Protocol I1F-MC-RHCG (c)

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

NCT04527380

Approval Date: 01-DEC-2023

Title Page

Protocol Title:

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

Protocol Number: I1F-MC-RHCG

Amendment Number: c

Compound: ixekizumab (LY2439821)

Brief Title:

An Open-Label Study of Ixekizumab (LY2439821) in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis

Study Phase: 3

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

EudraCT Number: 2018-000681-10

EU CT Number: 2023-507184-19-00

Approval Date: Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-126448

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*21-Sep-2022*
Amendment a	*06-Nov-2020*
Original Protocol	*06-Feb-2020*

Amendment c

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The purpose of this amendment is to align with EU Clinical Trial Regulation 536/2014 (EU-CTR) requirements. Lilly also takes the opportunity to include other clarifications, formatting, and editorial changes.

Overall changes, including the above, specific to certain protocol sections, and a brief rationale are provided in this table.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Added subsections • Regulatory Agency Identifier Numbers: EudraCT and EU CT Numbers • Study Population • Ethical Considerations of Benefit/Risk • Data Monitoring Committee	Compliance with EU-CTR
	Revised LTE Period in Treatment Arms and Duration from "156" to "160"	Alignment as per study schema diagram
4. Objectives and Endpoints	Revised Exploratory Study Visit for the LTE Period from "156" to "264"	Alignment as per study schema diagram
7.1. Treatments Administered	Updated authorization in Table RHCG.7.1.as defined by EU-CTR and the definition for study treatment. Revised the start visit for LTE period Under treatment regimen table, Dose, long term extension treatment period, added a note "Participants who are not switching to ixekizumab will undergo ETV at Visit 29 (Week 104)."	Compliance with EU-CTR Clarification
7.1.1. Packaging and Labelling	Added "Participants weighing >25 kg to <50.0 kg can opt for at-home administration when 40 mg prefilled syringe is made available for the trial"	Provision for at-home administration so that the doses can be prepared manually
7.7. Concomitant Therapy	Deleted "for participants entering the LTE"	Clarification
9.1.3.1. Childhood Health Assessment Questionnaire (CHAQ)	Revised "Parent's Global Assessment of Well-being" to "CHAQ"	Correction

10.3.1. General Statistical Considerations	Added a paragraph on handling of missing, unused, and spurious data	Compliance with EU-CTR
10.3.1.3. General Considerations for the LTE Period	Revised the end visit for the LTE period	Updated to align with the start and end visits mentioned as per the study schema diagram
Appendix 1. Abbreviations	Added new abbreviations to the list	Compliance with EU-CTR
Appendix 3. 12.3.1. Regulatory and Ethical Considerations	Added language regarding reporting of significant issues related to participant's safety, rights, and data integrity	
Appendix 3. 12.3.4. Data Protection	Updated the required language	
Appendix 5. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	Added details on adverse events	
	Added details on SAE regulatory reporting	
Appendix 6. Contraceptive Guidance and Collection of Pregnancy Information	Deleted "In an appropriate appendix of the protocol, add definitions of WOCBP, women of nonchildbearing potential, and postmenopausal state as provided in this document's section called "Section 9.2.2.2"	Correction
Throughout	Minor editorial/formatting changes made throughout	For clarity

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1. Synopsis

Title of Study:

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

Regulatory Agency Identifier Numbers:

EudraCT Number: 2018-000681-10

EU CT Number: 2023-507184-19-00

Rationale:

Ixekizumab has been approved for the treatment of plaque psoriasis in adult and pediatric participants, and adult psoriatic arthritis (PsA), radiographic axial spondyloarthritis (r-axSpA), and non-radiographic axSpA with objective signs of inflammation. Enthesitis related arthritis (ERA) and juvenile PsA (JPsA) bear resemblance to adult axSpA and PsA, respectively; therefore, therapeutic benefit of ixekizumab is expected in these 2 subtypes of juvenile idiopathic arthritis (JIA). There are currently only 2 biologics, both tumor necrosis factor (TNF) inhibitors, adalimumab and etanercept, approved for ERA, and only etanercept for JPsA, with certain age limitations. Ixekizumab may offer a therapeutic option for ERA and JPsA participants who are candidates for an initial biologic disease-modifying antirheumatic drug (bDMARD) therapy, as well as participants with primary or secondary efficacy failure or intolerance of prior bDMARD. Based on its well-established efficacy and safety profile in JIA, adalimumab was selected as a reference product. This study is part of the European Paediatric Investigation Plan (PIP), EMEA-001050-PIP02-18-M01, with the aim to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of ixekizumab when administered to pediatric participants with JIA subsets of ERA (including juvenile onset ankylosing spondylitis [JoAS]) and JPsA.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the JIA American College of Rheumatology (ACR) 30 response	Percentage of participants meeting the JIA ACR 30 response criteria at Week 16
Secondary for the Open Label Treatment (OLT) and Open Label Extension (OLE) Periods • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the other clinical responses, disease activity, and physical function measures • To evaluate the efficacy of adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on JIA ACR 30 and the other clinical responses, disease activity, and physical function measures	The following outcomes will be assessed at each regular study visit[a]: • Percentage of participants meeting the JIA ACR 30/50/70/90/100 response criteria • Changes from baseline in each of the 6 individual components of the JIA ACR core set variables as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the Childhood Health Assessment Questionnaire (CHAQ) o Acute-phase reactant (high-sensitivity C-reactive protein [hsCRP]) and erythrocyte sedimentation rate (ESR) • Change from baseline in Psoriasis Area and Severity Index (PASI) for JPsA participants with at least 3% Body Surface Area (BSA) at baseline • Change from baseline in Leeds Enthesitis Index (LEI) for participants with enthesitis at baseline • Proportion of participants with disease flare (flare defined as worsening of ≥30% from baseline in at least 3 of the 6 JIA ACR core set criteria and an improvement of ≥30% in no more than 1 of the criteria)
• To characterize ixekizumab pharmacokinetics (PK) in children with JIA subtypes of ERA (including JoAS) and JPsA • To evaluate the potential development of anti-ixekizumab antibodies and their impact on the efficacy and safety of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	• Trough concentrations of ixekizumab in participants with JIA subtypes of ERA (including JoAS) and JPsA • Percentage of participants with anti-ixekizumab antibodies

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

Abbreviations: ERA = enthesitis-related arthritis; ETV – early termination visit; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis.

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

Summary of Study Design:

Study I1F-MC-RHCG (RHCG) is a multicenter, randomized, open-label study of subcutaneous (SC) ixekizumab, with adalimumab as a reference arm, followed by an open-label extension (OLE) period with ixekizumab and adalimumab in children from 2 to less than 18 years of age with JIA subtypes of ERA (including JoAS) and JPsA. The long-term extension (LTE) period will evaluate the safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA and JPsA.

Treatment Arms and Duration:

The study consists of 2 arms. Participants in the ixekizumab arm will receive SC ixekizumab at the following dosing regimens:

- CCI every 4 weeks (Q4W) CCI [redacted]
- CCI Q4W CCI [redacted]
- CCI Q4W CCI [redacted]

Participants in the adalimumab arm (reference arm) will receive SC adalimumab at the following dosing regimens:

- CCI every 2 weeks (Q2W) CCI
- CCI Q2W CCI

Study RHCG will be conducted in 4 parts:

- Open-label treatment (OLT) Period: 16 weeks.
- OLE Period: 88 weeks.
- LTE Period: 160 weeks.
- Post-treatment follow-up (PTFU; Visits 801, 802, and 803): 4 to 12 weeks after the last visit.

Participants who complete the OLT period may continue to the OLE period of the study. Participants who complete the OLT and OLE periods of this study may participate in an open-label LTE period.

Participants receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 will be switched to ixekizumab in the OLE period. Participants receiving adalimumab during the OLT period who did attain a JIA ACR 30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period. The decision to switch for participants who achieved a JIA ACR 30 response will be left to the participant/participant's caregiver and investigator. A switch from adalimumab to ixekizumab during the OLE period may also occur at any other visit after Week 16 based on the participant/participant's caregiver and investigator's decision. After switching to ixekizumab, the participants will not have the option to resume adalimumab treatment during the remainder of the trial participation. Any adalimumab participants that complete the open label extension period of the study will be reassigned to ixekizumab starting with Treatment Period 3 (refer to Section 6.1 for additional details). Adalimumab participants who choose not to switch to ixekizumab at the end of the open label period will enter the PTFU and be considered study completers.

Participant who do not enroll in the LTE study or discontinued early (participants who have received at least 1 dose of study drug) should enter the PTFU period and complete through Visit 802. Participants may be followed beyond Visit 802 for continued monitoring of their neutrophil counts if determined by the sponsor/investigator that additional monitoring is needed. If a participant discontinues study drug early, the participant will complete the early termination visit (ETV) and then enter the PTFU period.

Study Population:

This study will enroll participants aged 2 to less than 18 years at baseline, with at least 3 active peripheral joints diagnosed with JIA and fulfilling the ILAR classification criteria for ERA (including JoAS) or JPsA but no other JIA category. Participants classified as ERA will have to be at least 6 years of age, which is aligned with the classification criteria. Eligible participants will have body weight of at least 10.0 kg at baseline. For the participants' safety, medical conditions such as active uveitis, active IBD, and personal or first-degree family history of IBD may preclude participation in the study.

Number of Participants:

At least 100 participants from 2 to less than 18 years of age with a diagnosis before age 16 years of JIA subsets of ERA (including JoAS) or JPsA are planned to enter the OLT period.

- For participants who are naive to bDMARD treatment (bDMARD-naive), at least 20 participants will be randomized to ixekizumab and at least 20 participants will be randomized to adalimumab. Randomization will be stratified based on the subtype of JIA (ERA or JPsA).
- The remaining participants (approximately 60 participants) who are either bDMARD- naive or have had an inadequate response or intolerance to bDMARD treatment (bDMARD-IR) will be assigned to ixekizumab.
- For all participants who complete the OLE, participants entering into the LTE will be assigned to ixekizumab.

Ethical Considerations of Benefit/Risk:

As only 2 bDMARDs, both TNF inhibitors, are currently approved to treat ERA and/or JPsA, and not all patients achieve an adequate primary response to them or may experience secondary treatment failure or intolerance, there is a high unmet need for bDMARDs with a different mechanism of action in these 2 JIA subtypes.

Based on the demonstrated comprehensive efficacy of ixekizumab in axSpA and PsA as well as acceptable safety profile, the reasonable probability of a positive benefit/risk warrants this study to be conducted.

Statistical Analysis:

A Bayesian analysis will be utilized to assess the primary endpoint of JIA ACR 30 response rate at Week 16. A positive study will satisfy at least 80% posterior probability of a JIA ACR 30 response rate greater than 50% in ixekizumab-treated participants, otherwise the study will be considered negative.

Categorical data will be summarized using descriptive statistics. The counts/proportions and 95% confidence interval will be reported. Continuous data will be summarized using descriptive statistics; mean, standard deviation, minimum, maximum, and median will be reported.

Descriptive summaries will be provided by treatment assignment (ixekizumab, adalimumab), JIA subtype (ERA, JPsA), bDMARD experience (bDMARD-naive or bDMARD-IR), and demographic features including sex and age group.

Pharmacokinetic data will be summarized using descriptive statistics.

An interim analysis will be performed to determine if the study should be stopped for futility when 40 ixekizumab-treated participants have completed 16 weeks of treatment. If the observed JIA ACR 30 response rate is less than 40% at interim, futility will be declared, and the study will be terminated after the applicable required regulatory agreements are obtained. All safety data will be descriptively summarized using corresponding populations.

Data Monitoring Committee:

Yes

2. Schedule of Activities

Table RHCG.2.1. Schedule of Activities – Open-Label Treatment Period

	Screening	Open-Label Treatment Period						Notes
Visit No	**V1**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	Baseline laboratory samples should be taken before administration of investigational product.
Study Week		**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	
Study Days (Approximately)	**-42 to -7d**	**0**	**14 ± 7d**	**28 ± 7d**	**56 ± 7d**	**84 ± 7d**	**112 ± 7d**	
Informed consent and assent	X							Parent/legal guardian signs (informed consent form) and participant signs (assent form) (as appropriate) per local requirements. Signatures should be obtained before any study assessments, examinations, or procedures. If participant turns 18 during study, informed consent form is signed.
Complete medical history	X							Including TB exposure.
Review pre-existing conditions	X	X						
Immunization history record	X							Immunizations occurred prior to study entry.
Immunization record		X					X	Immunizations occurred during the participation in the study.
Demographics	X							Full date of birth (day, month, and year), sex, and ethnicity. In countries where full date of birth is not permitted to be collected, country-specific adjustments will be made to collect only month and year.
Physical examination	X						X	Excluding pelvic, rectal, and breast examinations.
Height	X	X				X		
Weight	X	X	X	X	X	X	X	Weight to be recorded to nearest 10th of a kilogram.
Occipital frontal circumference measurement		X				X		Only in children up to 3 years of age.
Habits	X							Including caffeine, alcohol, and tobacco consumption. Assessment only for participants 12 years of age or older.

	Screening	Open-Label Treatment Period						Notes
Visit No	**V1**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	Baseline laboratory samples should be taken before administration of investigational product.
Study Week		**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	
Study Days (Approximately)	**-42 to -7d**	**0**	**14 ± 7d**	**28 ± 7d**	**56 ± 7d**	**84 ± 7d**	**112 ± 7d**	
Vital signs (BP, pulse, body temperature)	X	X	X	X	X	X	X	At baseline (Visit 2, Week 0), BP and pulse measured at least 30 minutes pre- and post-injection. BP and pulse should be measured pre- and post-injection at the other visits.
Inclusion/exclusion criteria	X	X						
Previous JIA therapy	X							
Concomitant medications, including medications for indication	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	See Section 9.2.2.3 for a complete list of AESIs. IBD events will be adjudicated.
Randomization		X						
Dispense study drug		X	X	X	X	X	X	See Section 7.1, for details.
Administer study drug		X	X	X	X	X	X	Ixekizumab is administered on site Q4W. Adalimumab is administered at home Q2W. For training purposes, the first doses may be administered at the site. See Section 7.1, for administration details.
Clinician Reported Measures								
Joint Assessment	X	X	X	X	X	X	X	
Enthesitis Assessment		X	X	X	X	X	X	It includes LEI and active enthesitis count.
Dactylitic Count		X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity		X	X	X	X	X	X	
Clinical Sacroiliitis		X	X	X	X	X	X	
Back Mobility (Schober's Test)		X	X	X	X	X	X	
Body Surface Area (BSA)		X	X	X	X	X	X	
Psoriasis Area and Severity Index (PASI)		X	X	X	X	X	X	
Columbia–Suicide Severity Rating Scale – Screening	X							Assessment only for participants 7 years of age or older at screening.
Columbia–Suicide Severity Rating		X	X	X	X	X	X	Assessment only for participants 7 years of

Scale – Since Last Assessed								age or older.
	Screening	**Open-Label Treatment Period**						**Notes**
Visit No	**V1**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	Baseline laboratory samples should be taken before administration of investigational product.
Study Week		**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	
Study Days (Approximately)	**-42 to -7d**	**0**	**14 ± 7d**	**28 ± 7d**	**56 ± 7d**	**84 ± 7d**	**112 ± 7d**	
Self-Harm Supplement Form	X	X	X	X	X	X	X	Assessment only for participants 7 years of age or older.
Uveitis Evaluation	X	X	X	X	X	X	X	Active uveitis to be excluded at screening. Investigators will assess if the participant has developed uveitis since last visit.
Patient/Parent Administered Measures								
Childhood Health Assessment Questionnaire (CHAQ)		X	X	X	X	X	X	
Tanner Stage Scale		X					X	Assessment only for participants 8 years or older. Once the participant reaches the score of 5 on this scale, no further assessments are needed.
EQ-5D-Y		X			X		X	Assessment only for participants 4 years or older.
Children's Depression Inventory 2 Short Form (CDI-2)		X		X	X		X	Assessment only for participants 7 years of age or older
Pain Numeric Rating Scale		X	X	X	X	X	X	
Morning Joint Stiffness Duration		X	X	X	X	X	X	
Parent's Global Assessment of Well-Being		X	X	X	X	X	X	
Laboratory Tests								
Acute phase reactant (hsCRP)		X	X	X	X	X	X	
Acute phase reactant (ESR)		X	X	X	X	X	X	To be performed locally and before the study drug administration at Week 16
RF	X							RF test not required if past result available.
HLA-B27				X				HLA-B27 test not required if past result is available.

QuantiFERON®-TB Gold, T-Spot or PPD (if applicable)	X							See Section 9.4.5 for details.
	Screening	**Open-Label Treatment Period**						**Notes**
Visit No	**V1**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	Baseline laboratory samples should be taken before administration of investigational product.
Study Week		**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	
Study Days (Approximately)	**-42 to -7d**	**0**	**14 ± 7d**	**28 ± 7d**	**56 ± 7d**	**84 ± 7d**	**112 ± 7d**	
Read PPD (if applicable)	X							See Section 9.4.5 for details. To be performed locally.
Chest x-ray	X							Only for participants with a positive or repeated not negative TB test(s) and according to local guidelines. See Section 9.4.5 for details
HIV/HCV	X							HCV antibody positive results require a follow-up test for HCV RNA. See Section 5.1.1 for details.
HBV (HBsAg, HBcAb, HBsAb)	X					X		Positive test for HBcAb requires a follow-up test for HBV DNA. See Section 5.1.1 for details.
Serum pregnancy test	X							Section 5.1.1 for details. Performed centrally. Females only.
Urine pregnancy test		X		X	X	X	X	Section 5.1.1 for details. Performed locally. Females only.
Clinical chemistry	X	X		X			X	
Hematology	X	X		X			X	
Urinalysis	X	X		X			X	May not be feasible in younger (non-toilet trained) participants. Failure to obtain will not be considered a protocol violation.
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)		X					X	Participants may not have flow cytometry testing due to blood volume limitations.
Immunogenicity testing		X		X		X	X	See Section 9.6.1. All samples for immunogenicity should be taken pre-dose when applicable and possible.
PK sample		X		X		X	X	At visits where study drug will be administered, PK samples should be collected prior to administration of study drug.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BP = blood pressure; d = days; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth; ESR = erythrocyte sedimentation rate; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; JIA = juvenile idiopathic arthritis; LEI = Leeds Enthesitis Index;
NK = natural killer; PPD = purified protein derivative; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; RF = rheumatoid factor; TB = tuberculosis; V = study visit; W = study week.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.

Table RHCG.2.2. Schedule of Activities – Open-Label Extension Period (V8 through V20)

	Open-Label Extension Treatment Period											Notes		
Visit No	**V8**	**V9 (TV)**	**V10 (TV)-**	**V11**	**V12 (TV)**	**V13 (TV)**	**V14**	**V15 (TV)**	**V16 (TV)**	**V17**	**V18 (TV)**	**V19 (TV)**	**V20**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment.
Study Week	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**W56**	**W60**	**W64**	**W68**	
Study Days (Approximately)	**140 ± 7d**	**168 ± 7d**	**196 ± 7d**	**224 ± 7d**	**252 ± 7d**	**280 ± 7d**	**308 ± 7d**	**336 ± 7d**	**364 ± 7d**	**392 ± 7d**	**420 ± 7d**	**448 ± 7d**	**476 ± 7d**	
Immunization record				X			X			X				Immunizations occurred during the participation in the study.
Physical examination				X			X			X				Excluding pelvic, rectal, and breast examinations.
Height	X			X			X			X				
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Occipital frontal circumference measurement	X			X			X			X				Only in children up to 3 years of age.
Habits										X				Including caffeine, alcohol, and tobacco consumption. Assessment only for participants 12 years of age or older.
Vital signs (BP, pulse, body temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	BP and pulse should be measured at least pre-injection.
Concomitant medications	X			X			X			X			X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.2.2.3 for a complete list of adverse events of special interest (AESI). IBD events will be adjudicated. During TV AEs are collected if spontaneously reported.
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 7.1 for details
Administer study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 7.1 for administration details and see Table RHCG.7.1 for treatment regimens.

Schedule of Activities – Open-Label Extension Period

	Open-Label Extension Treatment Period													Notes
Visit No	**V8**	**V9 (TV)**	**V10 (TV)-**	**V11**	**V12 (TV)**	**V13 (TV)**	**V14**	**V15 (TV)**	**V16 (TV)**	**V17**	**V18 (TV)**	**V19 (TV)**	**V20**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment.
Study Week	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**W56**	**W60**	**W64**	**W68**	
Study Days (Approximately)	**140 ± 7d**	**168 ± 7d**	**196 ± 7d**	**224 ± 7d**	**252 ± 7d**	**280 ± 7d**	**308 ± 7d**	**336 ± 7d**	**364 ± 7d**	**392 ± 7d**	**420 ± 7d**	**448 ± 7d**	**476 ± 7d**	
Clinician Reported Measures														
Joint Assessment	X			X			X			X			X	
Enthesitis Assessment	X			X			X			X			X	It includes LEI and active enthesitis count.
Dactylitic Count	X			X			X			X			X	
Physician's Global Assessment of Disease Activity	X			X			X			X			X	
Clinical Sacroiliitis	X			X			X			X			X	
Back Mobility (Schober's Test)	X			X			X			X			X	
Body Surface Area (BSA)	X			X			X			X			X	
Psoriasis Area and Severity Index (PASI)	X			X			X			X			X	
Columbia–Suicide Severity Rating Scale – Since Last Assessed	X			X			X			X			X	Assessment only for participants 7 years of age or older.
Self-Harm Supplement Form	X			X			X			X			X	Assessment only for participants 7 years of age or older.
Uveitis Evaluation	X			X			X			X			X	Investigators will assess if the participant has developed uveitis since last visit.

	Open-Label Extension Treatment Period													Notes
Visit No	**V8**	**V9 (TV)**	**V10 (TV)-**	**V11**	**V12 (TV)**	**V13 (TV)**	**V14**	**V15 (TV)**	**V16 (TV)**	**V17**	**V18 (TV)**	**V19 (TV)**	**V20**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment.
Study Week	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**W56**	**W60**	**W64**	**W68**	
Study Days (Approximately)	**140 ± 7d**	**168 ± 7d**	**196 ± 7d**	**224 ± 7d**	**252 ± 7d**	**28 0± 7d**	**308 ± 7d**	**336 ± 7d**	**364 ± 7d**	**392 ± 7d**	**420 ± 7d**	**448 ± 7d**	**476 ± 7d**	
Patient/Parent Administered Measures														
Childhood Health Assessment Questionnaire (CHAQ)	X			X			X			X			X	
Tanner Stage Scale	X									X				Assessment only for participants 8 years or older. Once the participant reaches the score of 5 on this scale, no further assessments are needed.
EQ-5D-Y	X			X			X			X			X	Assessment only for participants 4 years or older.
Children's Depression Inventory 2 Short Form (CDI-2)	X			X			X			X			X	Assessment only for participants 7 years of age or older.
Pain Numeric Rating Scale	X			X			X			X			X	
Morning Joint Stiffness Duration	X			X			X			X			X	
Parent's Global Assessment of Well-Being	X			X			X			X			X	To be completed by caregiver until participant is ≥14 years of age, at which time, the participant will complete their own questionnaires.
Laboratory Tests														
Acute phase reactant (hsCRP)	X			X			X			X			X	
Acute phase reactant (ESR)	X			X			X			X			X	To be performed locally.

	Open-Label Extension Treatment Period													Notes
Visit No	**V8**	**V9 (TV)**	**V10 (TV)-**	**V11**	**V12 (TV)**	**V13 (TV)**	**V14**	**V15 (TV)**	**V16 (TV)**	**V17**	**V18 (TV)**	**V19 (TV)**	**V20**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment.
Study Week	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	**W56**	**W60**	**W64**	**W68**	
Study Days (Approximately)	**140 ± 7d**	**168 ± 7d**	**196 ± 7d**	**224 ± 7d**	**252 ± 7d**	**280 ± 7d**	**308 ± 7d**	**336 ± 7d**	**364 ± 7d**	**392 ± 7d**	**420 ± 7d**	**448 ± 7d**	**476 ± 7d**	
HBV DNA (if applicable)				X			X			X				Positive for HBcAb require a follow up test for HBV DNA. See Section 5.1.1 for details.
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 5.1.1 for details. Females only. To be performed locally. In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential (WOCBP) with infrequent or irregular menstrual cycles.
Clinical chemistry				X			X			X			X	
Hematology				X			X			X			X	
Urinalysis				X			X			X			X	
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)				X			X			X			X	Participants may not have flow cytometry testing due to blood volume limitations.
Immunogenicity testing	X			X						X				See Section 9.6.1. All samples for immunogenicity should be taken pre-dose when applicable and possible.
PK sample	X			X						X				At visits where study drug will be administered, PK samples should be collected prior to administration of study drug.

