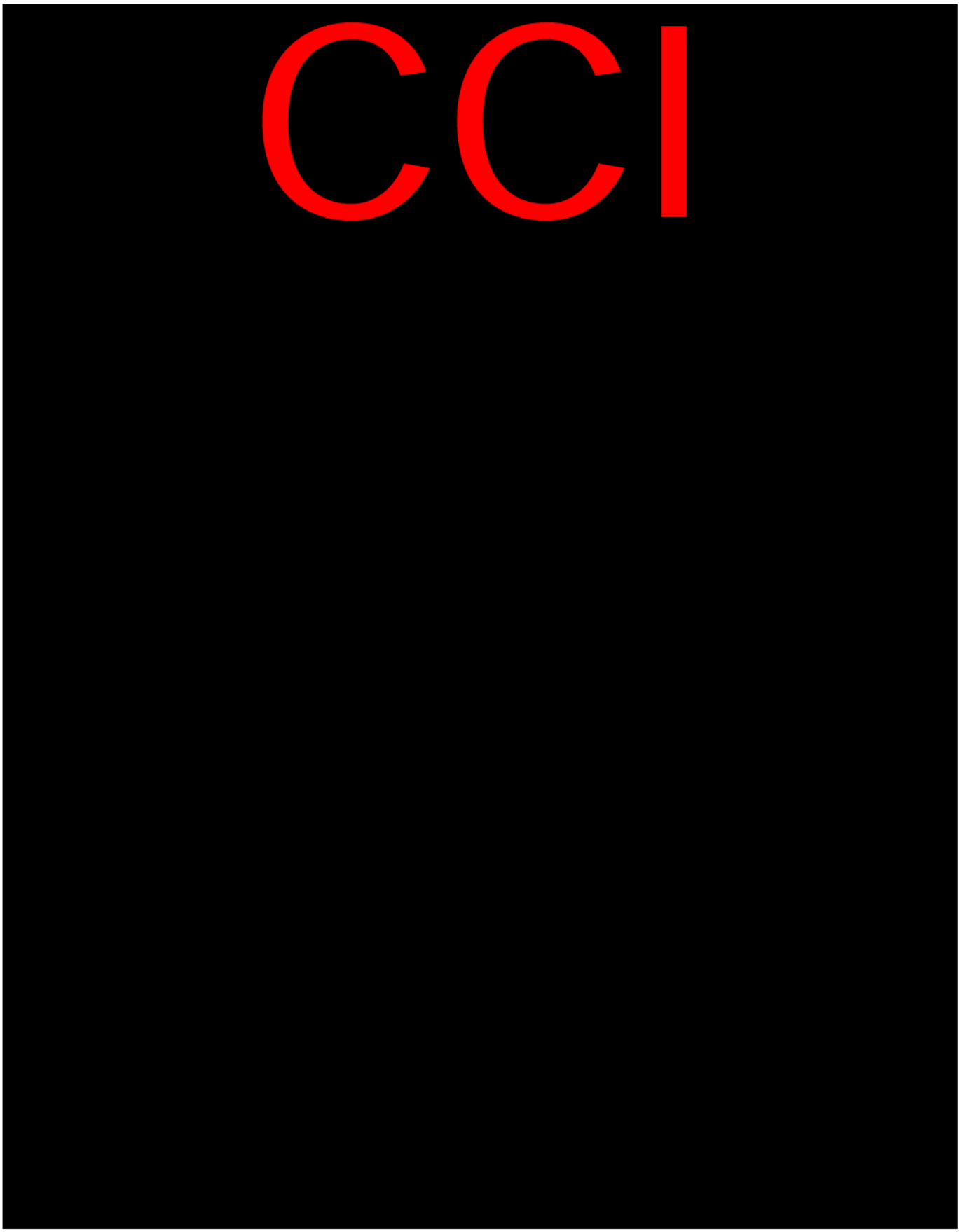

CCI

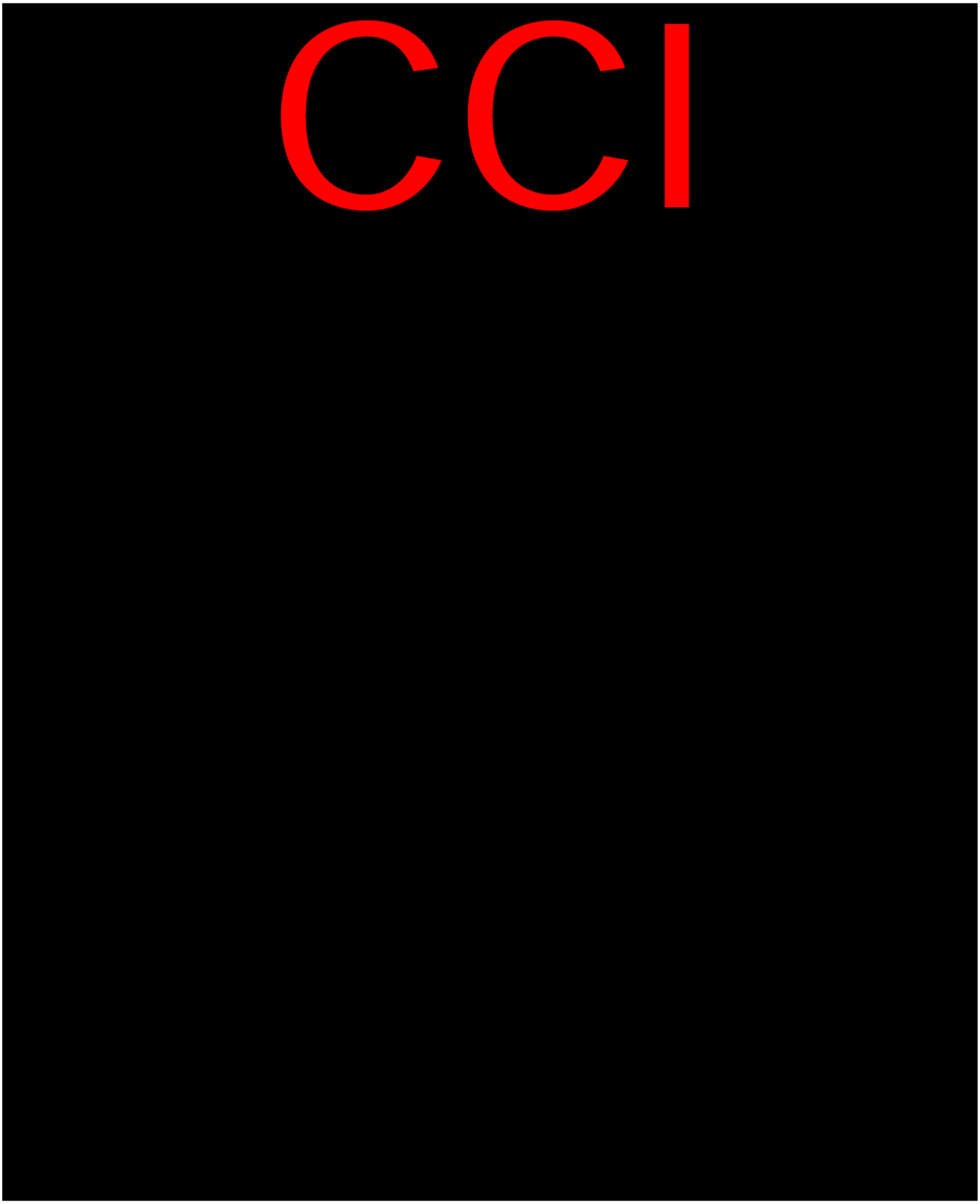

CCI


CCI