Schedule of Activities – Open-Label Extension Period (V21 onwards)

	Open-Label Extension Treatment Period									Notes
Visit No	**V21 (TV)**	**V22 (TV)**	**V23**	**V24 (TV)**	**V25 (TV)**	**V26**	**V27 (TV)**	**V28 (TV)**	**V29**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment. V803 is an additional follow- up based on neutrophil count (Section 5.1.4).
Study Week	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**	
Study Days (Approximately)	**504 ± 7d**	**532 ± 7d**	**560 ± 7d**	**588 ± 7d**	**616 ± 7d**	**644 ± 7d**	**672 ± 7d**	**700 ± 7d**	**728 ± 7d**	
Immunization record			X			X			X	Immunizations occurred during the participation in the study.
Physical examination			X			X			X	Excluding pelvic, rectal, and breast examinations.
Symptom-directed physical examination			X			X			X	Includes an assessment of rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.
Height			X			X			X	
Weight	X	X	X	X	X	X	X	X	X	
Vital signs (BP, pulse, body temperature)	X	X	X	X	X	X	X	X	X	BP and pulse should be measured at least pre-injection.
Concomitant medications			X			X			X	

	Open-Label Extension Treatment Period									Notes
Visit No	**V21 (TV)**	**V22 (TV)**	**V23**	**V24 (TV)**	**V25 (TV)**	**V26**	**V27 (TV)**	**V28 (TV)**	**V29**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment. V803 is an additional follow- up based on neutrophil count (Section 5.1.4).
Study Week	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**	
Study Days (Approximately)	**504 ± 7d**	**532 ± 7d**	**560 ± 7d**	**588 ± 7d**	**616 ± 7d**	**644 ± 7d**	**672 ± 7d**	**700 ± 7d**	**728 ± 7d**	
AEs	X	X	X	X	X	X	X	X	X	See Section 9.2.2.3 for a complete list of adverse events of special interest (AESI). IBD events will be adjudicated. During TV AEs are collected if spontaneously reported.
Dispense study drug	X	X	X	X	X	X	X	X	X	See Section 7.1 for details
Administer study drug	X	X	X	X	X	X	X	X	X	See Section 7.1 for administration details and see Table RHCG.7.1 for treatment regimens.
Clinician Reported Measures										
Joint Assessment			X			X			X	
Enthesitis Assessment			X			X			X	It includes LEI and active enthesitis count.
Dactylitic Count			X			X			X	
Physician's Global Assessment of Disease Activity			X			X			X	
Clinical Sacroiliitis			X			X			X	

	Open-Label Extension Treatment Period									Notes
Visit No	**V21 (TV)**	**V22 (TV)**	**V23**	**V24 (TV)**	**V25 (TV)**	**V26**	**V27 (TV)**	**V28 (TV)**	**V29**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment. V803 is an additional follow- up based on neutrophil count (Section 5.1.4).
Study Week	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**	
Study Days (Approximately)	**504 ± 7d**	**532 ± 7d**	**560 ± 7d**	**588 ± 7d**	**616 ± 7d**	**644 ± 7d**	**672 ± 7d**	**700 ± 7d**	**728 ± 7d**	
Back Mobility (Schober's Test)			X			X			X	
Body Surface Area (BSA)			X			X			X	
Psoriasis Area and Severity Index (PASI)			X			X			X	
Columbia–Suicide Severity Rating Scale – Since Last Assessed			X			X			X	Assessment only for participants 7 years of age or older.
Self-Harm Supplement Form			X			X			X	Assessment only for participants 7 years of age or older.
Self-Harm Follow-Up Form			X			X			X	A Self-Harm Follow-Up Form must be completed for each discrete event identified on the Self-Harm Supplement Form. If no events are reported in a certain visit, the form is not applicable.
Uveitis Evaluation			X			X			X	Investigators will assess if the participant has developed uveitis since last visit.

	Open-Label Extension Treatment Period									Notes
Visit No	**V21 (TV)**	**V22 (TV)**	**V23**	**V24 (TV)**	**V25 (TV)**	**V26**	**V27 (TV)**	**V28 (TV)**	**V29**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment. V803 is an additional follow- up based on neutrophil count (Section 5.1.4).
Study Week	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**	
Study Days (Approximately)	**504 ± 7d**	**532 ± 7d**	**560 ± 7d**	**588 ± 7d**	**616 ± 7d**	**644 ± 7d**	**672 ± 7d**	**700 ± 7d**	**728 ± 7d**	
Patient/ Parent Administered Measures										
Childhood Health Assessment Questionnaire (CHAQ)			X			X			X	
Tanner Stage Scale			X						X	Assessment only for participants 8 years or older. Once the participant reaches the score of 5 on this scale, no further assessments are needed.
EQ-5D-Y			X			X			X	Assessment only for participants 4 years or older.
Children's Depression Inventory 2 Short Form (CDI-2)			X			X			X	Assessment only for participants 7 years of age or older.
Pain Numeric Rating Scale			X			X			X	
Morning Joint Stiffness Duration			X			X			X	

	Open-Label Extension Treatment Period									Notes
Visit No	**V21 (TV)**	**V22 (TV)**	**V23**	**V24 (TV)**	**V25 (TV)**	**V26**	**V27 (TV)**	**V28 (TV)**	**V29**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment. V803 is an additional follow- up based on neutrophil count (Section 5.1.4).
Study Week	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**	
Study Days (Approximately)	**504 ± 7d**	**532 ± 7d**	**560 ± 7d**	**588 ± 7d**	**616 ± 7d**	**644 ± 7d**	**672 ± 7d**	**700 ± 7d**	**728 ± 7d**	
Parent's Global Assessment of Well-Being			X			X			X	To be completed by caregiver until participant is ≥14 years of age, at which time, the participant will complete their own questionnaires.
Laboratory Tests										
Acute phase reactant (hsCRP)			X			X			X	
Acute phase reactant (ESR)			X			X			X	To be performed locally.
HBV DNA (if applicable)			X			X			X	Positive for HBcAb require a follow-up test for HBV DNA. See Section 5.1.1 for details.
Urine pregnancy test	X	X	X	X	X	X	X	X	X	Section 5.1.1 for details. Females only. To be performed locally. In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential (WOCBP) with infrequent or irregular menstrual cycles.

	Open-Label Extension Treatment Period									Notes
Visit No	**V21 (TV)**	**V22 (TV)**	**V23**	**V24 (TV)**	**V25 (TV)**	**V26**	**V27 (TV)**	**V28 (TV)**	**V29**	Treatment visits (TV) are intended for the dispensation and/or site administration of the study treatment. V803 is an additional follow- up based on neutrophil count (Section 5.1.4).
Study Week	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**	**W100**	**W104**	
Study Days (Approximately)	**504 ± 7d**	**532 ± 7d**	**560 ± 7d**	**588 ± 7d**	**616 ± 7d**	**644 ± 7d**	**672 ± 7d**	**700 ± 7d**	**728 ± 7d**	
Clinical chemistry			X			X			X	Includes an assessment of rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.
Hematology			X			X			X	
Urinalysis			X			X			X	
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)			X			X			X	Participants may not have flow cytometry testing due to blood volume limitations.
Immunogenicity testing			X						X	See Section 9.6.1. All samples for immunogenicity should be taken pre-dose when applicable and possible.
PK sample			X						X	At visits where study drug will be administered, PK samples should be collected prior to administration of study drug.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BP = blood pressure; d = days; ETV = Early Termination Visit; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth; ESR = erythrocyte sedimentation rate; ETV = Early Termination Visit; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; JIA = juvenile idiopathic arthritis; LEI = Leeds Enthesitis Index; NK = natural killer; PPD = purified protein derivative; PK = pharmacokinetics; TV = treatment visit; V = study visit; W = study week, WOCBP = women of childbearing potential.

Table RHCG.2.3. Schedule of Activities – Long Term Extension Period (V30 through V42)

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.

Visit No	V30	V31	V32	V33	V34	V35	V36	V37	V38	V39	V40	V41	V42	Notes
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Immunization record	X			X			X			X				Immunizations occurred during the participation in the study.
Physical examination	X			X			X			X			X	Excluding pelvic, rectal, and breast examinations.
Height	X			X			X			X			X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	Weight will be recorded for every participant at every visit in the Study Drug Administration Log: • For participants CCI [redacted] weight will be recorded by study personnel. • For participants CCI [redacted] o At-home administration: weight will be recorded by the participant or caregiver in the Study Drug Administration

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
														Log. ○ Regular and on-site treatment visits (if applicable): weight will be recorded by the study personnel.
Habits	X												X	Including caffeine, alcohol, and tobacco consumption. Assessment only for participants 12 years of age or older.
Vital signs (BP, pulse, body temperature)	X			X			X			X			X	BP and pulse should be measured at least pre-injection.
Concomitant medications	X			X			X			X			X	
Adverse events (AEs)	X			X			X			X			X	See Section 9.2.2.3 for a complete list of adverse events of special interest (AESIs). IBD events will be adjudicated. Investigators will assess the AEs during the

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
														regular visits.
Dispense ixekizumab	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.1 for details. Participants CCI who opt for at-home administration will have the study drug dispensed during the regular visits only (that is, every 12 weeks). The rest of the participants will have the study drug dispensed during both the treatment visits and regular visits (that is, every 4 weeks).
Train on ixekizumab administration	X			X			X			X			X	Only for participants CCI who opt for at-home administration and/or their caregivers. See Section 7.1 for details. This training will occur throughout the study for those participants who reach CCI and opt for at-home administration.

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Administer ixekizumab	X	X	X	X	X	X	X	X	X	X	X	X	X	See Sections 7.1 for on-site and at-home administration details and Table RHCG.7.1 for treatment regimens. During regular visit, all participants (regardless of their weight) will receive ixekizumab injection on-site.
Clinician-Reported Measures														
Joint Assessment	X			X			X			X			X	
Enthesitis Assessment	X			X			X			X			X	It includes LEI and active enthesitis count.
Dactylitic Count	X			X			X			X			X	
Physician's Global Assessment of Disease Activity	X			X			X			X			X	
Clinical Sacroiliitis	X			X			X			X			X	
Back Mobility (Schober's Test)	X			X			X			X			X	
Body Surface Area (BSA)	X			X			X			X			X	
Psoriasis Area and Severity	X			X			X			X			X	

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Index (PASI)														
Columbia–Suicide Severity Rating Scale – Since Last Assessed	X			X			X			X			X	Assessment only for participants 7 years of age or older.
Self-Harm Follow-Up Form	X			X			X			X			X	A Self-Harm Follow-Up Form must be completed for each discrete event identified on the Self-Harm Supplement Form. If no events are reported in a certain visit, the form is not applicable.
Uveitis Evaluation	X			X			X			X			X	Investigators will assess if the participant has developed uveitis since last visit.
Study Drug Administration Log (Paper)														
Dispense Study Drug Administration Log	X			X			X			X			X	Dispensed only to participants CCI who have opted for at-home administration.
Check compliance with Study Drug Administration Log				X			X			X			X	See Section 6.4.

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Participant-/Parent-Administered Measures														
Childhood Health Assessment Questionnaire (CHAQ)	X			X			X			X			X	
Tanner Stage Scale	X												X	Assessment only for participants 8 years or older. If participants reached the score of 5 on this scale in Study RHCG, they do not have to complete this assessment in LTE. Once the participant reaches the score of 5 on this scale during LTE, no further assessments are needed.
EQ-5D-Y	X			X			X			X			X	Assessment only for participants 4 years or older.
Children's Depression Inventory 2 Short Form (CDI-2)	X			X			X			X			X	Assessment only for participants 7 years of age or older.
Pain Numeric	X			X			X			X			X	

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Rating Scale														
Morning Joint Stiffness Duration	X			X			X			X			X	
Laboratory Tests														
Acute phase reactant (hsCRP)	X			X			X			X			X	
Acute phase reactant (ESR)	X			X			X			X			X	To be performed locally.
Administer TB test(s) (if applicable)	TB testing required only based on clinical assessment of TB risk and according to local regulations and/or local standard of care (Section 9.4.6; Appendix 2). QuantiFERON®-TB Gold, T-Spot or PPD (if applicable) (Section 9.4.6; Appendix 2). PPD to be read locally.													
HCV antibody	X													HCV antibody positive results require a follow-up test for HCV RNA. See Section 9.4.4 for details.
HBV (HBsAg, HBcAb, HBsAb)	X													See Section 9.4.4 for details.
HBV DNA (if applicable)	X			X			X			X			X	Positive for HbcAb require a follow up test for HBV DNA. See Section 9.4.11.2 for details.
Urine pregnancy test	X			X			X			X			X	See Section 9.4.5 and Appendix 6 for details. Females only. To be performed locally.

Notes: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.														
Visit No	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**Notes**
Study Week	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**	
Study Days (Approximately)	**756 ± 7d**	**784 ± 7d**	**812 ± 7d**	**840 ± 7d**	**868 ± 7d**	**896 ± 7d**	**924 ± 7d**	**952 ± 7d**	**980 ± 7d**	**1008 ± 7d**	**1036 ± 7d**	**1064 ± 7d**	**1092 ± 7d**	
Treatment Visits			X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Clinical chemistry	X			X			X			X			X	
Hematology	X			X			X			X			X	
Urinalysis	X			X			X			X			X	
PK sample	X	X		X			X						X	At regular visits (i.e., when ixekizumab is administered on site to all the participants), PK samples should be collected prior to administration of ixekizumab.
Immunogenicity sample	X	X		X			X						X	See Section 9.6.1. All samples for immunogenicity should be taken predose when applicable and possible.

Abbreviations: BP = blood pressure; d = days; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IBD = inflammatory bowel disease; LEI = Leeds Enthesitis Index; No = number; PK = pharmacokinetics; PPD = purified protein derivative; TB = tuberculosis; V = study visit; W = study week.

Table RHCG.2.4. Schedule of Activities – Long Term Extension Period (V43 through V54)

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.													
Visit No	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**Notes**
Study Week	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	
Study Days (Approximately)	**1120 ± 7d**	**1148 ± 7d**	**1176 ± 7d**	**1204 ± 7d**	**1232 ± 7d**	**1260 ± 7d**	**1288 ± 7d**	**1316 ± 7d**	**1344 ± 7d**	**1372 ± 7d**	**1400 ± 7d**	**1428 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the on-site administration of the ixekizumab for the participants CCI who have opted for on-site administration.
Immunization record			X			X			X			X	Immunizations occurred during the participation in the study.
Physical examination			X			X			X			X	Excluding pelvic, rectal, and breast examinations.
Height			X			X			X			X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	Weight will be recorded for every participant at every visit in the Study Drug Administration Log: • For participants CCI weight will be recorded by study personnel. • For participants CCI o At-home administration: weight will be recorded by the participant or caregiver in the Study Drug Administration Log. o Regular and on-site treatment visits (if applicable): weight will be recorded by the study personnel.
Vital signs (BP, pulse, body temperature)			X			X			X			X	BP and pulse should be measured at least pre-injection.
Concomitant medications			X			X			X			X	
Adverse events (AEs)			X			X			X			X	See Section 9.2.2.3 for a complete list

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.													
Visit No	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**Notes**
Study Week	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	
Study Days (Approximately)	**1120 ± 7d**	**1148 ± 7d**	**1176 ± 7d**	**1204 ± 7d**	**1232 ± 7d**	**1260 ± 7d**	**1288 ± 7d**	**1316 ± 7d**	**1344 ± 7d**	**1372 ± 7d**	**1400 ± 7d**	**1428 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the on-site administration of the ixekizumab for the participants CCI who have opted for on-site administration.
													of AESIs. IBD events will be adjudicated. Investigators will assess the AEs during the regular visits.
Dispense study intervention	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.1 for details. • Participants CCI who have opted for at-home administration will have ixekizumab dispensed during the regular visits only (i.e., every 12 weeks). • The rest of the participants will have the study drug dispensed during both the treatment visits and regular visits (that is, every 4 weeks).
Train on ixekizumab administration			X			X			X			X	Only for participants CCI who opt for at-home administration and/or for their caregivers. See Section 7.1 for details. This training will occur throughout the study for those participants who reach CCI and opt for at-home administration.
Administer ixekizumab	X	X	X	X	X	X	X	X	X	X	X	X	See Sections 7.1 for on-site and at-home administration details and for treatment regimens. During regular visit, all participants (regardless of their weight) will receive ixekizumab injection on site.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.													
Visit No	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**Notes**
Study Week	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	
Study Days (Approximately)	**1120 ± 7d**	**1148 ± 7d**	**1176 ± 7d**	**1204 ± 7d**	**1232 ± 7d**	**1260 ± 7d**	**1288 ± 7d**	**1316 ± 7d**	**1344 ± 7d**	**1372 ± 7d**	**1400 ± 7d**	**1428 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the on-site administration of the ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Clinician-Reported Measures													
Joint Assessment			X			X			X			X	
Enthesitis Assessment			X			X			X			X	It includes LEI and active enthesitis count.
Dactylitic Count			X			X			X			X	
Physician's Global Assessment of Disease Activity			X			X			X			X	
Clinical Sacroiliitis			X			X			X			X	
Back Mobility (Schober's Test)			X			X			X			X	
Body Surface Area (BSA)			X			X			X			X	
Psoriasis Area and Severity Index (PASI)			X			X			X			X	
Columbia–Suicide Severity Rating Scale – Since Last Assessed			X			X			X			X	Assessment only for participants 7 years of age or older.
Self-Harm Supplement Form			X			X			X			X	Assessment only for participants 7 years of age or older.
Uveitis Evaluation			X			X			X			X	Investigators will assess if the participant has developed uveitis since last visit.
Study Drug Administration Log (Paper)													
Dispense Study Drug Administration Log			X			X			X			X	Dispensed only to participants CCI [redacted] who have opted for at-home administration.
Check compliance with Study Drug			X			X			X			X	See Section 6.4.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.													
Visit No	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**Notes**
Study Week	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	
Study Days (Approximately)	**1120 ± 7d**	**1148 ± 7d**	**1176 ± 7d**	**1204 ± 7d**	**1232 ± 7d**	**1260 ± 7d**	**1288 ± 7d**	**1316 ± 7d**	**1344 ± 7d**	**1372 ± 7d**	**1400 ± 7d**	**1428 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the on-site administration of the ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Administration Log													
Participant-/Parent-Administered Measures													
Childhood Health Assessment Questionnaire (CHAQ)			X			X			X			X	
Tanner Stage Scale												X	Assessment only for participants 8 years or older. Once the participant reaches the score of 5 on this scale during LTE, no further assessments are needed.
EQ-5D-Y			X			X			X			X	Assessment only for participants 4 years or older.
Children's Depression Inventory 2 Short Form (CDI-2)			X			X			X			X	Assessment only for participants 7 years of age or older
Pain Numeric Rating Scale			X			X			X			X	
Morning Joint Stiffness Duration			X			X			X			X	
Parent's Global Assessment of Well-Being			X			X			X			X	To be completed by caregiver until participant is >14 years of age, at which time, the participant will complete their own questionnaires.
Laboratory Tests													
Acute phase reactant (hsCRP)			X			X			X			X	
Acute phase reactant (ESR)			X			X			X			X	To be performed locally.
Administer TB	TB testing required only based on clinical assessment of TB risk and according to local regulations and/or local												QuantiFERON-TB Gold, T-Spot or

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart.													
Visit No	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**Notes**
Study Week	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	
Study Days (Approximately)	**1120 ± 7d**	**1148 ± 7d**	**1176 ± 7d**	**1204 ± 7d**	**1232 ± 7d**	**1260 ± 7d**	**1288 ± 7d**	**1316 ± 7d**	**1344 ± 7d**	**1372 ± 7d**	**1400 ± 7d**	**1428 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the on-site administration of the ixekizumab for the participants [redacted] who have opted for on-site administration.
test(s) (if applicable)	standard of care (Section 9.4.6; Appendix 2).												PPD (if applicable) (Section 9.4.6; Appendix 2). PPD to be read locally.
HBV DNA (if applicable)			X			X			X			X	Positive for HbcAb requires a follow up test for HBV DNA. See Section 5.1.1 for details.
Urine pregnancy test			X			X			X			X	See Section 5.1.1 and Appendix 2 for details. Females only. To be performed locally.
Clinical chemistry			X			X			X			X	
Hematology			X			X			X			X	
Urinalysis			X			X			X			X	
PK sample						X						X	At regular visits (for example, when ixekizumab is administered on site to all the participants), PK samples should be collected prior to administration of ixekizumab.
Immunogenicity sample						X						X	See Section 9.6.1. All samples for immunogenicity should be taken predose when applicable and possible.

Abbreviations: AESI = adverse event of special interest; BP = blood pressure; d = days; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth; ESR = erythrocyte sedimentation rate; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; LEI = Leeds Enthesitis Index; No = number; PK = pharmacokinetics; PPD = purified protein derivative; TB = tuberculosis; V = study visit; W = study week.

Table RHCG.2.5. Schedule of Activities – Long Term Extension Period (V55 through V66)

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.

Visit No	V55	V56	V57	V58	V59	V60	V61	V62	V63	V64	V65	V66	Notes
Study Week	**W208**	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	
Study Days (Approximately)	**1456 ± 7d**	**1484 ± 7d**	**1512 ± 7d**	**1540 ± 7d**	**1568 ± 7d**	**1596 ± 7d**	**1624 ± 7d**	**1652 ± 7d**	**1680 ± 7d**	**1708 ± 7d**	**1736 ± 7d**	**1764 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Immunization record			X			X			X			X	Immunizations occurred during the participation in the study.
Physical examination			X			X			X			X	Excluding pelvic, rectal, and breast examinations.
Height			X			X			X			X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	Weight will be recorded for every participant at every visit in the Study Drug Administration Log: • For participants CCI [redacted] weight will be recorded by study personnel. • For participants CCI [redacted] o At-home administration: weight will be recorded by the participant or caregiver in the Study Drug Administration Log. o Regular and on-site treatment visits (if applicable): weight will be recorded by the study personnel.
Vital signs (BP, pulse, body temperature)			X			X			X			X	BP and pulse should be measured at least pre-injection.
Concomitant medications			X			X			X			X	
Adverse events (AEs)			X			X			X			X	See Section 9.2 for a complete list of AESIs. IBD events will be

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.													
Visit No	**V55**	**V56**	**V57**	**V58**	**V59**	**V60**	**V61**	**V62**	**V63**	**V64**	**V65**	**V66**	**Notes**
Study Week	**W208**	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	
Study Days (Approximately)	**1456 ± 7d**	**1484 ± 7d**	**1512 ± 7d**	**1540 ± 7d**	**1568 ± 7d**	**1596 ± 7d**	**1624 ± 7d**	**1652 ± 7d**	**1680 ± 7d**	**1708 ± 7d**	**1736 ± 7d**	**1764 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
													adjudicated. Investigators will assess the AEs during the regular visits.
Dispense ixekizumab	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.1 for details. • Participants CCI [redacted] who opt for at-home administration will have the study drug dispensed during the regular visits only (that is, every 12 weeks). • The rest of the participants will have the study drug dispensed during both the treatment visits and regular visits (that is, every 4 weeks).
Train on ixekizumab administration			X			X			X			X	Only for participants CCI [redacted] who opt for at-home administration and/or their caregivers. See Section 7.2 for details. This training will occur throughout the study for those participants who reach CCI [redacted] and opt for at-home administration.
Administer ixekizumab	X	X	X	X	X	X	X	X	X	X	X	X	See Sections 7.2 for on-site and at-home administration details and for treatment regimens. During regular visit, all participants (regardless of their weight) will receive ixekizumab injection on site.
Clinician-Reported Measures													
Joint Assessment			X			X			X			X	
Enthesitis			X			X			X			X	It includes LEI and active enthesitis

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.													
Visit No	**V55**	**V56**	**V57**	**V58**	**V59**	**V60**	**V61**	**V62**	**V63**	**V64**	**V65**	**V66**	**Notes**
Study Week	**W208**	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	
Study Days (Approximately)	**1456 ± 7d**	**1484 ± 7d**	**1512 ± 7d**	**1540 ± 7d**	**1568 ± 7d**	**1596 ± 7d**	**1624 ± 7d**	**1652 ± 7d**	**1680 ± 7d**	**1708 ± 7d**	**1736 ± 7d**	**1764 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Assessment													count.
Dactylitic Count			X			X			X			X	
Physician's Global Assessment of Disease Activity			X			X			X			X	
Clinical Sacroiliitis			X			X			X			X	
Back Mobility (Schober's Test)			X			X			X			X	
Body Surface Area (BSA)			X			X			X			X	
Psoriasis Area and Severity Index (PASI)			X			X			X			X	
Columbia–Suicide Severity Rating Scale – Since Last Assessed			X			X			X			X	Assessment only for participants 7 years of age or older.
Self-Harm Supplement Form			X			X			X			X	Assessment only for participants 7 years of age or older.
Uveitis Evaluation			X			X			X			X	Investigators will assess if the participant has developed uveitis since last visit.
Study Drug Administration Log (Paper)													
Dispense Study Drug Administration Log			X			X			X			X	Dispensed only to participants CCI [redacted] who have opted for at-home administration.
Check compliance with Study Drug Administration Log			X			X			X			X	See Section 6.4.
Participant/Parent-Administered Measures													
Childhood Health			X			X			X			X	

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.													
Visit No	**V55**	**V56**	**V57**	**V58**	**V59**	**V60**	**V61**	**V62**	**V63**	**V64**	**V65**	**V66**	**Notes**
Study Week	**W208**	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	
Study Days (Approximately)	**1456 ± 7d**	**1484 ± 7d**	**1512 ± 7d**	**1540 ± 7d**	**1568 ± 7d**	**1596 ± 7d**	**1624 ± 7d**	**1652 ± 7d**	**1680 ± 7d**	**1708 ± 7d**	**1736 ± 7d**	**1764 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Assessment Questionnaire (CHAQ)													
Tanner Stage Scale												X	Assessment only for participants 8 years or older. Once the participant reaches the score of 5 on this scale during LTE, no further assessments are needed.
EQ-5D-Y			X			X			X			X	Assessment only for participants 4 years or older.
Children's Depression Inventory 2 Short Form (CDI-2)			X			X			X			X	Assessment only for participants 7 years of age or older
Pain Numeric Rating Scale			X			X			X			X	
Morning Joint Stiffness Duration			X			X			X			X	
Parent's Global Assessment of Well-Being			X			X			X			X	To be completed by caregiver until participant is ≥14 years of age, at which time, the participant will complete their own questionnaires.
Laboratory Tests													
Acute phase reactant (hsCRP)			X			X			X			X	
Acute phase reactant (ESR)			X			X			X			X	To be performed locally.
Administer TB test(s) (if applicable)	TB testing required only based on clinical assessment of TB risk and according to local regulations and/or local standard of care (Section 9.4.6; Appendix 2).												QuantiFERON-TB Gold, T-Spot or PPD (if applicable) (Section 9.4.6; Appendix 2). PPD to be read locally.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.													
Visit No	**V55**	**V56**	**V57**	**V58**	**V59**	**V60**	**V61**	**V62**	**V63**	**V64**	**V65**	**V66**	**Notes**
Study Week	**W208**	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	
Study Days (Approximately)	**1456 ± 7d**	**1484 ± 7d**	**1512 ± 7d**	**1540 ± 7d**	**1568 ± 7d**	**1596 ± 7d**	**1624 ± 7d**	**1652 ± 7d**	**1680 ± 7d**	**1708 ± 7d**	**1736 ± 7d**	**1764 ± 7d**	
Treatment Visits	X	X		X	X		X	X		X	X		Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
HBV DNA (if applicable)			X			X			X			X	Positive for HBcAb requires a follow up test for HBV DNA. See Section 5.1.1 for details.
Urine pregnancy test			X			X			X			X	See Section 5.1.1 for details. Females only. To be performed locally.
Clinical chemistry			X			X			X			X	
Hematology			X			X			X			X	
Urinalysis			X			X			X			X	
PK sample						X						X	At regular visits (i.e., when ixekizumab is administered on site to all the participants), PK samples should be collected prior to administration of ixekizumab.
Immunogenicity sample						X						X	See Section 9.6.1. All samples for immunogenicity should be taken predose when applicable and possible.

Abbreviations: AESI = adverse event of special interest; BP = blood pressure; d = days; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth; ESR = erythrocyte sedimentation rate; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; LEI = Leeds Enthesitis Index; No = number; PK = pharmacokinetics; PPD = purified protein derivative; TB = tuberculosis; V = study visit; W = study week.

Table RHCG.2.6. Schedule of Activities – Long Term Extension Period (V67 through V69)

Notes:
- Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.
- If ETV occurs on the same day as the scheduled visit, any assessments/procedures conducted during the scheduled visit should not be repeated for a separate ETV.
- The required post-treatment follow-up visits should occur for all study participants, except for those with concurrent infections (see Section 5.1.5 for details).

Visit No	**V67**	**V68**	**V69**	**Early termination**	**Post-Treatment Follow-Up Period (PTFU)**			**Notes**
				ETV	**V801**	**V802**	**V803**	V803 is an additional follow-up based on neutrophil count (Section 5.1.5).
Study Week	**W256**	**W260**	**W264**	**Any Week**	**LV (or ETV) + 4W**	**LV (or ETV) + 8W**	**LV (or ETV) + 12W**	
Study Days (Approximately)	**1792 ± 7d**	**1820 ± 7d**	**1848 ± 7d**	**Any Day**	**± 7d**	**± 7d**	**± 7d**	
Treatment Visits	X	X						Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Immunization record			X	X				Immunizations occurred during the participation in the study.
Physical examination			X	X				Excluding pelvic, rectal, and breast examinations.
Height			X	X				
Weight	X	X	X	X				Weight will be recorded for every participant at every visit in the Study Drug Administration Log: • For participants CCI [redacted] weight will be recorded by study personnel. • For participants CCI [redacted] o At-home administration: weight will be recorded by the participant or caregiver in the Study Drug Administration Log. o Regular and on-site treatment visits (if applicable): weight will be recorded by the study personnel.
Vital signs (BP, pulse, body temperature)			X	X				BP and pulse should be measured at least pre-injection.
Concomitant medications			X	X	X	X	X	
Adverse events (AEs)			X	X	X	X	X	See Section 9.2.2.3 for a complete list of AESIs. IBD events will be adjudicated. Investigators will assess the AEs during the regular

Notes:

- Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.
- If ETV occurs on the same day as the scheduled visit, any assessments/procedures conducted during the scheduled visit should not be repeated for a separate ETV.
- The required post-treatment follow-up visits should occur for all study participants, except for those with concurrent infections (see Section 5.1.5 for details).

Visit No	**V67**	**V68**	**V69**	**Early termination**	**Post-Treatment Follow-Up Period (PTFU)**			**Notes**
				ETV	**V801**	**V802**	**V803**	V803 is an additional follow-up based on neutrophil count (Section 5.1.5).
Study Week	**W256**	**W260**	**W264**	**Any Week**	**LV (or ETV) + 4W**	**LV (or ETV) + 8W**	**LV (or ETV) + 12W**	
Study Days (Approximately)	**1792 ± 7d**	**1820 ± 7d**	**1848 ± 7d**	**Any Day**	**± 7d**	**± 7d**	**± 7d**	
Treatment Visits	X	X						Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
								visits.
Dispense ixekizumab	X	X						See Section 6.1 for details. • Participants CCI [redacted] who opt for at-home administration will have the study drug dispensed during the regular visits only (that is, every 12 weeks). • The rest of the participants will have the study drug dispensed during both the treatment visits and regular visits (that is, every 4 weeks).
Administer ixekizumab	X	X						See Sections 7.1 for on-site and at-home administration details for treatment regimens. During regular visit, all participants (regardless of their weight) will receive ixekizumab injection on site.
Clinician-Reported Measures								
Joint Assessment			X	X				
Enthesitis Assessment			X	X				It includes LEI and active enthesitis count.
Dactylitic Count			X	X				
Physician's Global Assessment of Disease Activity			X	X				
Clinical Sacroiliitis			X	X				
Back Mobility (Schober's Test)			X	X				
Body Surface Area (BSA)			X	X				

Notes:

- Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.
- If ETV occurs on the same day as the scheduled visit, any assessments/procedures conducted during the scheduled visit should not be repeated for a separate ETV.
- The required post-treatment follow-up visits should occur for all study participants, except for those with concurrent infections (see Section 5.1.5 for details).

Visit No	**V67**	**V68**	**V69**	**Early termination**	**Post-Treatment Follow-Up Period (PTFU)**			**Notes**
				ETV	**V801**	**V802**	**V803**	V803 is an additional follow-up based on neutrophil count (Section 5.1.5).
Study Week	**W256**	**W260**	**W264**	**Any Week**	**LV (or ETV) + 4W**	**LV (or ETV) + 8W**	**LV (or ETV) + 12W**	
Study Days (Approximately)	**1792 ± 7d**	**1820 ± 7d**	**1848 ± 7d**	**Any Day**	**± 7d**	**± 7d**	**± 7d**	
Treatment Visits	X	X						Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Psoriasis Area and Severity Index (PASI)			X	X				
Columbia–Suicide Severity Rating Scale – Since Last Assessed			X	X				Assessment only for participants 7 years of age or older.
Self-Harm Supplement Form			X	X				Assessment only for participants 7 years of age or older.
Uveitis Evaluation			X	X				Investigators will assess if the participant has developed uveitis since last visit.
Study Drug Administration Log (Paper)								
Return Study Drug Administration Log (participant to site)			X	X				The Study Drug Administration Log needs to be collected only from the participants CCI [redacted] who have opted for at-home administration.
Participant-/Parent-Administered Measures								
Childhood Health Assessment Questionnaire (CHAQ)			X	X				
Tanner Stage Scale			X	X				Assessment only for participants 8 years or older. Once the participant reaches the score of 5 on this scale during LTE, no further assessments are needed.
EQ-5D-Y			X	X				Assessment only for participants 4 years or older.
Children's Depression			X	X				Assessment only for participant 7 years of age or older

Notes:

- Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.
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- The required post-treatment follow-up visits should occur for all study participants, except for those with concurrent infections (see Section 5.1.5 for details).

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Study Week	**W256**	**W260**	**W264**	**Any Week**	**LV (or ETV) + 4W**	**LV (or ETV) + 8W**	**LV (or ETV) + 12W**	
Study Days (Approximately)	**1792 ± 7d**	**1820 ± 7d**	**1848 ± 7d**	**Any Day**	**± 7d**	**± 7d**	**± 7d**	
Treatment Visits	X	X						Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Inventory 2 Short Form (CDI-2)								
Pain Numeric Rating Scale			X	X				
Morning Joint Stiffness Duration			X	X				
Parent's Global Assessment of Well-Being			X	X				To be completed by caregiver until participant is >14 years of age, at which time, the participant will complete their own questionnaires.
Laboratory Tests								
Acute phase reactant (hsCRP)			X	X				
Acute phase reactant (ESR)			X	X				To be performed locally.
Administer TB test(s) (if applicable)	TB testing required only based on clinical assessment of TB risk and according to local regulations and/or local standard of care Section 9.4.6; Appendix 2).							QuantiFERON-TB Gold, T-Spot or PPD (if applicable) (Section 9.4.6; Appendix 2) PPD to be read locally.
HBV DNA (if applicable)			X	X			X	Positive for HBcAb requires a follow up test for HBV DNA. See Section 9.4.4 for details.
Urine pregnancy test			X	X	X	X	X	See Section 9.4.5 and Appendix 6 for details. Females only. To be performed locally.
Clinical chemistry			X	X	X	X	X	
Hematology			X	X	X	X	X	

Notes:
- Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.
- If ETV occurs on the same day as the scheduled visit, any assessments/procedures conducted during the scheduled visit should not be repeated for a separate ETV.
- The required post-treatment follow-up visits should occur for all study participants, except for those with concurrent infections (see Section 5.1.5 for details).

Visit No	**V67**	**V68**	**V69**	**Early termination**	**Post-Treatment Follow-Up Period (PTFU)**			**Notes**
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Study Week	**W256**	**W260**	**W264**	**Any Week**	**LV (or ETV) + 4W**	**LV (or ETV) + 8W**	**LV (or ETV) + 12W**	
Study Days (Approximately)	**1792 ± 7d**	**1820 ± 7d**	**1848 ± 7d**	**Any Day**	**± 7d**	**± 7d**	**± 7d**	
Treatment Visits	X	X						Treatment visits are intended only for the dispensation and on-site administration of ixekizumab for the participants CCI [redacted] who have opted for on-site administration.
Urinalysis			X	X				
PK sample			X	X		X		At regular visits (i.e., when ixekizumab is administered on site to all the participants), PK samples should be collected prior to administration of ixekizumab.
Immunogenicity sample			X	X		X		See Section 9.6.1. All samples for immunogenicity should be taken predose when applicable and possible.

Abbreviations: AESI = adverse events of special interest; BP = blood pressure; d = days; DNA = deoxyribonucleic acid; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth; ESR = erythrocyte sedimentation rate; ETV = Early Termination Visit; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; LEI = Leeds Enthesitis Index; LV = Last Visit; No = number; PK = pharmacokinetics; PPD = purified protein derivative; RNA = ribonucleic acid; TB = tuberculosis; V = study visit; W = study week.

Notes: If ETV occurs on the same day as the scheduled visit, any assessments/ procedures conducted during the scheduled visit should not be repeated for a separate ETV. Post-Treatment Follow-Up Period — This applies only to participants who do not enter the long-term extension study. Treatment Visits are intended for the dispensation and/or site administration of the study treatment. Because of blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor provided weight-based prioritization chart.

3. Introduction

3.1. Study Rationale

This study is part of the European Paediatric Investigation Plan (PIP), EMEA-001050-PIP02-18- M01, with the aim to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of ixekizumab when administered to pediatric patients with juvenile idiopathic arthritis (JIA) categories of enthesitis-related arthritis (ERA) (including juvenile onset ankylosing spondylitis [JoAS]) and juvenile psoriatic arthritis (JPsA).

The study will include participants who are naive to biologic disease-modifying antirheumatic drugs (bDMARD-naive) and participants with an inadequate response (IR) or intolerance to treatment with at least one bDMARD (bDMARD-IR). The inclusion of bDMARD-naive and bDMARD-IR patients in this study is based on the unmet needs in both ERA and JPsA subsets of JIA. Adalimumab will serve as a reference arm in bDMARD-naive patients, allowing for a descriptive assessment in the same study as in bDMARD-naive patients on ixekizumab, thus providing assay sensitivity and context for the efficacy data.

The rationale for the long-term extension (LTE) period is to evaluate the long-term safety, tolerability, and efficacy of ixekizumab when administered to pediatric patients with JIA categories of ERA (including JoAS) and JPsA. In addition to the established safety profile for adult psoriasis, psoriatic arthritis, and axial spondyloarthritis, further assessments for the safety, tolerability, and efficacy data from this study are intended to establish a better understanding of the long-term benefit-risk relationship for ixekizumab in pediatric patients with ERA and JPsA.

3.2. Background

Disease background: **Juvenile idiopathic arthritis and its categories of enthesitis-related arthritis and juvenile psoriatic arthritis**

Juvenile idiopathic arthritis is a heterogeneous group of diseases characterized by idiopathic arthritis that starts before the age of 16 years and persists for at least 6 weeks. Juvenile idiopathic arthritis is the most common chronic rheumatic disease in children and a leading cause of short- and long-term disability (Ravelli and Martini 2007). The incidence and prevalence estimates for JIA vary greatly from 1.6 to 23 and from 3.8 to 400/100,000, respectively, depending on the classification, methodology, timing, and geography (Thierry et al. 2014).

According to the current second revision of the International League of Associations for Rheumatology (ILAR) classification of JIA, the group consists of 7 relatively homogeneous, mutually exclusive categories based on predominant clinical and laboratory features: systemic arthritis, oligoarthritis (persistent or extended), polyarthritis rheumatoid factor (RF) negative, polyarthritis RF positive, psoriatic arthritis (PsA), ERA, and undifferentiated arthritis (Petty et

al. 2004). Some forms of JIA are typically only seen in children, while others may be considered as childhood counterparts of adult diseases (Martini et al. 2019).

Enthesitis-related arthritis is characterized by the association of arthritis and enthesitis and is considered as the pediatric counterpart of ankylosing spondylitis (AS) or axial spondyloarthritis (axSpA). Other typical ERA features are: axial involvement, human leukocyte antigen-B27 (HLA-B27) positivity, acute anterior uveitis, and positive family history of spondyloarthritis (SpA) or related conditions (Colbert 2010; Tse and Laxer 2012). Enthesitis-related arthritis accounts for about 5% to 10% of all JIA cases, with a higher prevalence in non-Western European countries (Martini et al. 2019). Enthesitis-related arthritis mainly affects male patients and typically starts in late childhood or adolescence (Burgos-Vargas et al. 1997; Ravelli and Martini 2007; Consolaro et al. 2019). The most common sites of enthesitis are the calcaneal insertions of the Achilles tendon, plantar fascia, and tarsal area. Arthritis usually affects the joints of the lower extremities, including the hip. Axial (sacroiliac joint) involvement is of rarer occurrence than in adults and typically occurs later in the disease course. In addition to anterior uveitis, inflammatory bowel disease (IBD) may be an extra-articular manifestation. Although ERA is often remitting, some patients may develop cardiopulmonary and cerebrovascular complications, which are also leading causes of shorter life expectancy (Giancane et al. 2016).

The JPsA category byILAR criteria requires the simultaneous presence of arthritis and psoriasis or, if psoriasis is absent, the presence of arthritis and at least 2 of the following: (1) family history of psoriasis in a first-degree relative; (2) nail psoriasis (nail pitting or onycholysis); (3) dactylitis (Petty et al. 1998; Petty et al. 2004). Juvenile psoriatic arthritis represents about 2% to 11% of JIA cases and occurs with a biphasic distribution; early peak is at 2 to 4 years and later peak at 9 to 11 years of age (Ravelli and Martini 2007). The current JPsA category may however be heterogeneous and in need of further refinement (Martini et al. 2019.).

***Treatment of juvenile idiopathic arthritis* categories of enthesitis-related arthritis and juvenile psoriatic arthritis**

The goal of JIA treatment is rapid suppression of inflammation to reduce pain, prevent joint damage, maintain physical function and quality of life, and promote normal growth and development. Pharmacologic first-line treatment for patients with non-systemic JIA consists of nonsteroidal anti-inflammatory drugs (NSAIDs); intra-articular or short-term systemic use of corticosteroids may be considered in selected more severe cases. Persistent arthritis requires disease-modifying antirheumatic drug (DMARD) therapy. Methotrexate (MTX) is the most commonly used conventional synthetic DMARD (csDMARD), but a substantial proportion of patients do not achieve adequate response, may lose disease control over time or experience tolerability problems (Ringold et al. 2013; Hinze et al. 2015).

Biologic DMARDs (bDMARDs) have greatly improved treatment outcomes and prognosis of JIA. Current biologic treatment options for JIA include agents targeting

tumor necrosis factor (TNF) (etanercept, adalimumab), IL-6 (tocilizumab), CD28 (abatacept), and IL-1 (anakinra and canakinumab) (Giancane et al. 2016).

There are only 2 approved bDMARDs – the TNF inhibitors adalimumab and etanercept – for the treatment of ERA, while etanercept is the only bDMARD approved for the treatment of JPsA.

Adalimumab is a fully human monoclonal antibody against TNF and is approved in the EU for the treatment of active ERA in patients ≥6 years of age who have had an IR or intolerance to conventional therapy. Adalimumab is also approved in the EU for the treatment of pediatric plaque psoriasis, pediatric Crohn's disease, pediatric chronic non-infectious anterior uveitis, as well as polyarticular JIA (Humira® Summary of Product Characteristics [SmPC] 2020).

The safety and efficacy of adalimumab in ERA were assessed in a 12-week multicenter, randomized, double-blind, placebo-controlled study in 46 patients aged 6 to 17 years, followed by an open-label extension period. The primary endpoint was the percent change in the number of active joints with arthritis at Week 12, which was significantly greater in the adalimumab group than placebo group (-62.6% vs. -11.6%). Juvenile idiopathic arthritis American College of Rheumatology (ACR) 30/50/70/90 responses were achieved in 71%/68%/55%/42% of adalimumab-treated patients at Week 12, which was significantly more than on placebo (20%) for JIA ACR 70. Improvements were sustained through Week 52 of the open label adalimumab extension (Burgos-Vargas et al. 2015). Long-term effectiveness and acceptable safety profile of adalimumab with or without MTX have since been confirmed in larger registry studies in patients with non-systemic JIA, including ERA and JPsA (Klein et al. 2019).

Etanercept, a recombinant TNF receptor fusion protein, is approved in the EU for the treatment of JPsA and ERA in adolescents ≥12 years, for plaque psoriasis in children and adolescents
≥6 years, and for RF positive or negative polyarthritis, as well as extended oligoarthritis (Enbrel SmPC® 2019). Long-term extension studies of the original JIA trial cohorts and national registries have confirmed sustained clinical benefit and acceptable safety profile (Horneff et al. 2014; Constantin et al. 2016; Foeldvari et al. 2019). Etanercept has also been shown to reduce the progression of radiographic joint damage (Nielsen et al. 2008) and improve growth velocity and bone status in JIA patients (Billiau et al. 2010; Giannini et al. 2010). A drawback of etanercept in ERA and JPsA may be its lack of therapeutic impact on concomitant anterior uveitis and IBD (van der Heijde et al. 2017; Ward et al. 2019).

Although the currently approved bDMARDs enable significant improvements in JIA, there is still a substantial proportion of patients who fail to adequately respond or do not achieve long- lasting remission (Hinze et al. 2015). Thus, there is an unmet need for novel treatments, particularly those with alternative mechanisms of action.

Investigational product ixekizumab

Ixekizumab is an immunoglobulin (Ig) G subclass 4 (IgG4) monoclonal antibody that binds with a high affinity and specificity to interleukin (IL)-17A, a key proinflammatory cytokine in the pathophysiology of plaque psoriasis, PsA and axSpA (Leonardi et al. 2012; Taams et al. 2018; Robinson et al. 2019).

Interleukin-17A, a member of the IL-17 family, is mainly produced by inflammatory Th17 cells, a subset of T helper cells, but also by other T cells, neutrophils, and mast cells. Animal studies established the role of IL-17 signaling in ankylosing enthesitis and bone remodeling (Abe et al. 2009; Glatigny et al. 2012), and prophylactic administration of anti-IL-17 antibodies blocked the development of ankylosis in a spontaneous ankylosis mouse model (Ebihara et al. 2015).

Ixekizumab is approved in the EU (Taltz® SmPC), US (Taltz US package insert [USPI]), and several other countries for the treatment of adult patients with:

- moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy;
- active PsA;
- active radiographic axSpA/ankylosing spondylitis (r-axSpA/AS); and
- active non-radiographic axSpA (nr-axSpA) in patients with objective signs of inflammation.

In addition, ixekizumab has recently been approved for the treatment of moderate-to-severe plaque psoriasis in children from the age of 6 years and adolescents who are candidates for systemic therapy (Taltz SmPC and Taltz USPI).

The efficacy and safety of ixekizumab in adult patients with active PsA was primarily assessed in two Phase 3 randomized, double-blind, placebo-controlled studies involving 780 patients in total: SPIRIT-P1 (I1F-MC-RHAP) study in bDMARD-naive patients (Mease et al. 2017) and SPIRIT-P2 (I1F-MC-RHBE) study in patients who failed prior TNF inhibitor therapy for lack of efficacy or intolerance (Nash et al. 2017). In both studies the treatment with ixekizumab 80 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) or every 2 weeks (Q2W) with a starting dose of 160 mg ixekizumab, resulted in significant improvements in clinical disease activity, physical function and health-related quality of life compared to placebo at Week 24.
The ACR 20/50/70 response rates at Week 24 in patients treated with the approved ixekizumab dosing regimen Q4W were 58%/40%/23% in SPIRIT-P1 and 53%/35%/22% in SPIRIT-P2, which was significantly higher than placebo (30%/15%/6% and 20%/5%/0%, respectively) (Mease et al. 2017; Nash et al. 2017). The ACR 20/50/70 response rates at Week 24 on the active reference adalimumab arm in SPIRIT-P1 were 57%/39%/26% (Mease et al. 2017). In patients with pre-existing dactylitis or enthesitis, significantly more patients treated with ixekizumab Q4W than placebo achieved resolution at Week 24: 78% versus 24% and 39% versus 21%, respectively (Gladman et al. 2019). Among patients with ≥3% body surface area (BSA), higher proportions of

patients treated with ixekizumab Q4W than placebo attained Psoriasis Area and Severity Index (PASI) 75/90/100 responses (PASI75 67% vs. 9% at Week 12). Significant inhibition of radiographic progression on ixekizumab compared with placebo was demonstrated in SPIRIT-1 study at Week 24 (Taltz SmPC). Improvements in all PsA domains were maintained during open-label extension treatment with ixekizumab through 1 year (Genovese et al. 2018; van der Heijde et al. 2018; Kavanaugh et al. 2019).

Further, in a Phase 4 direct comparative study of ixekizumab versus adalimumab in bDMARD naive adult PsA patients (SPIRIT-H2H; I1F-MC-RHCF), ixekizumab was superior to adalimumab in the simultaneous achievement of ACR50 and PASI 100 responses at Week 24 (36%/28% respectively). Ixekizumab was non-inferior to adalimumab in achieving ACR50 response (51%/47% respectively) and superior in achieving PASI 100 response (60%/47% respectively). Significantly better results on ixekizumab compared with adalimumab were also seen for composite measures of disease activity and resolution of enthesitis (Humira SmPC 2020; Mease et al. 2020).

The efficacy and safety of ixekizumab were assessed in 960 patients with active axSpA in 3 randomized, double-blind, placebo-controlled studies: COAST-V (I1F-MC-RHBV) in bDMARD-naive patients with r-axSpA/AS (van der Heijde et al. 2018), COAST-W (I1F-MC-RHBW) in patients with r-axSpA/AS with IR or intolerance to TNF inhibitors (Deodhar et al. 2019), and COAST-X (I1F-MC-RHBX) in bDMARD-naive patients with nr-axSpA (Deodhar et al. 2020). Treatment with ixekizumab either at 80 mg Q4W or Q2W resulted in significant improvements compared with placebo in measures of disease activity, physical function, health related quality of life as well as spinal inflammation measured by magnetic resonance imaging (MRI) at Week 16 in both r-axSpA/AS studies (van der Heijde et al. 2018; Deodhar et al. 2019). Significantly more patients treated with the approved ixekizumab dosing regimen Q4W vs placebo achieved assessment in ankylosing spondylitis (ASAS)-40 response at Week 16: 48% vs 18% in COAST-V and 25% vs 13% in COAST-W; by comparison, ASAS40 response was achieved in 36% of patients treated with adalimumab as the active reference drug in COAST-V study. Further, significant improvements in ixekizumab compared with placebo were seen in both studies in the individual components of the ASAS response, including patient global assessment and spinal pain. Therapeutic effects of ixekizumab were maintained through Week 52 across the measures of disease activity, function, and objective inflammation (Dougados et al. 2019; Taltz SmPC 2020). Consistent therapeutic effects and safety profile of ixekizumab were recently demonstrated also in patients with non-radiographic axSpA with objective signs of inflammation (Deodhar et al. 2020).

The efficacy and safety of ixekizumab in pediatric participants (6 to <18 years old) with moderate-to-severe plaque psoriasis were assessed in a Phase 3, randomized, double-blind, placebo-controlled study of ixekizumab (IXORA-PEDS/I1F-MC-RHCD; Paller et al. 2020). A total of 171 participants were studied (115 participants on ixekizumab and 56 on placebo).

Ixekizumab was administered subcutaneously Q4W; the doses were weight-based (see Section 5.5 for details). Treatment with ixekizumab was superior to placebo for both coprimary endpoints at Week 12 ($p<0.001$):

- ≥75% improvement in PASI 75: Ixekizumab Q4W, 89%; placebo, 25%
- A static Physician's Global Assessment score of 0 or 1 (sPGA 0,1): Ixekizumab Q4W, 81%; placebo, 11%

Overall, treatment with ixekizumab in Study RHCD resulted in rapid and statistically significant improvements, compared with placebo, in skin involvement, itch, and health-related quality of life. These improvements persisted through 48 weeks of treatment.

In Study RHCD, the safety profile of ixekizumab was overall consistent with that seen in adult participants, with the exception of frequencies of conjunctivitis (2.6%), influenza (1.7%), and urticaria (1.7%), which were greater in pediatric participants compared to adults. In the IXORA-PEDs Randomized Clinical Trial that ran for 108 weeks, there were no new safety findings during Weeks 48 to 108 of the trial, including no new cases of inflammatory bowel disease or candida infection. (Paller et al. 2022).

3.3. Benefit/Risk Assessment

Based on the efficacy of ixekizumab demonstrated in the clinical studies of axSpA and PsA in adult patients (described in Section 3.2), as well as the pediatric study in plaque psoriasis, significant therapeutic benefits may be expected in pediatric patients with ERA and JPsA, which share clinical, imaging, immunopathologic, and genetic similarities with axSpA and PsA, respectively.

Across the approved indications of adult and pediatric plaque psoriasis, PsA, r-axSpA/AS, and nr-axSpA, ixekizumab has been shown to have a comparable risk profile.

Most common (≥1%) adverse reactions associated with ixekizumab treatment are injection site reactions, upper respiratory tract infections, nausea, and tinea infections. In clinical trials in adult patients with plaque psoriasis, the ixekizumab group had a higher rate of infections than the placebo group (27% vs. 23%). Upper respiratory tract infections, oral candidiasis, conjunctivitis and tinea infections occurred more frequently in the ixekizumab group than in the placebo group. A similar increase in the risk of infection was seen in placebo-controlled trials in patients with pediatric psoriasis, PsA and AS. Serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), occurred in the ixekizumab group in clinical trials. Anaphylaxis, including cases leading to hospitalization, has been reported in post marketing use with ixekizumab.