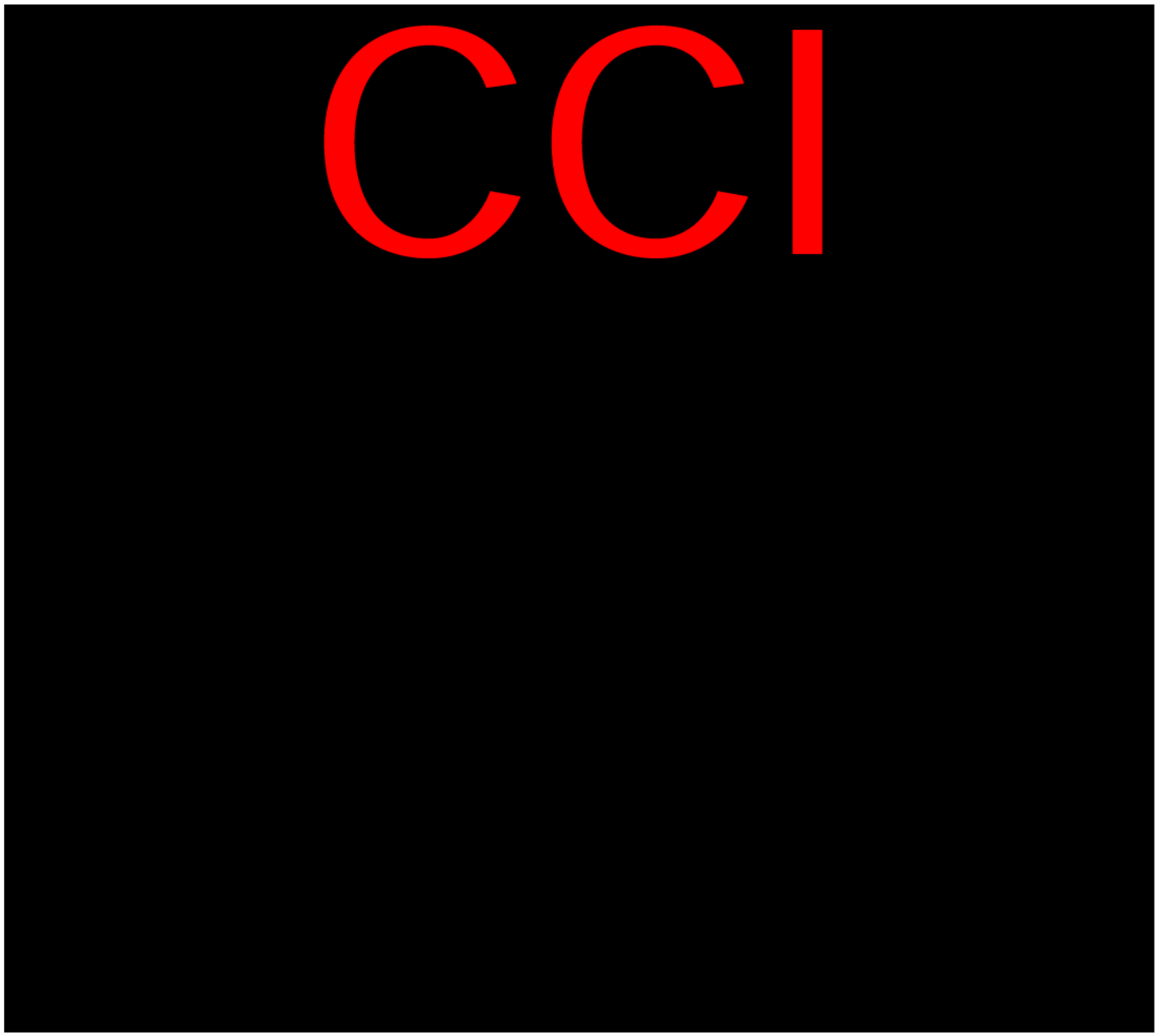

CCI

CCI


CCI


CCI


CCI


CCI

Leo Document ID = fa773f0c-386d-4721-bf56-08d9b82c9244

Approver: PPD

Approval Date & Time: 19-Jun-2020 20:40:37 GMT

Signature meaning: Approved