Ixekizumab has been evaluated so far in one placebo-controlled pediatric trial, which was conducted in patients with moderate-to-severe plaque psoriasis 6 to less than 18 years of age. A total of 171 patients were studied (115 patients on ixekizumab and 56 on placebo).

CCI [redacted]

Overall, the safety profile observed in pediatric patients with plaque psoriasis treated with ixekizumab Q4W is consistent with the safety profile in adult patients with plaque psoriasis with the exception of frequencies of conjunctivitis (2.6%), influenza (1.7%), and urticaria (1.7%). Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported and are considered to be an uncommon adverse effect. Crohn's disease occurred at a greater frequency in the ixekizumab group (0.9%) than the placebo group (0%) during the 12-week, placebo-controlled period. In adult patients with plaque psoriasis, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the ixekizumab 80 mg Q2W group (Crohn's disease 0.1%, ulcerative colitis 0.2%) than the placebo group (0%) during the 12-week, placebo- controlled period of clinical trials. In adult patients with AS, Crohn's disease and ulcerative colitis, including exacerbations, occurred in 2 patients (1.0%) and 1 patient (0.5%), respectively, in the ixekizumab 80 mg Q4W group, and 1 patient (0.5%) and 0%, respectively, in the placebo group during the 16-week, placebo-controlled period. Of these patients, serious events occurred in 1 patient in the ixekizumab 80 mg Q4W group and 1 patient in the placebo group.

Other adverse drug reactions and potential risks associated with ixekizumab treatment include: cytopenias (usually mild) and liver enzyme elevations. Data from clinical trials do not suggest an association between ixekizumab treatment and cerebrocardiovascular events, depression/suicidality, or malignancies. There are insufficient human data to establish the safety of ixekizumab during pregnancy.

Section 9.2.1 describes adverse events of special interest (AESI) in this protocol. Risk mitigation measures added to the protocol to address the important potential risks include appropriate inclusion and exclusion criteria, safety monitoring, and temporary and permanent discontinuation criteria.

More information about the known and expected benefits and risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of ixekizumab (LY2439821) are to be found in the Investigator's Brochure (IB).

Adalimumab was selected as an active reference treatment as it is 1 of the 2 bDMARDs that are currently approved for the treatment of ERA. There is also positive clinical experience with adalimumab in JPsA (Klein et al. 2019), and well-established efficacy and safety in adult axSpA and PsA. Adalimumab has 2 main advantages over etanercept, which is the other bDMARD approved for ERA: (1) adalimumab is approved for a broader age range of ERA patients than etanercept (≥6 years vs. ≥12 years of age); (2) adalimumab as an anti-TNF monoclonal antibody is efficacious in the treatment of IBD (Crohn's disease and ulcerative colitis), as well as for prevention of acute anterior uveitis attacks, which are both important comorbidities in SpA and SpA-like diseases (van der Heijde et al. 2017; Ward et al. 2019). Etanercept is approved for the treatment of JPsA; however, in children and adolescents ≥12 years of age only (Enbrel SmPC 2019).

As adalimumab is not approved for JPsA, and JPsA patients included in this study may be <6 years of age and weigh <15 kg, the approved dose of adalimumab for the treatment of

polyarticular JIA will be used in JPsA patients weighing 10 to <15.0 kg (Humira SmPC 2020).

Adalimumab has a well-established safety profile across 14 approved indications (Humira SmPC 2020): rheumatoid arthritis (RA), JIA (polyarticular JIA and ERA), axSpA (AS and axSpA without radiographic evidence of AS), PsA, adult and pediatric Crohn's disease, ulcerative colitis, adult and pediatric psoriasis, hidradenitis suppurativa, and adult and pediatric uveitis. The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, hemorrhage, pain or swelling), headache and musculoskeletal pain. Serious adverse reactions have been reported for adalimumab. Tumor necrosis factor antagonists, such as adalimumab, affect the immune system and their use may affect the body's defense against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and tuberculosis [TB]), hepatitis B virus (HBV) reactivation and various malignancies (including leukemia, lymphoma and hepatosplenic T-cell lymphoma) have also been reported with use of adalimumab. Serious hematological, neurological, and autoimmune reactions have also been reported. These include rare reports of pancytopenia; aplastic anemia; central and peripheral demyelinating events; and reports of lupus, lupus-related conditions, and Stevens-Johnson syndrome. In general, the AEs in pediatric patients were similar in frequency and type to those seen in adult patients. More detailed information about the known and expected benefits and risks of adalimumab may be found in the Summary of Product Characteristics (Humira SmPC 2020).

As only 2 bDMARDs, both TNF inhibitors, are currently approved to treat ERA and/or JPsA, and not all patients achieve an adequate primary response to them or may experience secondary treatment failure or intolerance, there is a high unmet need for bDMARDs with a different mechanism of action in these 2 JIA subtypes. Based on the demonstrated comprehensive efficacy of ixekizumab in axSpA and PsA as well as acceptable safety profile, the reasonable probability of a positive benefit/risk warrants this study to be conducted.

4. Objectives and Endpoints

Table RHCG.4.1 shows the objectives and endpoints of the study.

Table RHCG.4.1. Objectives and Endpoints

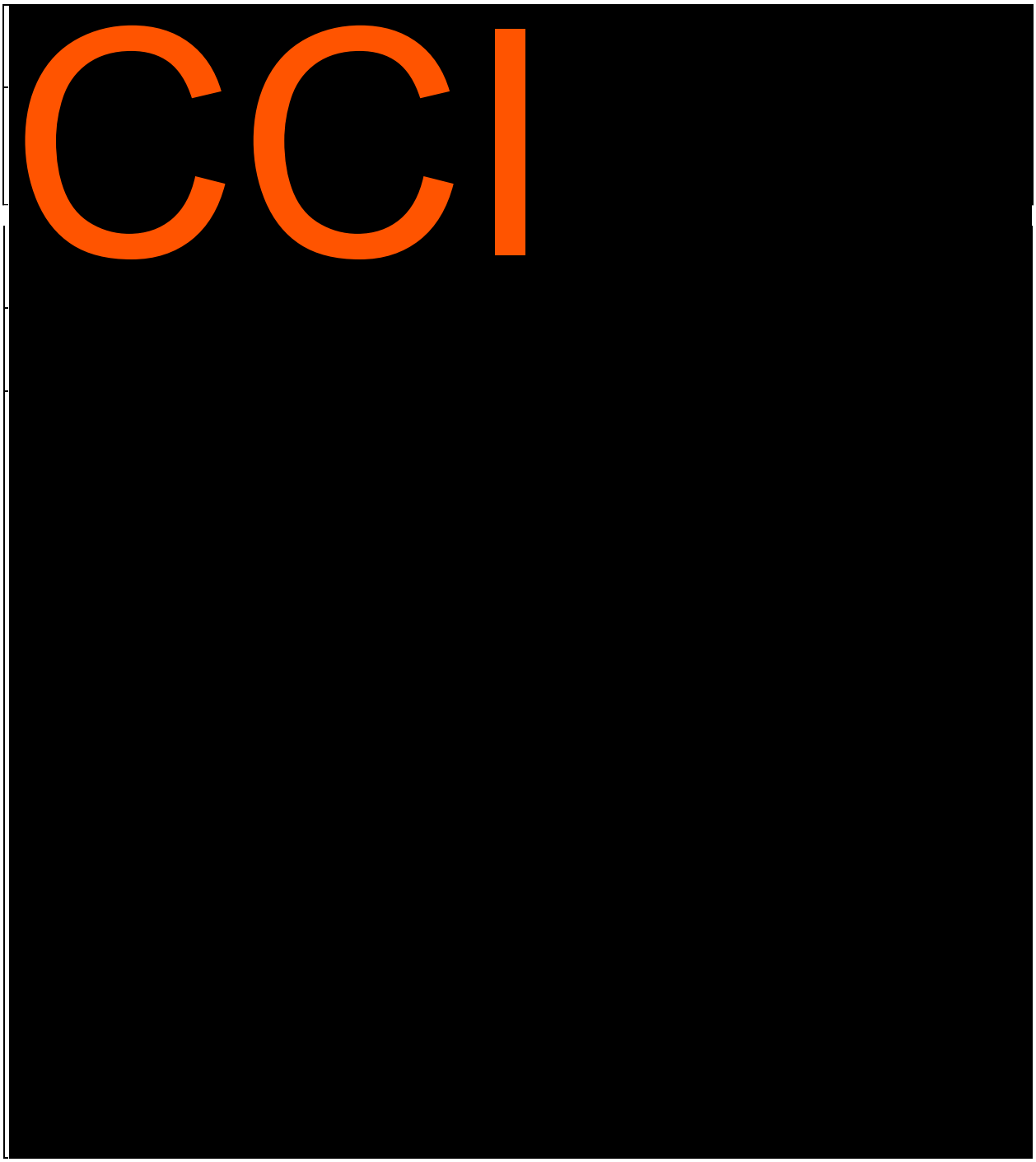
Objectives	Endpoints
Primary • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the JIA American College of Rheumatology (ACR) 30 response	Percentage of participants meeting the JIA ACR 30 response criteria at Week 16

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

• To characterize ixekizumab pharmacokinetics (PK) in children with JIA subtypes of ERA (including JoAS) and JPsA	• Trough concentrations of ixekizumab in participants with JIA subtypes of ERA (including JoAS) and JPsA

Objectives and Endpoints

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



Abbreviations: ERA = enthesitis-related arthritis; ETV = Early Termination Visit; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis.

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

5. Study Design

5.1. Overall Design

Study I1F-MC-RHCG (RHCG) is a multicenter, open-label, Phase 3 study of ixekizumab with adalimumab as a randomized reference arm in participants with JIA categories of ERA (including JoAS) and JPsA from 2 to less than 18 years of age, who are bDMARD-naive or bDMARD-IR as per investigator's judgement.

The study will be conducted in 5 parts, which includes screening and post-treatment follow up (PTFU) periods, in a 5-year study. The open-label treatment (OLT) period will include the OLT with ixekizumab or adalimumab up to Week 16. The open-label extension (OLE) period will provide OLT with ixekizumab or adalimumab up to Week 104. The LTE will provide OLT with ixekizumab only. The total study duration will include the screening period, 5-year treatment period, and PTFU period. Out of 100 participants, 40 will be randomly assigned into 1:1 ratio among naive bDMARD participants either to treatment arm (ixekizumab) or reference arm (adalimumab), and the remaining 60 participants will be randomly allocated either to naive or bDMARD-IR group at Visit 2 (Week 1). Participants receiving ixekizumab during the OLT period will continue to receive ixekizumab during the OLE period. Participants receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 will be switched to ixekizumab in the OLE period. Participants receiving adalimumab during the OLT period who did attain a JIA ACR 30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period. The decision to switch for participants who achieved a JIA ACR 30 response at Week 16 will be left to the participant/participant's caregiver and investigator. A switch from adalimumab to ixekizumab during the OLE period may also occur at any other visit after Week 16 based on the participant/participant's caregiver and investigator's decision. After switching to ixekizumab, the participants will not have the option to resume adalimumab treatment during the remainder of the trial participation.

Participants who complete the OLT and OLE are eligible to enter the LTE part of the study period. All participants entering the LTE portion of the study period will receive weight-based ixekizumab at Week 104. Participants who were previously assigned to adalimumab will be switched to ixekizumab as described in Section 7.1 Treatments Administered. If a participant previously assigned to adalimumab does not want to switch to ixekizumab in the LTE period of the study, the patient should initiate the early termination visit (ETV) process at Week 104. These participants will be considered to have completed the study. Participants who have completed PTFU will have completed the study. Participants who have received at least 1 dose of study drug and who discontinued early (patients who have received at least 1 dose of study drug) should enter the PTFU period and complete through Visit 802. Participants may be followed beyond Visit 802 for continued monitoring of their neutrophil counts or because of any other

safety concerns if determined by the sponsor/investigator that additional monitoring is needed. If a participant discontinues study drug early, the participant will complete the ETV and then enter the PTFU period.

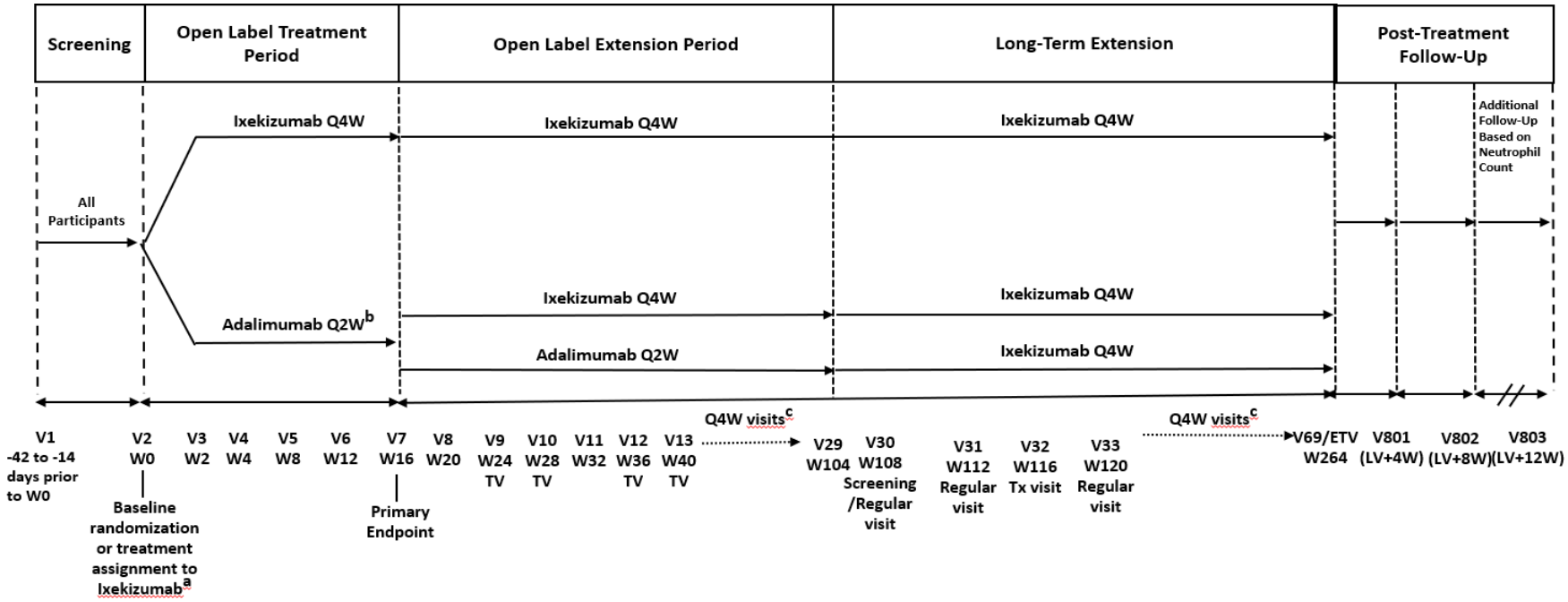
Interim analyses are described in Section 10.3.8. An interim analysis will be performed to determine if the study should be stopped for futility when 40 ixekizumab--treated participants have completed 16 weeks of treatment.

The study will enroll at least 100 participants with JIA categories of ERA or JPsA. Among participants who are bDMARD-naive, at least 20 participants will be randomized to ixekizumab and at least 20 participants will be randomized to adalimumab. Randomization will be stratified based on the subset of JIA (ERA or JPsA).

The remaining participants (approximately 60 participants) who are either bDMARD-naive or bDMARD-IR will be assigned to ixekizumab.

The LTE period will include the following on-site visits:

- Regular visits (every 12 weeks, with the exception of Visits 30 and 31/Weeks 108 and 112): both for participants CCI
    - During regular visits, ixekizumab will be administered on site to all participants (regardless of their weight).
- Treatment visits (every 4 to 8 weeks starting with Visit 32/Week 116): for participants CCI (and those participants CCI who have opted to receive ixekizumab on site).



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

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

b Participants receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 will be switched to ixekizumab in the OLE period. Participants receiving adalimumab during the OLT period who did attain a JIA ACR 30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period.

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

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

5.1.1. Screening and Baseline Periods

The Screening Period is from 7 up to 42 days prior to baseline. At screening, the parent or legal guardian will sign the informed consent form (ICF) and the participant will sign the assent form (as appropriate) per local requirements prior to any study assessments, examinations, or procedures being performed (Appendix 3). All screening procedures will be performed according to the Schedule of Activities (Section 2).

The preferred TB test is QuantiFERON® TB Gold test. In countries where the QuantiFERON®- TB Gold test is not available or due to investigator's judgement (e.g., need to reduce the volume of blood collected), T-spot or the purified protein derivative (PPD) test may be used. In the case of selecting the PPD test, the participant must return within 48 to 72 hours to read the skin test. The PPD test result does not need to be read at the site, but must be assessed by a trained healthcare professional, and documented results provided to the site as soon as possible.

Treatment with concomitant JIA therapies and topical corticosteroids during the study is permitted only as described in Section 7.7. Participants will remain on background MTX, other csDMARDs and oral, topical or ophthalmic corticosteroids if participants are on stable doses of these treatments at screening (see Sections 6.2 and 7.7. for details).

Participants with a positive HCV antibody will return to the site and have an HCV RNA sample drawn, which will be processed centrally. Results must be known prior to enrollment. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled.

Participants with a positive hepatitis B core antibody (HBcAb) will return to the site and have an HBV DNA sample drawn, which will be processed centrally. Results must be known prior to enrollment. Any enrolled participant who is HBcAb positive, regardless of hepatitis B surface antibody (HBsAb) status or level, must undergo HBV DNA testing per the Schedule of Activities (Section 2).

Pregnancy tests will be given prior to the first dose of investigational product for females ≥10 years of age (<10 years at investigator discretion) if menarche has been reached or if there is reason to believe the participant is sexually active. Pregnancy test results from baseline must be known prior to first dose of investigational product.

Investigators should review the vaccination status of the participant and ensure that the participant is up-to-date with all live immunizations and follow the local requirements for vaccination guidelines and schedule for immunosuppressed participants.

Participants who meet all the inclusion and none of the exclusion criteria (Section 6) will continue to baseline. At baseline, study eligibility for each participant will be reviewed based on all inclusion and exclusion criteria (Section 6).

Laboratory samples will be collected at screening and baseline and all assessments should be completed before the participant takes the first dose of investigational product. Owing to blood volume restrictions, some laboratory tests may not be collected for younger or lighter

weight participants based on Institutional Review Board (IRB) blood volume limitations. Laboratory samples are recommended to be collected as described in a sponsor-provided weight-based prioritization chart.

5.1.2. Open-Label Treatment Period

In the OLT period, participants will be randomly assigned to receive either SC ixekizumab Q4W or SC adalimumab Q2W for approximately 16 weeks. Evaluation of the primary endpoint will occur at Week 16. Randomization will be stratified based on the category of JIA (ERA or JPsA).

Among bDMARD-naive participants, at least 20 participants will be randomized to ixekizumab and at least 20 participants will be randomized to adalimumab. The remaining participants (approximately 60 participants) who are either bDMARD-naive or bDMARD-IR, will be assigned to ixekizumab.

Ixekizumab dosing will be as follows: CCI [redacted] Q4W thereafter; CCI [redacted] Q4W thereafter; CCI [redacted] Q4W thereafter.

Adalimumab dosing will be as follows: CCI [redacted] Q2W; and CCI [redacted] Q2W. Dosing of ixekizumab or adalimumab may not be changed in the OLT period.

Participants should remain under observation for at least 1 hour after the first ixekizumab dose to monitor for safety. Following the first injection, and if no problems occur with that injection, participants will be observed for 30 minutes following injection at all other study visits.

At Week 0 (baseline; Visit 2), routine safety assessments; laboratory tests; health outcomes assessments; and clinical, efficacy, and safety assessments will be performed on eligible participants according to the Schedule of Activities (Section 2).

Female participants of childbearing potential (age 10 and older if menarche has been reached or if there is reason to believe the participant is sexually active, or younger participants per investigator assessment of sexual maturity) will undergo a urine pregnancy test at the clinic on a monthly basis during scheduled regular visits through Week 104. Additional urine pregnancy testing may be performed at the investigator's discretion. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study drug (see Section 8.1).

Participants who discontinue the study for any reason during this period will stop treatment and continue to the ETV prior to entering the PTFU.

5.1.3. Open-Label Extension Period

In the OLE period, all participants who were receiving ixekizumab in the OLT period will continue to receive ixekizumab for approximately 88 weeks.

Participants receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 will be switched to ixekizumab in the OLE period. Participants receiving adalimumab during the OLT period who did attain a JIA ACR 30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period. Participants who are switched over to ixekizumab treatment after the OLT period will be treated as a separate group. The decision to switch for participants who achieved a JIA ACR 30 response will be left to the participant/participant's caregiver and investigator. A switch from adalimumab to ixekizumab during the OLE period may also occur at any other visit after Week 16 based on the participant/participant's caregiver and investigator's decision. For switching participants, the first ixekizumab dose can occur at any study visit during OLE period and after a minimum of 2 weeks after the last adalimumab dose (e.g., the subject that received the last dose of adalimumab at Week 14 will receive the first dose of ixekizumab at Week 16).

Switching from adalimumab to ixekizumab for a safety reason requires a washout period of sufficient length to allow the safety issue/parameter to resolve.

The participants switching to ixekizumab will not receive the starting ixekizumab dose but will receive the appropriate regular ixekizumab dose according to their weight at each visit. After switching to ixekizumab, the participants will not have the option to resume adalimumab treatment during the remainder of the trial participation. Rationale/justification for switching will be captured for any participant switching to ixekizumab and recorded in the participant's case report form.

Weight will be recorded, and dosing of ixekizumab and adalimumab will be adjusted during the OLE period according to the participant's weight at each visit.

5.1.4. Long-Term Extension Period

All procedures during the LTE period will be performed according to the Schedule of Activities (Section 2).

Study Visits

Participants CCI will have the option to self-administer ixekizumab at home (or have their caregivers administer it) after both the participants and their caregivers have received the appropriate training (see the SoA and Section 6.1 for details).

The LTE period will include the following on-site visits:

- Regular visits (every 12 weeks, with the exception of Visits 30 and 31/Weeks 108 and 112): both for participants CCI
    - During regular visits, ixekizumab will be administered on site to all participants (regardless of their weight)
- Treatment visits (every 4 to 8 weeks starting with Visit 32/Week 116): for participants CCI (and those participants CCI who have opted to receive ixekizumab on site)

Weight will be recorded, and dosing of ixekizumab will be adjusted during the LTE period according to the participant's weight at each visit.

5.1.5. Post-Treatment Follow-Up Period

Participants who have received at least 1 dose of study drug (including those who do not enter in the LTE period or discontinued early) should enter the PTFU period for a minimum of 12 weeks after their last regularly scheduled visits (or the date of their ETV). Required study visits should occur at 4 weeks after and at 8 weeks after the last regularly scheduled visit (or the date of the participant's ETV) (Visits 801 and 802, respectively), except for participants with concurrent infections that require systemic anti-infective therapy (described below).

If, at the last scheduled visit or ETV, a participant's neutrophil count is <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L) and less than the participant's baseline neutrophil count, the following measures should be taken:

- Participants with concurrent infection: If there is a concurrent infection that requires systemic anti-infective therapy, the participant should receive appropriate medical care and a repeat test for neutrophil count should be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count should be monitored using the required study visits in the PTFU period design at Visits 801 (4 weeks after resolution of infection), 802 (8 weeks after last visit), and 803 (if necessary; 12 weeks after last visit); additional visits may be required depending on the degree of neutropenia.
- Participants without concurrent infection: If there is no concurrent infection that requires systemic anti-infective therapy, the neutrophil count should be monitored using the required study visits in the PTFU period design, Visits 801 (4 weeks post ETV or last regularly scheduled visit), 802, and 803 (if necessary); additional visits may be required depending on the degree of neutropenia.
- For Visit 801 and subsequent visits, the following monitoring applies:
    - As long as a participant's neutrophil count is <1000 cells/μL (<1.00 × 10^3/μL or <1.00 GI/L) at any follow-up visit, the participant should return for additional visits at least Q4W (unscheduled visits may be required).
    - As long as a participant's neutrophil count is ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L) at any follow-up visit, the participant should return for additional visit(s) at least every 4 to 8 weeks (unscheduled visits may be required).
    - If at Visit 803 the participant's neutrophil count remains <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L) and less than the participant's baseline neutrophil count or if the investigator deems additional follow-up may be necessary, the investigator in consultation with Lilly or qualified designee will determine the appropriate management of the participant and the appropriate timing of additional contact(s) or visit(s).
    - If at Visit 802 or Visit 803 the participant's neutrophil count is ≥1500 cells/μL (≥1.50 × 10^3/μL or ≥1.50 × 10^3/μL) or greater than or equal to the

participant's baseline neutrophil count (whichever is lower), the participant's participation in the study will be considered complete unless the investigator deems additional follow-up necessary.

5.2. Number of Participants

At least 100 participants from 2 to less than 18 years of age with a diagnosis of JIA categories of ERA and JPsA are planned to enter the OLT period.

- For participants who are bDMARD-naive, at least 20 participants will be randomized to ixekizumab and at least 20 participants will be randomized to adalimumab. Randomization will be stratified based on the category of JIA (ERA or JPsA).
- The remaining participants (approximately 60 participants) who are either bDMARD- naive or bDMARD-IR will be assigned to ixekizumab.

5.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (Section 2). Participants on adalimumab completing Visit 29/Week 104 are considered to have completed the study treatment if they do not wish to continue on ixekizumab.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This is an open-label study to assess the efficacy, safety, tolerability, and PK of ixekizumab in children with JIA during the OLT period (Week 0 to Week 16), followed by an OLE period, including adalimumab as a randomized reference arm. The total study duration will be about 2 years, with the addition of 3 years of ixekizumab treatment in the LTE period.

Although the currently approved bDMARDs enable significant improvements in JIA, there is still a substantial proportion of participants who fail to adequately respond or do not achieve long-lasting remission (Hinze et al. 2015). Thus, there is an unmet need for novel treatments, particularly those with alternative mechanisms of action. The 2 categories of JIA included in this study – ERA and JPsA – are considered juvenile counterparts of adult axSpA and PsA, respectively. Ixekizumab has been shown before to be efficacious in improving signs and symptoms, physical function, and quality of life in adult participants with axSpA and JPsA at an acceptable safety profile. Hence, there is a potential for this study to demonstrate a clinically relevant benefit of ixekizumab therapy in participants with ERA and JPsA.

According to the PIP, the study will enroll participants aged 2 to less than 18 years. Participants with JPsA will be enrolled considering this age range. Participants with ERA will have to be at least 6 years or older at enrollment, as the disease typically starts at this age, which is also reflected in the classification criteria. Further, the classification criteria for ERA have low specificity if applied in younger children.

Study treatment will be provided during 2 study periods (OLT and OLE). Study treatment in OLT is designed to evaluate the primary endpoint, which is the percentage of participants meeting the JIA ACR 30 response criteria at Week 16. Evaluation of the primary endpoint at the Week 16 time point is appropriate, based on previous clinical trials.

Participants that do not achieve JIA ACR 30 response at Week 16 while on adalimumab, will be switched to ixekizumab without a washout period, due to a high need for treatment change/escalation. Evidence from studies in adult participants with IBD or RA suggests no significant safety risk is associated with direct switching between different monoclonal antibodies (Smolen et al. 2016; Mahagna and Ben-Horin 2019). To decrease any potential safety risk in switching participants, the minimum required period between the last adalimumab and first ixekizumab dose will be 2 weeks, and no higher starting dose of ixekizumab will be applied (van der Heijde et al. 2018).

The OLE period allows for long-term evaluation of safety and durability of efficacy in participants who receive ixekizumab. The PTFU will allow for continued safety monitoring after the last dose.

The open-label Bayesian approach is considered methodologically acceptable. The inclusion of adalimumab reference arm, with 1:1 randomization of bDMARD-naive participants to either ixekizumab or adalimumab, will allow for descriptive comparative statistics, thus providing assay sensitivity and context for ixekizumab efficacy data.

An active adalimumab reference arm was used before in the Phase 3 randomized placebo-controlled trials of ixekizumab in bDMARD-naive adult participants with PsA and axSpA (Mease et al. 2017; van der Heijde et al. 2018).

The inclusion of bDMARD-IR participants is driven by the unmet need in participants who had primary or secondary failure or intolerance to bDMARD therapy, including adalimumab.

The long-term open-label extension period allows participants with JIA to receive treatment with ixekizumab for an extended time and provides for collection of longer-term safety, tolerability, and efficacy data for ixekizumab in JIA subtypes of ERA and JPsA.

5.5. Justification for Dose

The efficacy, safety, and PK data from the Phase 3 program in adults with PsA were used to guide the dose and dosing regimen for investigation in pediatric participants with PsA in this study. The adult PK model and the adult ACR exposure response model in PsA participants were used to simulate the expected PK and pharmacodynamic (PD) responses across a range of ages and weights in pediatric participants to support the selection of the weight categories, the doses, and the dosing frequency to be used in this study. The recommended doses have been selected to target exposures in pediatric participants to be within the range of exposures observed in the Phase 3 adult PsA and axSpA studies with the 80 mg Q2W and 80 mg Q4W doses, which both had a positive benefit/risk ratio.

The dose is weight based, and it will be determined based on the participant's weight at Visit 2. If a participant changes weight category, dosing will not be adjusted up to Week 16 in the

OLT period. The dose will be adjusted according to the participant's weight during the OLE period and the LTE period.

Results from the modeling and simulation analyses support the following doses, dosing frequencies, and weight categories to be used in this study:

- CCI Q4W CCI
- CCI Q4W CCI
- CCI Q4W CCI

In addition, results have since become available from a study in which ixekizumab was administered to pediatric participants age 6 years to <18 years with moderate-to-severe psoriasis (Study RHCD). CCI Results show that ixekizumab was efficacious across all weight categories. Mean ixekizumab CCI for the CCI dosing regimens were 3.91 CCI of the study, respectively, and compare well to the CCI reported in the adult pivotal Phase 3 psoriasis studies at Week 12 of 3.48 µg/mL. There were limited PK data in participants weighing <25 kg.

Therefore, the pediatric psoriasis data confirms that the exposures achieved with the recommended dosing regimens for this study are similar to those achieved with the adult CCI Q4W dosing regimen. CCI Q4W dosing regimen is the recommended dosing regimen in adult participants with PsA and r-axSpA (AS), therefore this provides further support for their use in this study of JIA categories JPsA and ERA.

Participants in the adalimumab arm (reference arm) will receive SC adalimumab at the following dosing regimen:

- CCI Q2W for CCI
- CCI Q2W for CCI

Due to the similarities between the JIA subtypes of ERA and JPsA and because they are typically treated with the same therapies and doses, the same dose of adalimumab was selected for participants with ERA (as per the approved label) and JPsA. Because JPsA participants included in this study may be <6 years of age and weight <15 kg, the approved dose of adalimumab for the treatment of polyarticular JIA will be used in JPsA participants weighing 10 to <15.0 kg (SmPC; EMA 2020).

Participants treated with adalimumab who did not attain ACR 30 response at Week 16 will be switched to ixekizumab. As these participants are considered non-responders to adalimumab, a long washout period will not be required before the first ixekizumab dose, which can occur at a minimum 2 weeks after the last adalimumab dose. Switching from adalimumab to ixekizumab for a safety reason requires a washout period of sufficient length to allow the safety issue/parameter to resolve. To decrease potential safety risk in the transitional period, no higher ixekizumab starting dose will be administered to switching participants, and they

will receive regular ixekizumab doses according to their weight at each visit. The same dosing scheme will be used in participants who will switch from adalimumab to ixekizumab in the OLE period or at the completion of the OLE when entering the LTE at participant/caregiver's or investigator's discretion (minimum 2 weeks between the last adalimumab and first ixekizumab dose, no ixekizumab starting dose).

6. Study Population

The study will include participants aged 2 to less than 18 years at baseline, diagnosed with JIA and fulfilling the ILAR classification criteria for ERA (including JoAS) or JPsA but no other JIA category (Petty et al. 2004). Participants classified as ERA will have to be at least 6 years of age, which is aligned with the classification criteria. Participants will have to have active disease at enrollment, defined as at least 3 active peripheral joints; active sacroiliitis or enthesitis may be present but are not part of the inclusion criteria. The uniform inclusion criteria related to disease activity will allow the use of the same composite primary endpoint, namely JIA ACR 30 response, in both study population subsets, ERA and JPsA, which will facilitate data comparison. All participants will have to have body weight of at least 10.0 kg at baseline, which is to comply with the dosing instructions for ixekizumab and adalimumab. For the participants' safety, active uveitis, active IBD, and personal or first-degree family history of IBD will not be permitted at enrollment. Detailed Inclusion and Exclusion criteria are defined in Sections 6.1 and 6.2, respectively. The study population is expected to be representative of the general ERA and JpSA populations, allowing for a reliable assessment of ixekizumab efficacy in these 2 JIA categories, without an undue safety risk.

Prospective approvals of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria at enrollment:

Type of Participant and Disease Characteristics

[1] Have a diagnosis with onset before the age of 16 years of any of the following categories of JIA as defined by the ILAR criteria (Petty et al. 2004):

- ERA
- JPsA

[2] Have at least 3 active peripheral joints at screening and baseline. Active peripheral joint is defined as the presence of joint swelling or, in the absence of swelling, joint with limitation of motion plus pain on motion and/or tenderness on palpation.

Participant Characteristics

[3] Participants with ERA must be from 6 to less than 18 years of age at screening and baseline.

Participants with JPsA must be from 2 to less than 18 years of age at screening and baseline.

Full date of birth will be collected except in countries in which it is not allowed.

[4] Participants must weigh at least 10.0 kg.

[5] Male or nonpregnant, non-breastfeeding female participants.

Participants of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle).

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 12 weeks following the last dose of investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, post ovulation methods, and withdrawal are not acceptable methods of contraception.

Otherwise, participants and their partners of childbearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective for the entirety of the study and for at least 12 weeks following the last dose of ixekizumab. Participants and their partners of childbearing potential must agree to use contraception for 5 months after the last dose of adalimumab.

The following contraception methods are considered acceptable (the participant, and their partner, should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):

- Highly effective birth control methods:
    - Combined (estrogen- and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or implantable
    - Intrauterine device/intrauterine hormone releasing system
    - Vasectomized partner (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate).
- Effective birth control methods:
    - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
    - Diaphragm with spermicide
    - Cervical sponge
    - Cervical cap with spermicide

Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

Adolescent females who have started menses (even 1 cycle and any amount of spotting) are considered to be of childbearing potential.

Women of nonchildbearing potential are not required to use birth control and they are defined as:

- Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) and congenital anomaly such as Müllerian agenesis.

[6] All immunizations (live vaccines) are up-to-date in agreement with current immunization guidelines as noted by country specific pediatric authorities.

Informed Consent

[7] Both the child or adolescent and a parent or legal guardian are able to understand and fully participate in the activities of the clinical study and sign their assent and consent, respectively, in accordance to local guidelines.

6.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at enrollment:

Medical Conditions

[8] Fulfill the ILAR classification criteria for any other JIA category than ERA or JPsA.

[9] Have active or a history of IBD or history of IBD in a first degree relative: Crohn's disease, ulcerative colitis or undifferentiated IBD.

[10] Have evidence of active uveitis within 4 weeks prior to baseline.

Note: These participants may be rescreened only one time ≥4 weeks after resolution of acute symptoms.

[11] Have active fibromyalgia or other chronic pain condition or musculoskeletal disease that, in the investigator's opinion, would make it difficult to appropriately assess disease activity for the purposes of this study.

[12] Had a serious infection (e.g., pneumonia, cellulitis), have been hospitalized, have received intravenous antibiotics for an infection within 12 weeks prior to baseline (Week 0; Visit 2), had a serious bone or joint infection within 24 weeks prior to baseline, have ever had an infection of an artificial joint, or are immunocompromised to an extent that participation in the study would pose an unacceptable risk to the participant.

[13] Have or had herpes zoster or other clinically apparent varicella-zoster virus infection within 12 weeks prior to baseline.

[14] Have a positive test for HBV at screening defined as:

- positive for HBsAg or
- positive for HBcAb and positive for HBV DNA

Note: Participants who are HBsAg-, and HBcAb+ and HBV DNA negative may be enrolled in the study. Participants who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 9.4.11.2.

[15] Have HCV infection (hepatitis C antibody-positive and confirmed presence of HCV RNA.

[16] Have or had an infection typical of an immunocompromised host and/or that occurs with increased incidence in an immunocompromised host (including but not limited to *Pneumocystis jiroveci* pneumonia, histoplasmosis, or coccidioidomycosis) or have a known immunodeficiency.

[17] Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.

[18] Have evidence of active TB or latent TB.

[19] Major surgery within 8 weeks prior to screening or requiring major surgery during the study that in the opinion of the investigator in consultation with Lilly or its designee would pose an unacceptable risk to the participant.

[20] Have had surgical treatment of a joint within 8 weeks prior to randomization or will require such up to Week 16.

[21] History or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data. Participants with moderate to severe heart failure (New York Heart Association class III/IV) are not eligible for the study.

[22] Largely or wholly incapacitated, such as being bedridden.

[23] History of lymphoproliferative disease, or have signs or symptoms of lymphoproliferative disease, within 5 years prior to baseline; or have active or history of malignant disease within 5 years prior to baseline.

[24] History of chronic alcohol abuse, intravenous drug abuse, or other illicit drug abuse within the 2 years prior to screening.

[25] Presence of significant uncontrolled neuropsychiatric disorder that, in the opinion of the investigator, poses an unacceptable risk to the participant if participating in the study or of interfering with the interpretation of data; are, in the judgment of

the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

[26] Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia Suicide Severity Rating Scale (C-SSRS) or have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, and the ideation or behavior occurred within the past month.

[27] History of hypogammaglobulinemia or a serum Ig (IgG, IgM, or IgA) concentration less than the lower limit of normal of the reference range.

[28] Body temperature ≥38°C (100.5°F) at baseline.

[29] Have a known allergy or hypersensitivity to any biologic therapy (active substance or excipients) that would pose an unacceptable risk to the participant if participating in this study.

Prior/Concomitant Therapy

[30] Have used or is using any therapeutic agent targeted at reducing IL-17.

[31] Have initiated concomitant csDMARDs (such as, but not limited to, MTX, sulfasalazine (SSZ), and leflunomide) within 12 weeks prior to baseline or changed the dose within 8 weeks prior to baseline. The dose of csDMARDs is expected to remain stable throughout the OLT period and may only be adjusted for safety reasons.

[32] Concurrent use of any biologic agent (bDMARD) including: adalimumab <28 days, anakinra and etanercept within <14 days; abatacept <90 days; infliximab, certolizumab pegol, or alefacept <60 days; golimumab <90 days; rituximab <12 months; or any other biologic agent or small molecule (targeted synthetic DMARD) <5 half-lives prior to baseline (Week 0; Visit 2).

[33] MTX use at doses of >0.65 mg/kg/week or sulfasalazine at doses >30 mg/kg/day.

[34] Are currently receiving concomitant treatment with a combination of ≥2 csDMARDs (including MTX).

[35] Prior treatment with analgesics, including NSAIDs, on an unstable dose within 1 week of baseline.

[36] Prior treatment with any parenteral corticosteroid administered by intra-articular, intramuscular, or intravenous injection within 4 weeks of baseline.

[37] Oral corticosteroid use at average daily doses of greater than 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less, or have done so within 2 weeks prior to screening. If continuing oral corticosteroids, must be on stable dose for 4 weeks prior to baseline.

[38] Had a live vaccination within 12 weeks prior to baseline (Week 0, Visit 2), intend to have a live vaccination during the course of the study or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study

within 12 weeks prior to baseline.

Prior/Concurrent Clinical Trial Experience

[39] Currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[40] Discontinued within 30 days of study entry from any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[41] If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[42] Previously completed or withdrawn from this study or any other study investigating ixekizumab.

Laboratory Assessments

[43] Have any of the following specific abnormalities on screening laboratory tests:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN)
- Total bilirubin level (TBL) ≥1.5 × ULN
- Alkaline phosphatase (ALP) ≥2 × ULN
- Hemoglobin <10.0 g/dL (100.0 g/L)
- Total white blood cell (WBC) count <3000 cells/μL (<3.00 × 10^3/μL or <3.00 billion/L)
- Neutropenia (absolute neutrophil count [ANC] <1500 cells/μL) (<1.50 × 10^3/μL or <1.50 billion/L)
- Lymphopenia (lymphocyte count <1000 cells/μL) (<1.00 × 10^3/μL or <1.00 billion/L)
- Thrombocytopenia (platelet count <100,000/μL) (<100 × 10^3/μL or <100 billion/L)

In the case of any of the aforementioned laboratory abnormality, the test may be repeated once during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

[44] Screening laboratory test values outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the participant's participation in the study.

Other Exclusions

[45] Donated blood, bone marrow or stem cells within 4 weeks prior to screening or intend to donate during the course of the study.

[46] Are immediate family of investigator or site personnel directly affiliated with this study. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

[47] Are Lilly employee's immediate family. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

[48] Are unwilling or unable to comply with the use of a data collection instrument to directly record data from the participant and/or legal guardian.

6.2.1. *Rationale for Exclusion of Certain Study Candidates*

The rationale for the exclusion criteria is as follows:

Exclusion Criteria [8] to [11] exclude individuals with conditions that may confound safety or efficacy analyses.

Exclusion Criteria [12] to [18] exclude individuals who are at an increased risk for infections or infectious complications.

Exclusion Criteria [19] to [29] exclude individuals with previous or concomitant medical conditions that increase the risk for their participation in the study.

Exclusion Criteria [30] to [38] exclude individuals who are taking or who may take JIA medications or treatments that may interfere with the ability to assess the safety and efficacy of ixekizumab.

Exclusion Criteria [39] to [42] exclude individuals whose participation in the study may introduce bias.

Exclusion Criteria [43] to [44] exclude individuals with laboratory parameters that may increase the risk for their participation in the study.

Exclusion Criteria [45] to [48] exclude individuals whose participation in the study may introduce bias.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details,

eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Re-screened participants should be assigned a new participant number. When re-screening, the screening tests and procedures should be repeated. Those who test positive for latent TB at screening or who have a documented history of a positive TB test but no documented history of at least 4 weeks of appropriate latent TB treatment, may be re-screened following appropriate treatment. Other reasons for re-screening must be discussed, approved, and documented by the Lilly Medical Team (Clinical Research Scientist [CRS]/Clinical Research Physician).

Individuals may be rescreened 1 time. The interval between rescreenings should be at least 4 weeks. Individuals who are to be rescreened must first sign a new ICF/assent form as applicable (Appendix 3). Such individuals will be assigned a new participant number.

7. Treatments

7.1. Treatments Administered

Study treatment is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

This study involves administration of ixekizumab by SC injection Q4W or adalimumab by SC injection Q2W. The ixekizumab and adalimumab doses in this study are based on weight (Table RHCG.7.1).

Table RHCG.7.1. Treatment Regimens

Regimen	Dose Week 0	Dose Open-Label Treatment Period (Week 2 to Week 14)	Dose Open-Label Extension Treatment Period (Week 16 to Week 104)	Dose Long Term Extension Treatment Period (Week 104 to Week 264)	Authorized as defined by EU Clinical Trial Regulation
Ixekizumab CCI	CCI SC injections)	CCI Q4W SC injection	CCI Q4W SC injection	CCI Q4W SC injection	Authorized and not used according to EU marketing authorization
Ixekizumab CCI	CCI SC injection	CCI Q4W SC injection	CCI Q4W SC injection	CCI Q4W SC injection	Authorized and not used according to EU marketing authorization
Ixekizumab CCI	CCI SC injection	CCI Q4W SC injection	CCI Q4W SC injection	CCI Q4W SC injection	Authorized and not used according to EU marketing authorization

Adalimumab CCI	CCI SC injection	CCI Q2W SC injection	**Responder[a]:** Adalimumab CCI Q2W SC injection **Non-responders or participants opting to switch to ixekizumab[a]:** Appropriate dose according to weight Q4W (without a starting dose).	**All adalimumab participants will switch to ixekizumab. Appropriate dose according to weight Q4W (without a starting dose). Participants who are not switching to ixekizumab will undergo ETV at Visit 29 (Week 104).**	Authorized and not used according to EU marketing authorization
Adalimumab CCI	CCI SC injection	CCI Q2W SC injection	**Responders[a]:** Adalimumab CCI Q2W SC injection **Non-responders or participants opting to switch to ixekizumab[a]:** Appropriate dose according to weight Q4W (without a starting dose).	Adalimumab CCI	Authorized and not used according to EU marketing authorization

Abbreviations: ACR 30 = 30% improvement in American College of Rheumatology criteria; JIA = juvenile idiopathic arthritis; OLE = open-label extension; OLT = open-label treatment; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

[a] Participants receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 will be switched to ixekizumab in the OLE period. Participants receiving adalimumab during the OLT period who did attain a JIA ACR 30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period. The decision to switch for participants who achieved a JIA ACR 30 response will be left to the participant/participant's caregiver and investigator. A switch from adalimumab to ixekizumab during the OLE period may also occur at any other visit after Week 16 based on the participant/patent's caregiver and investigator's decision.

Note: When switching from adalimumab to ixekizumab, the participant will not receive the ixekizumab starting dose, but will receive the appropriate ixekizumab dose per the participant's weight. The minimum required period between the last dose of adalimumab and first dose of ixekizumab is 2 weeks.

This study involves administration of ixekizumab and adalimumab (as a reference arm) by SC injection.

Ixekizumab doses will be prepared by study site personnel. All doses will be administered on site. The study drug should be at room temperature when injected. Possible injection sites include the abdomen, thigh, and upper arm (using the arm contralateral for blood samples for PK). The injection site should not be in a psoriatic lesion and should be rotated to another area for subsequent doses at the same visit as well as the next visit.

Dosing

The selected ixekizumab doses are:

1) CCI Q4W CCI
2) CCI Q4W CCI
3) CCI Q4W CCI

CCI

Post-Administration Observation

Participants should remain under observation for at least 1 hour after the first dose to monitor for safety. Following the first injection, and if no problems occur with that injection, participants will be observed for 30 minutes following injection at all other study visits.

CCI

Participants initiating treatment with ixekizumab at Week 0 (Visit 2) will receive the starting dose. The participants switching from adalimumab to ixekizumab during the study (starting at Week 16) will not receive the starting dose but will receive the appropriate regular dose according to their weight at each visit. Switching participants from the adalimumab to ixekizumab dosing treatment regimen should follow the post-administration observation guidelines.

Participants requiring the starting dose of CCI of ixekizumab will receive CCI SC injections. Participants requiring the starting doses of CCI of ixekizumab will receive 1 SC injection, except for participants with a body weight of CCI who will receive the starting dose of 40 mg in CCI These 2 injections will be separated by a minimum of 60 minutes. As per previous instructions in the protocol, the second CCI of ixekizumab will require a 30-minute observation period after the administration.

Participants requiring a lower dose of ixekizumab will have the dose prepared by CCI

CCI [redacted]

The selected adalimumab doses are:

1) CCI [redacted] Q2W for CCI [redacted]

2) CCI [redacted] Q2W for CCI [redacted]

For training purposes, the proper procedures for the administration of the initial injection of adalimumab will be performed by clinical staff at Week 0 (Visit 2). Each participant or participant's caregiver must return to the clinical site for all injections and to be trained to inject adalimumab under the supervision of the investigator staff until the investigator judges the participant or participant's caregiver sufficiently competent to perform the injections independently. After this time, the participant or the participant's caregiver will be allowed to inject adalimumab at home.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the participant or participant's caregiver;
- verifying that instructions are followed properly;
- maintaining accurate records of investigational product dispensing and collection; and
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

The study drug will be supplied by the sponsor in accordance with current good manufacturing practices (cGMP).

Ixekizumab will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study-specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. Participants weighing >25 kg to <50.0 kg can opt for at-home administration when 40 mg prefilled syringe is available for the trial.

Adalimumab (originator or biosimilar) will be supplied by the sponsor or its designee in accordance with cGMP. Adalimumab will be supplied in 2 presentations to be administered based on participant's weight:

- 20 mg in a single-use prefilled syringe, or
- 40 mg in a single-use prefilled syringe.

Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the study drug. Clinical study materials will be labeled according to the country's regulatory requirements. All study drugs will be

stored, inventoried, reconciled, and destroyed according to applicable regulations.

7.2. Method of Treatment Assignment

Participants who meet all criteria for enrollment will be randomized or assigned, as appropriate, to treatment at Visit 2. Participants who are bDMARD-naive will be randomized to ixekizumab or adalimumab in a 1:1 ratio. At least 20 participants will be randomized to ixekizumab and 20 participants to adalimumab. Randomization will be stratified based on the category of JIA (ERA or JPsA). The remaining participants (approximately 60 participants) who are bDMARD-naive or bDMARD-IR will be assigned to ixekizumab. In practice, this will be accomplished by randomizing the first 40 bDMARD-naive participants entering the study according to the ratio and stratification described above, with all the subsequent bDMARD-naive participants being assigned to ixekizumab.

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

In the OLE period, all participants who were receiving ixekizumab in the OLT period will continue to receive ixekizumab for approximately 88 weeks.

Participants receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 will be switched to ixekizumab in the OLE period. Participants receiving adalimumab during the OLT period who did attain a JIA ACR 30 response at Week 16 will be given the option to switch or not to switch to ixekizumab in the OLE period. The decision to switch for participants who achieved a JIA ACR 30 response will be left to the participant/participant's caregiver and investigator. A switch from adalimumab to ixekizumab during the OLE period may also occur at any other visit after Week 16 based on the participant/participant's caregiver and investigator's judgment. All participants who enter into the LTE will receive ixekizumab.

7.2.1. Selection and Timing of Doses

Participants will be randomized to treatment or will receive their assigned study drug as outlined in Sections 7.1 and 7.2.

The doses will be administered at approximately the same time on each day. For injections that are missed and not administered on the scheduled day of the week, the missed dose should be administered within 5 days of the originally scheduled day. Dates of subsequent study visits should not be modified according to the delay of the injection of the missed scheduled dose.

The actual time of all dose administrations will be recorded in the participant's case report form (CRF).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

During the OLT period, participants will receive either ixekizumab or adalimumab based on their Week 0 (Visit 2) weight category and are not allowed to modify the treatment regimen up to Week 16. During the OLE period, all participants will receive ixekizumab or adalimumab based on each visit weight, which means that the dose will be adjusted according to weight category throughout the period as needed.

During the LTE period, all participants will receive ixekizumab based on their weight at each visit, which means that the dose will be adjusted according to weight category throughout the period as needed. No other modifications of dose are permitted.

7.5. Preparation/Handling/Storage/Accountability

Study drug will be supplied by Lilly or its representative in accordance with cGMP and will be supplied with lot numbers, expiration dates, and certificates of analysis, as applicable.

The study drug should be stored as stated on the label. Sites will be required to monitor temperature of the on-site storage conditions for the study drug.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

Instructions for the administration of adalimumab will be provided by the sponsor.

7.6. Treatment Compliance

Every attempt will be made to select participants/caregivers who have the ability to understand and comply with instructions. The investigator is responsible for discussing methods with the participant and caregiver before randomization to ensure high treatment compliance.

Ixekizumab: Throughout the study, site personnel will record information about injections

in the Study Drug Administration Logs, including the date, time, and anatomical location of administration of study drug (for treatment compliance); syringe number; who prepared and administered the study drug; and the reason if study drug was not fully administered.

Adalimumab: The participant or caregiver will record information in a Study Drug Administration Log, including the date, time, and anatomical location of administration of adalimumab (for treatment compliance); carton number; who administered the investigational product; and the reason if investigational product was not fully administered.

Participant compliance with the study drug will be assessed at each visit. Compliance will be assessed by the number of injections needed versus the number of injections administered to the participants. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication electronic case report form (eCRF).

Participants will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study.

Additional drugs are to be avoided unless required to treat AEs or for the treatment of an ongoing medical condition. If the need for concomitant medication arises for an AE or for appropriate medical management, the investigator should base decisions on the participant and clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0; Visit 2) and/or during the course of the study, must be documented with the start and stop dates on the Concomitant Medications eCRF (Section 9.4).

Treatment with concomitant JIA therapies during the study is permitted only as described below. The dosages of concomitant treatment may be adjusted during the OLT period only for safety reasons. After the completion of OLT, the concomitant medications may be adjusted based on the discretion of the investigator.

- Chronic stable use of oral corticosteroids is permitted and defined as daily doses of ≤10 mg/day or ≤0.2 mg/kg/day prednisone equivalent, whichever is less. Participants must be on a stable dose for at least 2 weeks prior to screening and 4 weeks prior to baseline and remain on the same dose throughout the OLT period study. Participants should not receive other systemic corticosteroids during the study including intra- muscular or intra-articular corticosteroids. Topical, intranasal, intra-ocular, and inhaled corticosteroids are permitted.
- Chronic stable use of MTX or SSZ is permitted and defined as MTX dose of ≤0.65 mg/kg/week (with a maximum dose of 25 mg/week) or SSZ dose of ≤30 mg/kg/day (with a maximum dose of 3 g/day). Participants must initiate MTX or SSZ at least

12 weeks prior to baseline and remain on the same dose at least 8 weeks prior to baseline and throughout the OLT period study. The dose may only be adjusted for safety reasons. Local standard of care should be followed for concomitant administration of folic acid.

- Chronic stable usage of csDMARDs (other than MTX or SSZ) is permitted if initiated at least 12 weeks prior to baseline and unchanged within 8 weeks prior to baseline.
- Concomitant usage of 2 or more csDMARDs (including MTX) is not allowed.
- Chronic stable use of NSAIDs and analgesics is permitted. Participants must be on a stable dose for at least 1 week prior to baseline and throughout the OLT period; dose reductions and/or termination of NSAIDs and analgesics are permitted for safety reasons.
- Beginning with Week 20/Visit 8, intra-articular joint and bursal corticosteroid injections may be given at doses and intervals at the investigator's discretion. Injected joints will be considered active joints for the remainder of the study and for efficacy assessments.

The following therapies will not be permitted during the course of the study as specified in the exclusion criteria (Section 6.2):

- bDMARDs
- Targeted synthetic DMARDs or small molecules, including but not limited to janus kinase (JAK) inhibitors and apremilast
- Live vaccines are not recommended within 12 weeks prior to baseline or during the course of the study. The investigator may base any decisions about live vaccinations on a benefit-risk assessment. Use of nonlive seasonal vaccinations and/or emergency vaccinations (such as rabies or tetanus vaccinations) is allowed.

  Note: With the exception of live vaccines, no adjustment to the vaccination schedule is required.

Only for participants who discontinued study treatment and have entered the PTFU period, JIA therapy with another agent previously excluded during the treatment period of the study may be allowed, as determined appropriate by the investigator and approved by Lilly medical.

Table RHCG.7.2. Concomitant JIA Therapies

Drug Class	As Needed	Chronic Use	Conditions for Use
MTX[a]	No	Yes	If on MTX, must be on a stable average dose of ≤0.65 mg/kg/week (maximum dose 25 mg/week) for 12 weeks prior to baseline and unchanged dose within 8 weeks prior to baseline and throughout OLT period (until Week 16)[b].
SSZ[a]	No	Yes	If on SSZ, must be on a stable average dose of ≤30 mg/kg/day (maximum dose 3 g/day) for 12 weeks prior to baseline and unchanged dose within 8 weeks prior to baseline and throughout OLT period (until Week 16)[b].
csDMARDs other than MTX or SSZ[a]	No	Yes	If receiving csDMARDs (other than MTX or SSZ), must be on a stable dose for 12 weeks prior to baseline and unchanged dose within 8 weeks prior to baseline and throughout OLT period (until Week 16)[b].
Oral corticosteroids	No	Yes	If receiving oral corticosteroids, daily dose must be ≤10 mg/day or ≤0.2 mg/kg/day prednisone equivalent, whichever is less. Must be on stable dose for at least 2 weeks prior to screening and 4 weeks prior to baseline and throughout OLT period (until Week 16)[b].

Drug Class	As Needed	Chronic Use	Conditions for Use
NSAIDs including cyclooxygenase-2 inhibitors	No	Yes	Must be on stable dose at least 1 week prior to baseline and throughout OLT period (until Week 16)[b].
Analgesics	No	Yes	Must be on stable dose at least 1 week prior to baseline and throughout OLT period (until Week 16)[b]. Permitted analgesics include: • acetaminophen • opioids (e.g., tramadol, codeine, or morphine) • local anesthetics (e.g., lidocaine), and • topical anesthetics

Abbreviations: csDMARD = conventional synthetic disease-modifying antirheumatic drug; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; OLT = open-label treatment; SSZ = sulfasalazine.

[a] Concomitant use of ≥2 of any csDMARDs is not allowed.

[b] Dose adjustments may only be made for safety reasons during OLT period (until Week 16).

7.8. Treatment After the End of the Study

7.8.1. Study Extensions

Participants who complete the OLT and OLE periods of this study will be eligible to participate in the open-label LTE part of this study.

7.8.2. Treatment After Study Completion

Ixekizumab will not be made available to participants after conclusion of the study. Adalimumab will be made available to participants until Week 104. After Week 104, all adalimumab participants will be assigned to ixekizumab or will end participation in the study.

7.9. Special Treatment Considerations

Participants will be screened for eligibility in the study as described in Sections 6.1 and 6.2 will be informed of the study-specific restrictions and requirements of the study. Participants/ caregivers who are not willing to comply with the study restrictions and requirements of the study will not be eligible for enrollment.

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash,
- pruritus (itching),
- urticaria (hives),
- angioedema (e.g., swelling of the lips and/or tongue), and

- anaphylactic reaction.

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

For an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample is to be drawn as soon as possible to test for antidrug antibodies (ADAs) (Section 9.6.1).

This study involves administration of ixekizumab and adalimumab (as a reference arm) by SC injection. During the OLT period, bDMARD-naive participants will receive either ixekizumab or adalimumab based on their Week 0 (Visit 2) weight category. Due to ixekizumab and adalimumab dosing guidance for the pediatric population, participants must have a weight ≥10.0 kg at baseline.

8. Discontinuation Criteria

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 3.

8.1. Discontinuation from Study Treatment

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for an early discontinuation visit and PTFU, if applicable.

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- Participant decision:
  - the participant or the participant's designee, for example parents or legal guardian, requests to discontinue investigational product.
- Discontinuation due to a hepatic event or liver test abnormality. Participants who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic safety eCRF.
- Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with Lilly Medical.
- In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5 × ULN), the study drug should be **interrupted** and close hepatic monitoring initiate (see Appendix 4) if one or more of these conditions occur:

Elevation	Exception
ALT or AST >8 × ULN	
ALT or AST >5 × ULN for more than 2 weeks	
ALT or AST >3 × ULN and either TBL >2 × ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2 × ULN.
ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3 × ULN, when the source of increased ALP is the liver	
ALP >2.5 × ULN and TBL >2 × ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2 × ULN.
ALP >2.5 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal.

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.

Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests

- In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5 × ULN), the study drug should be **interrupted** if one or more of these conditions occur:

Elevation	Exception
ALT or AST >4 × baseline	
ALT or AST >3 × baseline for more than 2 weeks	
ALT or AST >2 × baseline and either TBL >2 × ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2 × ULN.
ALT or AST >2 × baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5 × baseline, when the source of increased ALP is the liver	
ALP >2 × baseline and TBL >2 × ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2 × ULN.
ALP >2 × baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.

Resuming study drug after elevated liver tests

- Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited nondrug etiology is identified. Otherwise, the study drug should be discontinued.

In addition, patients will be discontinued from the study drug under the following circumstances:

- Neutrophil (segmented) counts:
  - <500 cells/μL
  - ≥500 and <1000 cells/μL (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
  - ≥1000 and <1500 cells/μL (based on 3 test results) and an infection that is not fully resolved
  - white blood cell count <1000 cells/μL (1.00×10^3/μL or 1.00 billion/L)
  - lymphocyte count <200 cells/μL (0.20×10^3/μL or 0.20 billion/L)
  - platelet count <50,000 cells/μL

  Note: Temporary interruption rules (see Section 8.1.2) must be followed where applicable. For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator the laboratory abnormality is due to intercurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds following the resolution of the intercurrent illness or other identified factor may the investigator restart investigational product after consultation with Lilly Medical.

In addition, participants will be discontinued from the investigational product in the following circumstances:

- The participant experiences a severe AE or SAE or has a clinically significant change in a laboratory value that, in the opinion of the investigator, merits discontinuation of the study drug and appropriate measures being taken. This includes evidence of active viral hepatitis or active TB. In such cases, Lilly or its designee is to be notified immediately.
- Clinically significant systemic hypersensitivity reaction following SC administration of study drug that does not respond to symptomatic medication or results in clinical sequelae.
- The participant becomes pregnant.
- The participant develops malignancy.
- The participant has a positive TB test using QuantiFERON®-TB Gold or T-Spot or PPD and is assessed as having latent TB infection (see Section 9.4.5), and/or develops symptoms or signs of tuberculosis.
- The participant develops IBD.
- The participant develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the “Suicidal Ideation” portion of the C-SSRS) or develops suicide-related behaviors as recorded on the C-SSRS.
- Note: It is recommended that the participant be assessed by an appropriately trained professional (e.g., psychiatrist, clinical psychologist, social worker

etc.) to assist in deciding whether the participant is to be discontinued from the study.

- If the investigator, after consultation with Lilly Medical, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the investigational drug.

Participants discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

In some circumstances, participants may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. See Section 9.4.5 for details regarding managing participants who test positive for TB at any time during the study.

Participants requiring surgery at any time during the study should interrupt administration of the investigational product beginning 8 weeks before the surgery, or as early as possible, and resume administration of the investigational product only after complete wound healing.

8.2. Discontinuation from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice(GCP)
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit

should be conducted, as shown in the Schedule of Activities (Section 2). See Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the participant will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study. The joint assessor (or designee) should be a rheumatologist or skilled joint assessor and will be responsible for completing the joint counts for swelling, tenderness, and limited range of motion. Additionally, the assessor will perform the following assessments: Physician's Global Assessment of Disease Activity, PASI, BSA, Enthesitis and Dactylitis assessment, Clinical Sacroiliitis, Back Mobility (Schober's test), and Uveitis Evaluation. To ensure consistent joint evaluation throughout the study, individual participants should be evaluated by the same assessor for all study visits whenever possible.

Investigators or relevant clinical staff will provide age-appropriate explanations to all children prior to any assessment or procedure.

Staff trained or experienced in pediatric phlebotomy should perform blood draws at the clinic. Blood draws should be consolidated, and the number of attempts should be kept to the minimum number required. The number of sampling attempts should be minimized, in keeping with local guidelines and procedures. For example, it is recommended that after one unsuccessful attempt, another experienced person should take over the procedure.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment

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

9.1.1.1. JIA ACR 30 Core Set Variables

The JIA ACR 30 core set variables are defined as follows:

- number of active joints in 73 joints (active joint defined as a joint that is swollen, or in the absence of swelling, has loss of passive motion accompanied by either pain on motion or joint tenderness)
- number of joints with limited range of motion in 69 joints
- Physician's Global Assessment of Disease Activity (21-circle Visual Analogue Scale [VAS]) (Section 9.1.1.1.1. Physician's Global Assessment of Disease Activity)
- Parent's Global Assessment of Well-Being
- Physical function as assessed by the Childhood Health Assessment Questionnaire (CHAQ) (Section 9.1.3.1)
- Erythrocyte sedimentation rate [ESR])

9.1.1.1.1. Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is used to assess the participant's current disease activity as it relates to their signs and symptoms. The instrument uses a 21-circle VAS ranging from 0 to 10 (using 0.5 increments) where 0 = "no activity" and 10 = "maximum activity" (Filocamo et al. 2010).

9.1.2. Secondary Efficacy Assessments

The secondary efficacy outcomes assessed at each regular visit for all participants are as follows:

- percentage of participants meeting JIA ACR 30/50/70/90/100 response criteria,
- changes from baseline in each of the 6 individual components of the JIA ACR core set variables, and
- proportion of participants with disease flare (flare defined as worsening of ≥30% from baseline in at least 3 of the 6 JIA ACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria).

In addition, for JPsA participants with plaque psoriasis (at least 3% BSA at baseline), the following secondary efficacy endpoint will be assessed at each regular visit:

- change from baseline in PASI.

In addition, for participants with enthesitis at baseline, the following secondary efficacy endpoint will be assessed at each regular visit:

- change from baseline in Leeds Enthesitis Index (LEI).

9.1.2.1. JIA ACR 50, 70, 90, and 100

JIA ACR 50, JIA ACR 70, JIA ACR 90, and JIA ACR 100 responses are secondary efficacy endpoints and are improvements of at least 50%, at least 70%, at least 90% and at least 100%, respectively, in the JIA ACR criteria set. The JIA ACR 50, JIA ACR 70, JIA ACR 90 and JIA ACR 100 are calculated similarly to JIA ACR 30, as described in Section 9.1.1.1.

9.1.2.1.1. Percentage of Body Surface Area (BSA)

The joint assessor (or designee) will evaluate the percentage involvement of psoriasis on each participant's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the participant's hand (including the palm, fingers, and thumb) (NPF 2009).

9.1.2.1.2. Psoriasis Area and Severity Index (PASI)

The PASI will be used to assess plaque psoriasis. The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, trunk, arms, and legs). It also assesses the severity of erythema (redness), plaque induration/infiltration (thickness), and desquamation (scaling) in each region, yielding an overall score of 0 (no psoriasis) to 72 (most severe disease [Fredriksson and Pettersson 1978]).

The head, upper extremities, lower extremities, and trunk are assessed separately and then combined, using weighting based on the surface area represented by each area (head = 0.1, upper extremities = 0.2, trunk = 0.3, and lower extremities = 0.4). The degree of erythema, induration, and scale in each area is judged on a 0 to 4 scale, the sum of which represents disease severity. The area of involvement of each area is graded from 0 to 6, depending on the estimated percentage of lesional area (0 = 0%, 1 = 1% to 9%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%). These body scores are multiplied by the disease severity score and the weighting for each body area, yielding a score between 0 and 72. The PASI score will be program-generated.

Further practical details help the assessment: (1) the neck is assessed as part of the head; (2) the axillae and groin are assessed as part of the trunk; (3) the buttocks are assessed as part of the lower limbs; (4) when scoring the severity of erythema, scales should not be removed.

9.1.2.1.3. Enthesitis Assessment

Active enthesitis will be assessed in 2 ways: LEI as a separate outcome measure, and active enthesitis count as a component of the Juvenile Spondyloarthritis Disease Activity Index (JSpADA).

LEI measures enthesitis at 3 bilateral sites (lateral epicondyle, left and right; medial femoral condyle, left and right; and Achilles tendon insertion, left and right). Each of the 6 sites is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score (range 0 to 6) (Healy and Helliwell 2008; Mease 2011).

The Active Enthesitis Count includes any tender enthesis to a maximum of 10 (Weiss et al. 2014). For the purposes of this study, assessment of the Active Enthesitis Count will include the 6 entheseal sites of the LEI plus 4 additional sites: greater trochanter on the femur- hip flexor insertion (left and right), and inferior pole of the patella - infrapatellar insertion (left and right). The Active Enthesitis Count will be assessed based on 10 entheseal sites. There is no weighing of particular entheses, the scoring is as follows: 0 entheses = score 0; 1 to 2 entheses = score 0.5; >2 entheses = score 1 (Weiss et al. 2014).

The LEI and Active Enthesitis Count are to be assessed by the investigator or health care provider who meets study qualifications for study assessments.

9.1.3. Health Outcomes Measures

The self-reported questionnaires will be administered according to the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

9.1.3.1. Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ assesses health status and physical function in children with juvenile arthritis over the past week, which the parent or legal guardian completes, regardless of the age of the participant.

The CHAQ has 2 indices – the Disability Index and the Discomfort Index.

The Disability Index contains 30 items grouped into the following 8 domains (not including assistive devices/aids questions): physical function, dressing, and grooming (4 items); arising (2 items); eating (3 items); walking (2 items); hygiene (5 items); reach (4 items); grip (5 items); and activities (5 items). Each item is scored from 0 to 3 (0 = no difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do or not applicable) (Singh et al. 1994).

The Discomfort Index of the CHAQ includes (Ruperto et al. 2001):

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

The questionnaires will be administered according to the Schedule of Activities (Section 2).

Note: For all participants, the CHAQ will be provided to the parent/guardian of the participant through Visit 7/Week 16 of the study. Starting with Visit 8, any participant ≥14 years of age will complete the "CHAQ" of well-being form administered for the remainder of the research program.

9.1.4. Exploratory Efficacy Assessments

9.1.4.1. Total and Tender Dactylitic Digit Count

Dactylitis is defined as swelling of a digit that extends beyond the joint margin (Petty et al. 2004). The assessor will first assess the participant for the presence of dactylitis and will record the total number of dactylitic digits in the participant's hands and feet (dactylitic digit count range 0 to 20). Tenderness will be assessed, and the number of tender dactylitic digits will be recorded (tender dactylitic digit count range 0 to 20) (Helliwell et al. 2005).

9.1.4.2. Juvenile Arthritis Disease Activity Score-27 (JADAS-27)

The Juvenile Arthritis Disease Activity Score-27 (JADAS-27) score is a validated composite disease activity measure for JIA (Consolaro et al. 2012). Recently, the scoring system was adapted to use the 27-joint count (Bazso et al. 2009), and high-sensitivity C-reactive protein (hsCRP) or ESR for the inflammatory marker component (Nordal et al. 2012). The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles.

JADAS-27 score will be determined based on 4 components:

- Physician's Global Assessment of Disease Activity (Section 9.1.1.1.1. Physician's Global Assessment of Disease Activity),
- Parent's Global Assessment of Well-Being (from CHAQ; Section 9.1.3),
- Number of joints with active disease (27-joint assessment), and
- hsCRP or ESR, as applicable.

9.1.4.3. EuroQol-Five Dimensions-Youth (EQ-5D-Y)

The European Quality of Life EuroQol-Five 5 Dimensions-Youth (EQ-5D-Y) is a widely used, generic questionnaire that assesses health status "today" (The EuroQol Group 2014). It is completed by parents or caregiver (proxy) for children aged 4 to 7 years; for children aged 8 years and older, the EQ-5D-Y will be self-completed (children aged <4 years will not complete this assessment per developer recommendation); respondents will continue with the version of the instrument they begin the study with even if their age changes during the course of the study. Children who attain age 4 during the course of the study will not be included in this assessment due to a nonexistent baseline assessment. The questionnaire consists of 2 parts: the first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 3 possible levels of response (no problems, some problems, or a lot of problems). This part of the EQ-5D-Y can be used to generate a health state index score, which is often used to compute quality-adjusted life years for utilization in health economic analyses. The health state index score is calculated based on the responses to the 3 dimensions, providing a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility.

The second part of the questionnaire consists of a VAS on which the participant rates their perceived health state from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability, and validity (Ravens-Sieberer et al. 2010). The scale will be given to the parent or caregiver/participant by the site investigator and self-completed by the parent or caregiver/participant while they are at the site. The investigator will be responsible for checking for missing responses.

9.1.4.4. Juvenile Spondyloarthritis Disease Activity Index (JSpADA)

The JSpADA is a validated composite disease activity measure for juvenile SpA (JSpA). The JSpADA includes 8 items that measure arthritis, enthesitis, sacroiliitis, morning stiffness, pain, uveitis, back mobility, and laboratory inflammatory markers. Each item is considered to be of equal importance and is assigned a maximum score of 1 without weighting. The range of possible JSpADA scores is 0 to 8, where higher scores indicate more disease activity (Weiss et al. 2014).

JSpADA score will be determined as follows:

- active joint count: 0 joints = 0, 1 to 2 joints = 0.5, >2 joints = 1
- active enthesitis count: 0 entheses = 0, 1 to 2 entheses = 0.5, >2 entheses =1
- pain over the past week as assessed using a 0 to 10 Numeric Rating Scale (0 = no pain; 10 = pain as bad as your child can imagine: 0 = 0, 1 to 4 = 0.5, 5 to 10 = 1)
- hsCRP level related to JSpA activity: normal = 0, 1 to 2 times normal = 0.5, >2 times normal = 1
- morning stiffness >15 minutes: Absent = 0, Present = 1
- clinical sacroiliitis (defined as the presence of ≥2 of the following: tenderness on examination; positive Patrick's test or flexion, abduction and external rotation (FABER) test; and inflammatory back pain): Absent = 0, Present = 1
- uveitis (any uveitis including acute/symptomatic and chronic/asymptomatic disease): Absent = 0, Present =1
- back mobility (abnormal back mobility defined as modified Schober's test <20 cm): Normal = 0, Abnormal = 1

The JSpADA score is obtained by summing the total for each item (maximum total per item = 1; JSpADA range is 0 to 8).

9.1.4.5. Morning Joint Stiffness Duration

As one of the assessments to determine the JSpADA score, the parent/caregiver will indicate if the duration of their child's morning joint stiffness was >15 minutes since the previous visit. Responses are yes/no.

Note: For all participants, morning stiffness will be assessed by the parent/guardian of the participant through Visit 7/Week 16 of the study. Starting with Visit 8, any participant ≥14 years of age will complete the morning stiffness assessment form administered for the remainder of the research program.

9.1.5. Appropriateness of Assessments

All assessments utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

9.2. Adverse Events

Adverse events will be reported by the study participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE (Appendix 5) and remain responsible for follow-up of AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 8).

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF and Assent Form (as applicable) are signed, study site personnel will record via electronic data entry the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product, via electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form (ICF)	Participation in study has ended	As soon as possible upon site awareness	AE case report form (CRF)	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants receiving ixekizumab	After the start of study intervention	At least 5 terminal half-lives after the last dose	Within 24 hours (see Section 9.4.5)	SAE CRF	SAE paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A

PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; N/A = not applicable; PC = product complaint; SAE = serious adverse event.
* Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

9.2.2. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged in-participant hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in- participant hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedule of Activities.

All AEs will be collected from the signing of the ICF until participation in study has ended.

Medical occurrences that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF.

All AEs occurring after signing the ICF and Assent Form (as applicable) are recorded by the site in the CRF/electronic data entry and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the electronic data entry.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2.2. Pregnancy

Collection of pregnancy information: ***Male participants with partners who become pregnant***

- The investigator will attempt to collect pregnancy information on a male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive ixekizumab.
- After obtaining the necessary signed informed consent and/or assent from the pregnant female partner directly,
    - the investigator will record pregnancy information on the appropriate form and submit it to the sponsor
    - within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

See Section 8.2 about the discontinuation of participants who become pregnant.

9.2.2.3. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) will be evaluated specifically to determine the safety and tolerability of ixekizumab over the range of doses selected for this clinical study.

AESIs for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia),
- liver biochemical test changes/enzyme elevations (ALT, AST, bilirubin, and ALP),
- infections,
- immunogenicity,
- injection-site reactions,
- allergic reactions/hypersensitivities,
- cerebrocardiovascular events,
- malignancies,
- depression,
- inflammatory bowel disease, and

- interstitial lung disease.

If infections, injection-site reactions, or allergic/hypersensitivity reactions are reported, study sites will provide details on these events as instructed on the eCRF. Investigators will also educate participants and/or caregivers about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions. A blood sample will be collected when possible for any participant who experiences an AE of allergic reactions/hypersensitivities during the study.

In the case of suspected IBD, the participant should be referred to a gastroenterologist (preferably pediatric gastroenterologist) for evaluation and management. Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis or Crohn's disease will be collected, and the events will be adjudicated by an external Clinical Events Committee (CEC) composed of gastroenterologists with expertise in IBD. The role of the CEC is to adjudicate defined clinical events in a consistent, and unbiased manner throughout a study. The importance of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For this study, any dose of ixekizumab greater than 80 mg within a 24-hour time period will be considered an overdose. Any dose of adalimumab greater than 40 mg within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose. In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately
- For adalimumab patients, please reference the product label for additional information
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- For ixekizumab participants only, obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-

by-case basis)

- Document the quantity of the excess dose as well as the duration of the overdose in the CRF

9.4. Safety

Any clinically significant findings from physical examination, vital signs measurements, or laboratory measurements that result in a diagnosis and that occur after the participant receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF. These events will also be considered as an AE if the event does not result in a diagnosis but is considered clinically significant by the investigator.

9.4.1. Physical Examination

The complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed according to the Schedule of Activities (Section 2). This examination will determine whether the participant meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for treatment-emergent adverse event (TEAE) assessment. All physical examinations throughout the study should include a symptom- directed physical evaluation as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.

9.4.2. Tanner Stage Scale

The Tanner Stage Scales are a series of line drawings that are designed to aid the participant or caregiver in appropriately assessing the sexual maturity of the participant at the time of the visit (Chavarro et al. 2017). Participants 8 years and older will be assessing their sexual maturity according to the Schedule of Activities (Section 2).

Once the participant reaches the score 5 in the scale, no further assessments are needed.

9.4.3. Vital Signs

For each participant, vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the participant receives the first dose of study treatment should be reported to Lilly or its designee as an AE via electronic data entry.

9.4.4. Laboratory Tests

For each participant, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

Blood volume restrictions are anticipated to be applicable for participants 2 to <8 years old and particularly for participants 10.0 to <20.0 kg in body weight; however, it may be used for older participants if local regulations require restrictions on blood volumes. The Blood Volume Prioritization Tool is provided in Appendix 7.

Due to blood volume restrictions, some laboratory samples may not be collected (for example, cell flow cytometry in case needed to reduce blood volumes of a certain visit). Laboratory samples should be collected as described in a sponsor-provided weight-based prioritization chart.

Additional allowances to accommodate blood volume restrictions may include, but are not limited to the following:

- Blood draws for Visit 1 and Visit 2 may be divided over 2 days if the 24-hour blood volume limit is exceeded.
- Hepatitis B virus DNA will be collected as a reflex test prior to Visit 2 and is only required for participants who are positive for HBcAb.
- Hepatitis C virus RNA will be collected as a reflex test prior to Visit 2 and is only required for participants who are positive for HCV antibody.

Use of local anesthetics or devices consistent with local prescribing information is permitted during the study visit to ease discomfort associated with venipunctures. Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical study.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the participant receives the first dose of investigational product should be reported to Lilly or its designee as AE via electronic data entry.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

9.4.5. Pregnancy Testing

See the Schedule of Activities (Section 2) for frequency of pregnancy testing and Appendix 2 and Appendix 6 for additional details about these tests. As per Clinical Trial Facilitation Group (CTFG) recommendation: In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential (WOCBP) with infrequent or irregular menstrual cycles.

At Screening

Serum pregnancy tests will be given prior to the first dose of the study intervention for females ≥10 years of age (<10 years at investigator discretion) if menarche has been reached or if there is reason to believe the participant is sexually active. Pregnancy test results at screening must be known prior to first dose of the study intervention.

Open-Label Treatment, Open-Label Extension Treatment, and Long-Term Extension Periods

Female participants of childbearing potential (age 10 and older if menarche has been

reached or if there is reason to believe the participant is sexually active, or younger participants per investigator assessment of sexual maturity) will undergo a urine pregnancy test at the clinic on a monthly basis during scheduled visits through Week 264 or the ETV. Additional urine pregnancy testing may be performed at the investigator's discretion. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention (see Section 8.1.1).

During the Post-Treatment Follow-Up Period

As indicated in the Schedule of Activities, urine pregnancy tests will be collected during each of the post-treatment follow-up visits.

9.4.6. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless the x-ray or results from a chest x-ray obtained within 6 months prior to the study are available or the results from the TB testing (QuantiFERON® TB Gold, T-Spot or PPD) if aligned with local practice.

The chest x-ray or results will be reviewed by the investigator or designee and considered along with the participant's medical history, assessment of risk factor for *M. tuberculosis* infection and physical examination to exclude participants with active TB infection.

Participants will be tested as indicated in the Schedule of Activities (Section 2) for evidence of *M. tuberculosis* infection.

TB testing - QuantiFERON® TB Gold will be the preferred testing option for TB. The QuantiFERON® TB Gold test may be performed locally or centrally. If the QuantiFERON®-TB Gold test is indeterminate (not negative), 1 retest is allowed. If the retest for the QuantiFERON®-TB Gold test is indeterminate (not negative), the participant is excluded from enrollment in the study.

In countries where the QuantiFERON®-TB Gold test is not available or due to investigator's judgement (e.g., need to reduce the volume of blood collected), the T-Spot or PPD test may be used. In the case of selecting the PPD test, the participant must return within 48 to 72 hours to read the skin test.

A positive PPD skin test response for this study is defined as ≥5-mm induration between 48 and 72 hours after PPD application, regardless of Bacillus Calmette-Guérin vaccination history.

Participants with documentation of a negative QuantiFERON®-TB Gold test or T-Spot result or PPD result within 3 months prior to baseline (Week 0; Visit 2) are not required to have a TB test at Visit 1 unless medical history, including assessment for TB infection risk factors, chest x-ray, or physical examination indicate that testing should be done. Documentation of this test result must include a record of the size of the induration response (<5-mm induration) or the laboratory report of the QuantiFERON®-TB Gold test or T-Spot result. A PPD test recorded as negative without documenting the size of induration will require a retest.

Participants with a PPD skin test ≥5 mm induration or a positive QuantiFERON®-TB Gold or T-Spot test but no evidence of active TB, and participants who have a documented history of a positive TB test but no documented history of completion of a full, appropriate latent TB treatment course, who are assessed as having latent TB infection may be re-screened 1 time and may be enrolled without repeating a QuantiFERON®-TB Gold, T-Spot or PPD test if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection therapy with no evidence of hepatotoxicity (ALT/AST must remain ≤2 × ULN) upon retesting of serum ALT/AST prior to randomization,
- commitment by the participant and the caregiver for the participant to complete a full course of standard prophylaxis for TB, and
- meet all other inclusion/exclusion criteria for participation.

Such participants must complete appropriate latent TB infection therapy to remain eligible for continued study participation. If rescreening occurs within 6 months of the screening chest x-ray, a repeat of chest x-ray for considering enrollment is not required.

If a participant with a positive QuantiFERON®-TB Gold or T-Spot or PPD is fully assessed by the investigator and the investigator determines that the participant has no risk factors for and no symptoms or signs of *M. tuberculosis* infection, the investigator may contact Lilly Medical to discuss the possibility of a false-positive test result.

Participants with positive TB test results on file: Participants with a documented prior history of a positive TB test and participants who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB should not have a TB test performed at Visit 1. Such participants with no history of re-exposure to TB since their treatment was completed and no evidence of active TB are eligible to participate in the study. Participants who have had household contact with a person with active TB are excluded unless an appropriate and documented course of prophylaxis for TB was completed.

Participants are to be monitored on a regular basis for any symptoms or signs of active TB and for any new risk factors for TB infection, with full medical evaluation including TB testing when medically indicated. Participants that exhibit symptoms of active TB should be referred to a specialist in the care of participants with TB.

Any clinically significant findings from chest x-rays and/or TB testing that result in a diagnosis and that occur after the participant signs the ICF should be reported to Lilly or its designee as an AE via eCRF.

9.4.7. Uveitis Evaluation

At each study visit, the investigator will ask the participant/caregiver whether they developed uveitis since the last visit and evaluate the participant for any symptoms of acute anterior uveitis since the last visit as specified in the Schedule of Activities (Section

2). If the participant has no prior ophthalmologist-diagnosed uveitis and develops eye pain or discomfort, eye redness, blurring of vision, or any other symptoms suggestive of acute anterior uveitis, the participant must be evaluated by an ophthalmologist. It is expected that all children with JIA will be on screening and regular evaluation with ophthalmologists based on local/regional/national guidelines.

9.4.8. Children's Depression Inventory 2 Short Form (CDI-2)

The Children's Depression Inventory-2 (CDI-2) short form is modeled after the Beck Depression Inventory and is a 12-item self-reported scale designed to measure depressive symptoms in children and adolescents (ages 7 years and older) (Helsel and Matson 1984; Kovacs 1992; Ahlen and Ghaderi 2017). The instrument has a recall period of the past 2 weeks and responses use a 3- item Likert scale. A higher score indicates more clinically severe depression.

9.4.9. Columbia–Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group Treatment of Adolescent Suicide Attempters (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events and is administered by the clinician.

The instrument is validated for use in children ages 7 to 11 (using the Children C-SSRS) as well as adults ages 12 and older (using the Adult C-SSRS form). The instrument is a composite instrument with responses being a mixture of Yes/No, ordinal and nominal scales. Higher scores indicate higher suicidal ideation and behavior.

The sites will use the appropriate version according to the age. Respondents will continue with the version of the instrument they begin the study with even if their age changes during the course of the study.

9.4.10. Self-Harm Supplement Form

The Self-Harm Supplement Form is part of the C-SSRS instrument. It consists of 1 question and is completed at any visit, including baseline visits by the clinician. The question asks for the number of suicidal or non-suicidal self-injurious behaviors the participant experienced since last assessment.

For each unique event identified, a questionnaire (Self-Harm Follow-Up Form), which collects supplemental information on the self-injurious behavior, must be completed. This information is then documented in the eCRF.

9.4.11. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Refer to Interim Analyses Section 10.3.8) for information about additional analyses of the safety data.

9.4.11.1. Hepatic Safety Monitoring

Close hepatic monitoring[a]

Laboratory tests (Appendix 4), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN, except for patients with Gilbert's syndrome
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline, except for patients with Gilbert's syndrome

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] All ULN values should be age adjusted (AAULN) for participants <18 years of age.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels. Special care should be taken to minimize the volume of blood taken during hepatic monitoring.

Comprehensive hepatic evaluationa

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:

ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN with hepatic signs/symptoms[b], or ALT or AST ≥5 × ULN
ALP <1.5 × ULN	ALP ≥3 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline with hepatic signs/symptoms[b], or ALT or AST ≥3 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] All ULN values should be age adjusted (AAULN) for participants <18 years of age.

[b] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR and direct bilirubin, if TBL was elevated, tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

Based on the participant's age, medical history, and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for viral hepatitis A, B, C, E; autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, MRI, or CT scan). Consider additional tests, based on the medical history and clinical picture, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Special care should be taken to prioritize more pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a pediatric hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:[a]

1. Elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 × ULN)
    - In participants with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests

2. Elevated TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline
3. Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN)
    - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be a SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the two consecutive blood tests should be at least 2 days.

[a] All ULN values should be age adjusted

9.4.11.1.1. Hepatic Safety Data Collection

Additional safety data should be collected via the electronic data entry if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests,
- elevated serum TBL to ≥2 × ULN (except for cases of known Gilbert's syndrome),
- elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests,
- participant discontinued from treatment due to a hepatic event or abnormality of liver tests, or
- hepatic event considered to be an SAE.

9.4.11.2. Hepatitis B Monitoring

Participants who are HBsAg- and HBcAb+ at screening, regardless of other hepatitis B testing results, will have a plasma HBV DNA specimen obtained to be analyzed by the central laboratory. Such participants who are determined to be HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 to 4 months during treatment and 12 weeks after the last dose of ixekizumab. Participants who are found to be HBV DNA positive (detectable) at screening will be excluded from the trial.

Any enrolled participant with a positive HBV DNA test result at any time must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy.

Study investigators should consult with a specialist physician in the care of participants with hepatitis (for example, infectious disease or hepatologist subspecialists) on whether to continue any immunosuppressant therapy including investigational product for a period of time while antiviral therapy is being initiated. Timing of withdrawal from investigational product should be based on recommendation of the consulting specialist physician in conjunction with the investigator and local or regional medical guidelines or standards of care.

Upon discontinuation from investigational product, the participant should be discontinued from the study. Any participant who discontinues the study for any reason will complete the ETV before entering the PTFU.

9.4.11.3. Growth Monitoring

Height and weight will be measured at baseline and postbaseline for the assessment of physical growth according to the Schedule of Activities (Section 2). Occipital frontal circumference will be collected in participants up to 3 years of age. Height, weight and occipital frontal circumference changes in pediatric participants (both at an individual and group level) will be reviewed by the data monitoring committee (DMC).

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous samples of approximately 2 mL each will be collected to determine the serum concentrations of ixekizumab.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

Pharmacokinetic samples will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, bioanalytical validation, and/or bioanalytical method cross-validation.

9.6. Pharmacodynamics

9.6.1. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against ixekizumab. Antibodies may be further characterized for their ability to neutralize the activity of ixekizumab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of ixekizumab. All samples for immunogenicity should be taken pre-dose when applicable and possible.

Treatment-emergent antidrug antibodies (TE-ADAs) are defined in Section 10.3.6. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken every 3 months for up to 1 year from last dose or until the ADA titer returns to baseline (i.e., no longer TE-ADA positive).

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and Ethical Review Boards allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to ixekizumab. Any samples remaining after 15 years will be destroyed.

9.7. Pharmacogenomics

Not applicable

9.8. Biomarkers

Not applicable

9.9. Medical Resource Utilization and Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The Bayesian methodology results in a posterior distribution which rigorously quantifies the uncertainty around the estimate of the JIA ACR 30 response. The primary objective of this study is to detect a JIA ACR 30 response rate of at least 50% for ixekizumab-treated participants at Week 16.

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

- a study success rate greater than 80% if the true JIA ACR 30 response is at 60%
- a false-positive rate of less than 1% if the true JIA ACR 30 response is placebo-like at 35%

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

Overall, approximately 100 participants will be assigned to therapy in this study.

Of the 80 ixekizumab-treated participants in this study, 20 bDMARD-naive participants will be randomized to ixekizumab. An additional 20 participants will be randomized to adalimumab (1:1 randomization to ixekizumab or adalimumab). The remaining 60 participants who are either bDMARD-naive or bDMARD-IR will be assigned to ixekizumab in the OLT period.

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

10.2. Populations for Analyses

For analysis purposes, populations are defined based on the different treatment period in Table RHCG.10.1.

Table RHCG.10.1. Populations Based on Treatment Period

Population	Description
Enrolled	All participants who sign informed consent.
ITT population	All participants, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the ITT Population during the OLT period. Participants will be analyzed according to the treatment to which they were assigned.
OLE period population	All participants who receive at least 1 dose of either treatment in OLE.
OLE period adalimumab switchers (switchers)	Participants initially randomized to adalimumab who switch to ixekizumab in the OLE period

Populations Based on Treatment Period

Population	Description
OLT safetypopulation	All participants who received at least 1 dose of either treatment product in OLT.
LTE safetypopulation	All participants who received at least 1 dose of ixekizumab in the LTE period.
PTFU period population	Safety analyses for the Post-Treatment Follow-Up Period will be conducted on the Post-Treatment Follow-Up Period population, defined as all randomized participants who received at least 1 dose of study treatment at any time during the study period, and have entered the Post-Treatment Follow-Up Period. Participants will be analyzed according to the treatment in which they were assigned.

Abbreviations: ITT=intend-to-treat; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment; PTFU = post-treatment follow-up.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed statistical analysis plan (SAP) describing the statistical methodologies will be developed by Lilly or its designee.

Continuous data will be summarized in terms of number of observations, mean, standard deviation, minimum, maximum, and median. Categorical data will be summarized as frequency counts and percentages. The proportions and 95% confidence intervals will be reported.

A futility analysis will be conducted using the JIA ACR 30 response rate observed in the first 40 ixekizumab participants who have the opportunity to complete OLT period (Week 16).
Adding an interim analysis for lack of benefit will reduce the risk of unnecessarily exposing pediatric participants to a treatment that does not meet the desired efficacy threshold. The study will stop for futility if the observed JIA ACR 30 response rate is less than 40% among participants who have had opportunity to complete Week 16 at the time of the interim analysis.

All efficacy and safety data will be descriptively summarized in each treatment period using corresponding populations, including switchers. No inferential comparisons will be made between treatment groups. Continuous vital signs, body weight, growth velocity, and other continuous safety variables, including laboratory variables, will be summarized.

Any change to the data analysis methods described in the protocol will require an

amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the SAP.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

10.3.1.1. General Considerations for the OLT Period

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

Efficacy baseline will be defined as the last available value before the first injection for efficacy and health outcomes. In most cases, this will be the measure recorded at Week 0 (Visit 2). For efficacy measures, if the participant does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

10.3.1.2. General Considerations for the OLE Period

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

For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first injection in the OLT period and, in most cases, will be the value recorded at Week 0 (Visit 2).

Unless otherwise specified, for the safety analyses during the OLE period, baseline is defined as the last available value before first injection of either ixekizumab or adalimumab in the OLE period. In most cases, this will be the measure recorded at Week 16 (Visit 7).

Safety and efficacy data for participants in the OLE period adalimumab switchers population will be summarized separately using descriptive statistics without inferential statistics. Safety baseline for switchers is defined as the last available value before first injection of ixekizumab or adalimumab in the OLE period.

All efficacy and safety data collected will be summarized using descriptive statistics.

10.3.1.3. General Considerations for the LTE Period

The LTE period starts at the first injection of ixekizumab at Week 104 (Visit 29) and

ends at Week 264 (Visit 69) or at ETV (between Weeks 104 and 264).
Note: Participants will be administered ixekizumab only until the treatment period at Week 68 (Visit 260).

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

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

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

10.3.1.4. General Considerations for the Post-Treatment Follow-up (PTFU) Period

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

Safety data will be summarized using descriptive statistics without inferential statistics by the study treatment the participant was receiving prior to entering PTFU period. Safety baseline is defined as the last available value immediately before entering PTFU period.

10.3.1.5. Missing Data Imputation Methods

10.3.1.5.1. Non-responder Imputation for Clinical Response

Summaries for all categorical efficacy and health outcomes variables will include a summary that uses a nonresponder imputation (NRI) approach. In this approach, participants will be considered a non-responder if they do not meet the clinical response criteria at any specified analysis time point. Participants without at least 1 observation on study treatment will also be defined as a non-responder for the NRI analysis. All participants who discontinue the study treatment will be defined as non-responders for the NRI analysis for categorical variables, such as JIA ACR 30/50/70/90/100, from the time of discontinuation and onward.

10.3.1.5.2. Modified Baseline Observation Carried Forward

Summaries for all continuous efficacy and health outcomes variables will include a summary that uses a modified baseline observation carried forward (mBOCF) approach. In this approach, the baseline observation will be carried forward to the corresponding endpoint for evaluation for participants who discontinue study treatment due to an AE.

10.3.1.5.3. Last Observation Carried Forward

The last non-missing observation before discontinuation of study treatment will be carried forward (LOCF) to the corresponding endpoint for evaluation of participants who

discontinue study treatment for any reason other than due to an AE. Participants without at least 1 post baseline observation will not be included for evaluation, except for participants who discontinue study treatment due to an AE.

10.3.2. Treatment Group Comparability

10.3.2.1. Participant Disposition

The number of participants along with enrolled, ITT, OLE, LTE, PTFU, and switchers populations will be summarized. Frequency counts and percentages will be presented. All participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported along with their reason for discontinuation. Reasons for discontinuation from the study will be summarized.

10.3.2.2. Participant Characteristics

Participant characteristics and baseline clinical measures will be summarized by treatment group. Baseline characteristics will include gender, age, height, weight, body mass index (BMI), race, geographic region, and subtype of JIA (ERA, JPsA). Baseline clinical measurements may include the following:

- previous DMARD experience (bDMARD, csDMARD),
- concurrent csDMARDs use (in total and by individual csDMARDs such as MTX and SSZ),
- JIA ACR core set
- PASI
- BSA
- LEI
- total and tender dactylitic digit count.

10.3.2.3. Concomitant Therapy

Previous and concomitant medications will be summarized for participants who enter each treatment period and presented by World Health Organization (WHO) Anatomic Therapeutic Class Level 1 and generic name.

10.3.2.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for each treatment period. Participant compliance with investigational product will be assessed at each visit. Participants will be considered compliant for each study period if they miss <20% of the expected doses, do not miss 2 consecutive doses, and do not overdose. Proportions of participants compliance will be summarized. Participant compliance will be further defined in the SAP.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy endpoint is the percentage of ixekizumab treated participants meeting JIA ACR 30 response criteria at Week 16, as defined in Section 9.1.1. A Bayesian analysis will be utilized to assess the primary endpoint of JIA ACR 30 response rate at Week 16. A positive study will satisfy at least 80% posterior probability that the JIA ACR 30 response rate in ixekizumab-treated participants is greater than 50%. The posterior distribution will be computed using the relatively noninformative Jeffreys' prior, Beta (0.5, 0.5).

10.3.3.2. Secondary Analyses

Secondary efficacy and health outcomes analyses will be based on study periods and study populations as outlined in Table RHCG.10.2.

Table RHCG.10.2. Secondary Efficacy and Health Outcomes Analyses OLT, OLE, and LTE Periods

Study Period	Analysis Population
OLT period	ITT population
OLE period	OLE period population
OLE period	Adalimumab switcher
LTE period	LTE period population

Abbreviations: ITT = intent-to-treat; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment.

For the OLT period, summary statistics will be performed for endpoints at each participant visit as outlined in Table RHCG.10.3.

Table RHCG.10.3. Summary Statistics OLT Period

Efficacy Measure	Population
JIA ACR 30/50/70/90/100 response from baseline	ITT Population
Change from baseline for individual JIA ACR components	ITT Population
Proportion of participants with disease flare	ITT Population
Change from baseline in PASI	ITT Population – Participants with plaque psoriasis (at least 3% BSA) at baseline
Change from baseline in LEI	ITT Population – Participants with enthesitis at baseline

Abbreviations: ACR = American College of Rheumatology; BSA = body surface area; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; LEI = Leeds Enthesitis Index; OLT = open-label treatment; PASI = Psoriasis Area and Severity Index.

For the OLE period, summary statistics will be performed for the endpoints at each participant visit as outlined in Table RHCG.10.4:

Table RHCG.10.4. Summary Statistics OLE Period

Efficacy Measure	Population
JIA ACR 30/50/70/90/100 response from baseline	OLE period population
Change from baseline for individual JIA ACR components	OLE period population
Proportion of participants with disease flare	OLE period population
Change from baseline in PASI	OLE period population – participants with plaque psoriasis (at least 3% BSA) at baseline
Change from baseline in LEI	OLE period population – participants with enthesitis at baseline

Abbreviations: ACR = American College of Rheumatology; BSA = body surface area; JIA = juvenile idiopathic arthritis; LEI = Leeds Enthesitis Index; OLE = open-label extension; PASI = Psoriasis Area and Severity Index.

Analyses for the PTFU period will be described in the SAP.

Table RHCG.10.5 Summary Statistics: Long-Term Extension Period

Efficacy Measure	Population
JIA ACR 30/50/70/90/100 response from baseline[a]	LTE population
Change from baseline for individual JIA ACR components	LTE population
Change from baseline in PASI	LTE population – Participants with plaque psoriasis (at least 3% BSA) at baseline
Change from baseline in LEI	LTE population – Participants with enthesitis at baseline

Abbreviations: ACR = American College of Rheumatology; BSA = body surface area; JIA = juvenile idiopathic arthritis; LEI = Leeds Enthesitis Index; LTE = long-term extension; PASI = Psoriasis Area and Severity Index.

[a] Baseline for all the measures in this table = baseline of the originating study.

Analyses for the PTFU period will be described in the SAP.

10.3.3.3. Exploratory Analyses

Analyses will be conducted for the exploratory efficacy objectives as defined in Section 4. Complete details will be described in the SAP.

10.3.4. Safety Analyses

Safety, including the following but not limited to, will be summarized:

- infections,
- injection-site reactions,

- B-, T-, and natural killer (NK)-cell levels
- AEs, treatment emergent AEs (TEAEs)
- SAEs,
- AEs that lead to discontinuation,
- Other AESIs,
- WBC count and RBC count,
- Laboratory analytes (including hematology and chemistry [including ALT and AST], neutrophil counts and immunogenicity),
- Exposure to study drug,
- CDI-2 score
- C-SSRS
- self-harm,
- vital signs, and
- growth and maturation (including growth velocity).

Immunization history will be summarized at baseline, and any unexpected outcomes or effects related to standard-of-care vaccination will be summarized.

Primary safety analyses will be summarized and analyzed by treatment groups (ixekizumab and adalimumab) as described in Section 10.3.1.1 for the OLT safety population in the OLT period and Section 10.3.1.2 for the OLE period population in the OLE period.

Summaries of safety data collected during the PTFU period will be presented for the PTFU period population.

10.3.4.1. Adverse Events

Adverse events are considered TEAEs if they first occur or worsen after the start of treatment during a study period. In the case of a missing onset date for an AE, an AE with a start date equal to or greater than the dosing date will be considered a TEAE. For each TEAE, the severity is recorded according to the participant's or physician's perceived severity of the event (mild, moderate, or severe).

Treatment-emergent adverse events, SAEs including deaths, AEs that lead to investigational product discontinuation, and AEs by maximum severity and relationship to investigational product will be summarized by the Medical Dictionary for Regulatory Activities System Organ Class (SOC) and Preferred Term (PT). Treatment-emergent adverse events will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs, TEAEs by maximum severity, and TEAEs considered possibly related to study drug. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

Medical Dictionary for Regulatory Activities groupings of PTs will be used to investigate AESIs.

Adverse events of special interest will also be presented by severity. Adverse events of special interest will include cytopenias, liver function test changes/enzyme elevations, infections, immunogenicity, injection site reactions, allergic/hypersensitivity reactions, cerebrocardiovascular events, malignancies, depression, IBD, and interstitial lung disease.

10.3.4.2. Clinical Laboratory Tests

Laboratory assessments will be presented as mean changes from baseline and as incidence of treatment-emergent abnormal, high, or low laboratory values. Shift tables will be presented for selected parameters.

- For categorical laboratory tests:
    - Treatment-emergent abnormal value = a change from normal at all baseline visits to abnormal at any time postbaseline.
- For continuous laboratory tests:
    - Treatment-emergent high value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline.
    - Treatment-emergent low value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

10.3.4.3. Vital Signs, Physical Findings, and Other Safety Evaluations

Vital signs will be presented as mean changes from baseline and as incidence of abnormal values.

CDI-2 total scores will be summarized as mean changes from baseline. Columbia Suicide Severity Rating Scale responses will be listed by participants and visit. Only participants that show suicidal ideation/behavior or self-injurious behavior with suicidal intent will be displayed (i.e., if a participant answers are all “no” for the C-SSRS, then that participant will not be displayed). Self-Harm Follow-Up Form will be listed.

Other data, including body weight and height will be summarized. Weight, height, and BMI data will be merged to the Centers for Disease Control and Prevention standard growth data by age and gender to compare participants’ growth with the standard.

Further analyses may be performed.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

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

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

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

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

Additional analyses may be performed upon receipt of the data.

Details about the analyses to be conducted will be contained in the PK/PD analysis plan.

10.3.6. Evaluation of Immunogenicity

Treatment-emergent antidrug antibody is defined as any occurrence of a 4-fold (2-dilution) increase in titer over the pretreatment baseline titer. In the case of a negative result at baseline, treatment-emergent immunogenicity is defined as an increase in titer to ≥1:10.

The analyses of TE-ADA effects will be conducted on all evaluable participants within the defined safety population. Evaluable participants will be identified as positive, negative, or inconclusive for TE-ADA and neutralizing antidrug antibody (NAb), as well as low, moderate, or high titer (as defined in the SAP). The incidence of participants with positive, negative, or inconclusive TE-ADA and NAb and low, moderate, or high titer at baseline and postbaseline will be summarized by treatment group.

10.3.7. Other Analyses

10.3.7.1. Subgroup Analyses

For both treatments (ixekizumab and adalimumab), summary statistical analyses will be conducted for JIA ACR 30 at each regular visit for the following subset of participants: ERA and JPsA. Additional subgroups may be described in the SAP.

10.3.7.2. Exploratory Analysis

Analyses will be conducted for the exploratory efficacy objectives as defined in Section 4. Complete details will be described in the SAP.

10.3.8. Interim Analyses

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

An interim analysis will be performed to determine if the study should be stopped for

futility when 40 ixekizumab-treated participants have completed 16 weeks of treatment. If the observed JIA ACR 30 response rate is less than 40% at interim, futility will be declared, and the study will be terminated, after the applicable required regulatory agreements are obtained. Due to the open-label feature, and because there is no stopping rule for early efficacy, there will be no adjustment for multiple testing in the interim analysis or final Bayesian primary analyses.

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

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

Additional analyses and snapshots of study data may be performed after the planned interim analysis to inform the need for an additional interim analysis, and after all participants complete OLT period (Week 16) to fulfill the need for regulatory interactions or publication purposes.

10.3.9. Adjudication Committee

Data on suspected IBD as identified by events possibly indicative of ulcerative colitis or Crohn’s disease will be collected, and the events will be adjudicated by an external CEC composed of gastroenterologists with expertise in IBD.

Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the CEC charter.

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12. Appendices

Appendix 1. Abbreviations

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
ACR	American College of Rheumatology
ACR 30	30% improvement in American College of Rheumatology criteria
active joint	Joint that is swollen, or in the absence of swelling, has loss of passive motion accompanied by either pain on motion or joint tenderness
ADA	antidrug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AS	ankylosing spondylitis
assent	Affirmative agreement of a child to participate in research or to undergo a medical intervention. Lack or absence of expression of dissent or objection must not be interpreted as assent. When obtaining child assent, relevant elements of informed consent should be provided appropriate to the child's capability to understand (ICH 2016).
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	inadequate response or intolerance to at least one prior bDMARD

blinding/masking	A single-blind study is one in which investigators and/or staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but investigators and/or staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigators or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BSA	body surface area
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDI-2	Children's Depression Inventory 2 Short Form
CEC	Clinical Events Committee
cGMP	good manufacturing practices
CHAQ	Childhood Health Assessment Questionnaire
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	C-reactive protein
CRS	Clinical Research Scientist
C-SSRS	Columbia Suicide Severity Rating Scale
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
disease flare	Worsening of 30% or more in at least 3 of the 6 JIA ACR core criteria for JIA and an improvement of 30% or more in no more than 1 of the criteria
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.

enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-Y	European Quality of Life-Five Dimensions–Youth
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
ETV	early termination visit
FABER	flexion, abduction and external rotation
FACTS™	Fixed and Adaptive Clinical Trials Simulator version 6.0
FDA	Food and Drug Administration
GDPR	EU General Data Protection Regulation
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HLA-B27	human leukocyte antigen-B27
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgG4	immunoglobulin G subclass 4
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.

Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IR	inadequate response
IRB	Institutional Review Board
ITT	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
JADAS-27	Juvenile Arthritis Disease Activity Score-27
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
JIA ACR 30	30% improvement in American College of Rheumatology criteria
JoAS	juvenile onset ankylosing spondylitis
JPsA	juvenile psoriatic arthritis
JSpA	juvenile spondyloarthritis
JSpADA	Juvenile Spondyloarthritis Disease Activity Index
LEI	Leeds Enthesitis Index
LOCF	last non-missing observation carried forward
LTE	long-term extension
mBOCF	modified baseline observation carried forward
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the

	error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MRI	magnetic resonance imaging
MTX	Methotrexate
NAb	neutralizing antidrug antibody
NIMH	National Institute of Mental Health
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
OLT	open-label treatment
PASI	Psoriasis Area and Severity Index
PC	product complaint
PD	Pharmacodynamic
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PPD	purified protein derivative
PsA	psoriatic arthritis
PT	Preferred Term
PTFU	post-treatment follow-up
Q2W	every 2 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
r-axSPA	radiographic axial spondyloarthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan

SC	Subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SpA	Spondyloarthritis
SSZ	Sulfasalazine
SUSAR	suspected unexpected serious adverse reaction Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TASA	Treatment of Adolescent Suicide Attempters
TB	Tuberculosis
TBL	total bilirubin level
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TNF	tumor necrosis factor
ULN	upper limit of normal
USPI	US package insert
VAS	Visual Analogue Scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

Appendix 2. Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory.

- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests

Hematology[a,b,c]	**Clinical Chemistry**[a,b,c]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Neutrophils, juvenile (bands)	
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose
Urinalysis[a,b,c,d]	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	
Glucose	**Pregnancy Test** (females only)[c,e]
Ketones	Serum pregnancy test
	Urine pregnancy test
Blood	
Urine leukocyte esterase	**Other Tests**
	Human immunodeficiency virus antibody[f]
	Hepatitis B surface antigen (HBsAg)[f]
Cell Flow Cytometry	Hepatitis B surface antibody[f]
(B cells, T cells, CD4+T cells, CD8+T cells,	Hepatitis B core antibody[f]
and NK cells)	Hepatitis C virus antibody[f,g]
	Hepatitis B virus DNA[h]
	High sensitivity C-reactive protein (hsCRP)[i]
	HLA-B27
	QuantiFERON®-TB Gold or T-Spot or PPD[j]
	Acute phase reactant (ESR)k
	Pharmacokinetic sample

Abbreviations: ESR = erythrocyte sedimentation rate; HLA-B27 = human leukocyte antigen-B27; NK = natural killer; PPD = purified protein derivative; RBC = red blood cells; TB = tuberculosis; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Results will be confirmed by the central lab at the time of initial testing.

[c] Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.

[d] Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.

[e] Serum pregnancy test will be performed centrally at screening only, prior to the first dose of the study intervention, for all females aged ≥10 years (<10 years at investigator's discretion) if menarche is reached or if there is reason to believe that the participant is sexually active. After screening, urine

pregnancy test will be performed locally for females of childbearing potential. As per Clinical Trial Facilitation Group (CTFG) recommendation: In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles.

f Test required at Visit 1 only to determine eligibility of participant for the study.

g A positive hepatitis C antibody result will be confirmed with presence of HCV RNA.

h HBV DNA testing will be done on those participants who are HBcAb+ at screening. For participants who are positive for HBcAb, a follow-up test for HBV DNA is required. Participants with a positive HBcAb will return to the site and have HBV DNA samples drawn, which will be processed centrally. Anyenrolled participant who is HBcAb positive, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule.

i Test results of hsCRP and lymphocyte subsets will be blinded after Week 16 and the test results will not be sent to the study sites.

j As stated in the Schedule of Activities (Section 2), TB testing is required only based on clinical assessment of TB risk and according to local regulations and/or local standard of care (Section 9.4.5). For countries where the QuantiFERON®-TB Gold test is not available the T-Spot or PPD test may be used.T-Spot or PPD to be performed/read locally.

k Sponsor-provided; assayed by clinical study site.

Recommended Laboratory Testing for Hypersensitivity Events

Lab testing should be performed at the time of a Systemic Hypersensitivity Event. Important information about why, when, and what to test for are provided below. The management of the adverse event may warrant lab testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a Systemic Hypersensitivity Event is not performed for diagnostic purposes. Its intent is several fold:

- To help characterize and classify systemic hypersensitivity reactions
- To meet regulatory expectations
- To improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis

When should labs be obtained?

- In the presence of generalized urticaria or if anaphylaxis is suspected*
- After the participant has been stabilized, obtain a sample within 1 to 2 hours of the event, however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

What labs should be obtained?

- tryptase*

- antidrug antibody (ADA) and LY2439821 (LY) concentration (pharmacokinetic)
  - ADA testing should include drug-specific immunoglobulin E (IgE)
  - If a drug-specific IgE assay isn't available, a commercially available alternative test that can indicate the presence of drug specific IgE in serum is the basophil activation test (BAT)#.
- complement
  - C3a and C5a
- cytokines
  - Interleukin (IL)-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

*If a tryptase sample is obtained more than 2 hours after the event (that is, within 2-12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for N- methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

#The BAT is an in vitro cell-based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE but is not specific for IgE. If an in vivo assay is called for, the passive cutaneous anaphylaxis (PCA) assay may be performed in rodents or NHP, is commercially available, and only requires a serum sample. Skin prick testing in humans is a sensitive and specific assay for drug-specific IgE but requires qualification of the method in negative controls and participants with documented Type I hypersensitivity to the drug.

Appendix 3. Study Governance Considerations

Regulatory, Ethical, and Study Oversight Conditions

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
    - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and the participant's legally authorized representative, defined as parent(s) or legal guardian, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their representative, parent(s), or legal guardian will be required to provide a statement of informed consent/assent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that legally acceptable representative, parent(s), or legal guardian consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally acceptable representative, parent(s), or legal guardian. The acceptable person obtaining the informed consent must also sign the ICF. The person obtaining the informed consent must also sign the ICF.
- Participants and their legally acceptable representative, parent(s), or legal guardian must be reconsented and reassented to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be reconsented if they reach the age of majority during the study, in order to continue participating. A copy of the ICF(s) must be provided to the participant or the participant's legally acceptable representative, parent(s), or legal guardian.

Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and

prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

Rationale for collection of full date of birth

This study includes participants aged from 2 years to <18 years. Within this vast age range, participants' expected height and weight, as well as normal ranges for laboratory tests, vary by both age and sex. Therefore, it is necessary to collect the full date of birth (day, month, and year) for all pediatric participants to appropriately analyze and interpret changes in growth and laboratory parameters.

- In countries where local regulations do not permit collection of the full date of birth, providing the supporting regulatory/ethics documentation is available, at a minimum, the month and year of birth must be collected on the eCRF.

Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data.

Data are available to request 6 months after the indication studied has been approved in the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement.

Data and documents, including the study protocol, SAP, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment

for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk- Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and

timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (participant-focused outcome instrument) will be collected via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded into an instrument per the Schedule of Activities (for example, hand-held device). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Data from complaint forms submitted to Sponsor will be encoded and stored in the global product complaint management system.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Data Quality Assurance Section above.

Study and Site Start and Closure

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be

closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

In accordance with the sponsor’s publication policy the results of this study will be submitted for publication by a peer-reviewed journal.

Investigator Information

Physicians with experience in the diagnosis and treatment of rheumatology and pediatric rheumatology will participate as investigators in this clinical trial.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with Lilly, or its designee's, clinical research physician.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA, quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG, quantitative)
HAV total antibody	Immunoglobulin M (IgM, quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[c]	Anti-actin antibody[b]

Hematology	**Clinical Chemistry**
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[c]	EBV DNA[c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Types 1 and 2) antibody
HEV RNA[c]	HSV (Types 1 and 2) DNA[c]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviation: INR = international normalized ratio.

[a] Not required if anti-actin antibody istested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Appendix 5. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 9.2 for the list of sponsor medical devices.

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug–drug interaction. • Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it

is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy). Note: The condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if the event were more severe.

c. Requires in-participant hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to the hospital for observation and/or treatment that would not have been appropriate in the physician's office or out-participant setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

Recording and Follow-up of AE and/or SAE and Product Complaints

AE, SAE, and PC Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page for AE/SAE and the PC Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, *not* when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the sponsor or the sponsor's designee will be the electronic data collection tool. • If the electronic system is unavailable or if a pregnancy is reported, then the site will use the paper SAE or pregnancy data collection tools to report the event within 24 hours. • The site will enter SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the medical monitor or SAE by telephone.
- Contacts for SAE reporting can be found in the site training documents.

Reporting of SAEs

SAE Reporting via Paper Form
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the site training documents.

Regulatory Reporting Requirements

SAE Regulatory Reporting
• Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. • The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. • An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB will notify the IRB/IEC, if appropriate according to local requirements.

Appendix 6. Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female is defined as, women with:
   - At least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note.
     OR
   - With spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced the amenorrhea. And if ≤ age 50, has an FSH of ≥40 mIU/mL and estradiol of ≤30 pg/mL.

Contraception guidance for women of childbearing potential (WOCBP):

This outlines the rules for WOCBP to ensure they do not become pregnant during the study.

See guidance for specific patient populations below:

Women of childbearing potential who are completely abstinent as their preferred and

usual lifestyle or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ postovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

Women of childbearing potential who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative (serum/urine) test result at screening followed by a negative (urine/serum) result within 24 hours prior to treatment exposure. See the protocol Schedule of Activities for subsequent pregnancy testing requirements.
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These forms of contraception must be used for the duration of the study.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

Appendix 7. I1F-MC-RHCG Blood Volume Prioritization Tool

Due to blood volume restrictions, some laboratory samples may not be collected.

This appendix (Blood Volume Prioritization Tool) provides guidance on blood sample prioritization for participants who will participate in the study. This tool includes a separate table for each of the following age groups:

- 15 years and older (page 173-174)
- 8 years to <15 years (page 175-176)
- 2 years to <8 years (page 177-178)
- Blood volume calculations (page 179)

Blood Volume Prioritization

Recommendations for Participants ages 15 yrs and older

Laboratory Test (all tests per protocol)	V1	V2	V3	V4	V5	V6	V7	V8	V11	V14	V17	V20	V23	V26	V29
Chemistry/hs-CRP (includes serum B-HCG, Rheumatoid Factor at screening)	4.7	4.7		4.7			4.7		4.7	4.7	4.7	4.7	4.7	4.7	4.7
Hematology (w/ANC)	1.2	1.2		1.2			1.2		1.2	1.2	1.2	1.2	1.2	1.2	1.2
Flow Cytometry		4.9					4.9		4.9	4.9	4.9	4.9	4.9	4.9	4.9
Hepatitis B/C Initial Screening	4.7														
HIV Screening/Confirmation	1.1														
TB Quantiferon (4 mL) or PPD Test (if applciable)	4.0														
HBV DNA Reflex Confirmation (separate day, 4.9 mL) HCV RNA Reflex Confirmation (separate day, 4.9 mL)	X														
HBV DNA monitoring - (4.9 mL, if applicable)	X					X			X	X	X		X	X	X
hs-CRP (V3, V5, V6, V8 only, otherwise with chem)			1.1		1.1	1.1		1.1							
Rheumatoid Factor (with Chem)															
HLA-B27				2.7											
ESR		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PK Sample (to be collected for patients on active LY)		2.6		2.6		2.6	2.6	2.6	2.6		2.6		2.6		2.6
Immunogenicity (ADA and Nab)		4.7		4.7		4.7	4.7	4.7	4.7		4.7		4.7		4.7
Actual Blood Volume by Visit (mL)	**15.7**	**19.6**	**2.6**	**17.4**	**2.6**	**9.9**	**19.6**	**9.9**	**19.6**	**12.3**	**19.6**	**12.3**	**19.6**	**12.3**	**19.6**

Abbreviations: ADA = antidrug antibody; ANC = absolute neutrophil count; B-HCG = Beta-Human Chorionic Gonadotropin; Chem = Chemistry; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hs-CRP = high sensitivity C-reactive protein; Nab = neutralizing antidrug antibody; PK = pharmacokinetic; PPD = purified protein derivative; TB = tuberculosis; V = visit.

Blood Volume Prioritization

Recommendations for Participants ages 15 yrs and older

Laboratory Test (all tests per protocol)	V30	V31	V33	V36	V39	V42	V45	V48	V51	V54	V57	V60	V63	V66	V69	ET	V801	V802	V803
Chemistry/hs-CRP (includes serum B-HCG, Rheumatoid Factor at screening)	4.7		4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	1.1	1.1	1.1
Hematology (w/ANC)	1.2		1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Flow Cytometry																			
Hepatitis B/C Initial Screening (with Chem)																			
HIV Screening/Confirmation																			
TB Quantiferon (4 mL) or PPD Test (if applicable)																			
HBV DNA Reflex Confirmation (separate day, 4.9 mL) HCV RNA Reflex Confirmation (separate day, 4.9 mL)	X																		
HBV DNA monitoring - (4.9 mL, if applicable)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
hs-CRP (V3, V5, V6, V8 only, otherwise with chem)																			
Rheumatoid Factor (with Chem)																			
HLA-B27																			
ESR	1.5		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5			
PK Sample (to be collected for patients on active LY)	2.6	2.6	2.6	2.6		2.6		2.6		2.6		2.6		2.6	2.6	2.6		2.6	
Immunogenicity (ADA and Nab)	4.7	4.7	4.7	4.7		4.7		4.7		4.7		4.7		4.7	4.7	4.7		4.7	
Actual Blood Volume by Visit (mL)	**14.7**	**7.3**	**14.7**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**14.7**	**14.7**	**2.3**	**9.6**	**2.3**

Abbreviations: ADA = antidrug antibody; ANC = absolute neutrophil count; B-HCG = Beta-Human Chorionic Gonadotropin; Chem = chemistry; ESR = erythrocyte sedimentation rate; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-

B27 = human leukocyte antigen-B27; hs-CRP = high sensitivity C-reactive protein; Nab = neutralizing antidrug antibody; PK = pharmacokinetic; PPD = purified protein derivative; TB = tuberculosis; V = visit.

Blood Volume Prioritization

Recommendations for Participants age 8 to < 15 yrs

Laboratory Test (all tests per protocol)	V1	V2	V3	V4	V5	V6	V7	V8	V11	V14	V17	V20	V23	V26	V29
Chemistry/hs-CRP (includes serum B-HCG, Rheumatoid Factor at screening)	4.7	4.7		4.7			4.7		4.7	4.7	4.7	4.7	4.7	4.7	4.7
Hematology (w/ANC)	1.2	1.2		1.2			1.2		1.2	1.2	1.2	1.2	1.2	1.2	1.2
Flow Cytometry		4.9					4.9		4.9	4.9	4.9	4.9	4.9	4.9	4.9
Hepatitis B/C Initial Screening	4.7														
HIV Screening/Confirmation	1.1														
TB Quantiferon (4 mL) or PPD Test (if applicable)	4.0														
HBV DNA Reflex Confirmation (separate day, 4.9 mL) HCV RNA Reflex Confirmation (separate day, 4.9 mL)	X														
HBV DNA monitoring, if applicable (separate day, 4.9mL)	X					X			X	X	X		X	X	X
hs-CRP (V3, V5, V6, V8 only, otherwise with chem)			1.1		1.1	1.1		1.1							
Rheumatoid Factor (with Chem)															
HLA-B27				2.7											
ESR		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PK Sample (to be collected for patients on active LY)		2.6		2.6		2.6	2.6	2.6	2.6		2.6		2.6		2.6
Immunogenicity (ADA and Nab)		4.7		4.7		4.7	4.7	4.7	4.7		4.7		4.7		4.7
Actual Blood Volume by Visit (mL)	**15.7**	**19.6**	**2.6**	**17.4**	**2.6**	**9.9**	**19.6**	**9.9**	**19.6**	**12.3**	**19.6**	**12.3**	**19.6**	**12.3**	**19.6**

Abbreviations: ADA = antidrug antibody; ANC = absolute neutrophil count; B-HCG = Beta-Human Chorionic Gonadotropin; Chem = Chemistry; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hs-CRP = high sensitivity C-reactive protein; Nab = neutralizing antidrug antibody; PK = pharmacokinetic; PPD = purified protein derivative; TB = tuberculosis; V = visit.

Blood Volume Prioritization

Recommendations for Participants age 8 to < 15 yrs

Laboratory Test (all tests per protocol)	V30	V31	V33	V36	V39	V42	V45	V48	V51	V54	V57	V60	V63	V66	V69	ET	V801	V802	V803
Chemistry/hs-CRP (includes serum B-HCG, Rheumatoid Factor at screening)	4.7		4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	1.1	1.1	1.1
Hematology (w/ANC)	1.2		1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Flow Cytometry																			
Hepatitis B/C Initial Screening (with Chem)																			
HIV Screening/Confirmation																			
TB Quantiferon (4 mL) or PPD Test (if applicable)																			
HBV DNA Reflex Confirmation (separate day, 4.9 mL) HCV RNA Reflex Confirmation (separate day, 4.9 mL)	X																		
HBV DNA monitoring, if applicable (separate day, 4.9mL)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
hs-CRP (V3, V5, V6, V8 only, otherwise with chem)																			
Rheumatoid Factor (with Chem)																			
HLA-B27																			
ESR	1.5		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5			
PK Sample (to be collected for patients on active LY)	2.6	2.6	2.6	2.6		2.6		2.6		2.6		2.6		2.6	2.6	2.6		2.6	
Immunogenicity (ADA and Nab)	4.7	4.7	4.7	4.7		4.7		4.7		4.7		4.7		4.7	4.7	4.7		4.7	
Actual Blood Volume by Visit (mL)	**14.7**	**7.3**	**14.7**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**14.7**	**14.7**	**2.3**	**9.6**	**2.3**

Abbreviations: ADA = antidrug antibody; ANC = absolute neutrophil count; B-HCG = Beta-Human Chorionic Gonadotropin; Chem = Chemistry; ESR = erythrocyte sedimentation rate; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hs-CRP = high sensitivity C-reactive protein; Nab = neutralizing antidrug antibody; PK = pharmacokinetic; PPD = purified protein derivative; TB = tuberculosis; V = visit.

Blood Volume Prioritization

Recommendations for Participants age 2 to < 8 yrs

Laboratory Test (all tests per protocol)	V1	V2	V3	V4	V5	V6	V7	V8	V11	V14	V17	V20	V23	V26	V29
Chemistry/hs-CRP (includes serum B-HCG, Rheumatoid Factor at screening)	4.7	4.7		4.7			4.7		4.7	4.7	4.7	4.7	4.7	4.7	4.7
Hematology (w/ANC)	1.2	1.2		1.2			1.2		1.2	1.2	1.2	1.2	1.2	1.2	1.2
Flow Cytometry *(if eligible)*		X					X		X	X	X	X	X	X	X
Hepatitis B/C Initial Screening	4.7														
HIV Screening/Confirmation	1.1														
PPD Test (if applicable)															
HBV DNA Reflex Confirmation (separate day, 4.9 mL) HCV RNA Reflex Confirmation (separate day, 4.9 mL)	X														
HBV DNA monitoring, if applicable (separate day, 4.9mL)	X					X			X	X	X		X	X	X
hs-CRP (V3, V5, V6, V8 only, otherwise with chem)			1.1		1.1	1.1		1.1							
Rheumatoid Factor (with Chem)															
HLA-B27				2.7											
ESR		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PK Sample (to be collected for patients on active LY)		2.6		2.6		2.6	2.6	2.6	2.6		2.6		2.6		2.6
Immunogenicity (ADA and Nab)		4.7		4.7		4.7	4.7	4.7	4.7		4.7		4.7		4.7
Actual Blood Volume by Visit (mL)	**11.7**	**14.7**	**2.6**	**17.4**	**2.6**	**9.9**	**14.7**	**9.9**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**

Abbreviations: ADA = antidrug antibody; ANC = absolute neutrophil count; B-HCG = Beta-Human Chorionic Gonadotropin; Chem = Chemistry; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hs-CRP = high sensitivity C-reactive protein; Nab = neutralizing antidrug antibody; PK = pharmacokinetic; PPD = purified protein derivative; V = visit.

Blood Volume Prioritization

Recommendations for Participants age 2 to < 8 yrs

Laboratory Test (all tests per protocol)	V30	V31	V33	V36	V39	V42	V45	V48	V51	V54	V57	V60	V63	V66	V69	ET	V801	V802	V803
Chemistry/hs-CRP (includes serum B-HCG, Rheumatoid Factor at screening)	4.7		4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	1.1	1.1	1.1
Hematology (w/ANC)	1.2		1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Flow Cytometry *(if eligible)*																			
Hepatitis B/C Initial Screening (with Chem)																			
HIV Screening/Confirmation																			
PPD Test (if applicable)																			
HBV DNA Reflex Confirmation (separate day, 4.9 mL) HCV RNA Reflex Confirmation (separate day, 4.9 mL)	X																		
HBV DNA monitoring, if applicable (separate day, 4.9mL)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
hs-CRP (V3, V5, V6, V8 only, otherwise with chem)																			
Rheumatoid Factor (with Chem)																			
HLA-B27																			
ESR	1.5		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5			
PK Sample (to be collected for patients on active LY)	2.6	2.6	2.6	2.6		2.6		2.6		2.6		2.6		2.6	2.6	2.6		2.6	
Immunogenicity (ADA and Nab)	4.7	4.7	4.7	4.7		4.7		4.7		4.7		4.7		4.7	4.7	4.7		4.7	
Actual Blood Volume by Visit (mL)	**14.7**	**7.3**	**14.7**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**7.4**	**14.7**	**14.7**	**14.7**	**2.3**	**9.6**	**2.3**

Abbreviations: ADA = antidrug antibody; ANC = absolute neutrophil count; B-HCG = Beta-Human Chorionic Gonadotropin; Chem = Chemistry; ESR = erythrocyte sedimentation rate; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hs-CRP = high sensitivity C-reactive protein; Nab = neutralizing antidrug antibody; PK = pharmacokinetic; PPD = purified protein derivative; V = visit.

Blood Volume Prioritization

Blood Volume Calculations

Blood Volume Calculations

- Local restrictions may apply with regard to allowed volume of samples within 24 hours.
- Please ensure that you are compliant with local restrictions as applicable.

Conservative guidance is:
1% of total blood volume for age and weight per 24 hours

Conservative estimate of total blood volume is 80 mL/kg

15 years or older (and ≥40kg) → (80mL/kg X40kg)/100 = **32mL per 24 hours**
15 year old 5th percentile of weight is 40kg (CDC)

8 to <15 years (and 20 to <40kg) → (80mL/kg X 20kg)/100 = **16mL per 24 hours**
8 year old 5th percentile of weight is 20kg (WHO)

6 to <8 years (and 15 to <20kg) → (80mL X15kg)/100 = **12mL per 24 hours**
6 year old 5th percentile of weight is 16kg (WHO)

2 to <6 years (and 10 to <15kg) → (80mL X10kg)/100 = **8mL per 24 hours**
2 year old 5th percentile of weight is 10kg (CDC)

Abbreviations: CDC = Centers for Disease Control; WHO = World Health Organization.

Appendix 8. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional Circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing Changes under Exceptional Circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent/assent from the participant will be obtained, as applicable, and/or as required by Ethical Review Boards and local regulations. Assent will also be obtained to the same parameters, with consent for participants reaching the legal age for consent during the trial for continued participation, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- a change in the location of study intervention administration,

- alternate delivery of ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed. The following changes in study conduct will not be considered protocol deviations.

1. Remote Visits

In source documents and the CRF, the study site should capture the visit location and method, with a specific explanation for any data missing because of missed in-person site visits.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to,

- Immunization record
- AEs and product complaints
- Concomitant medications
- Clinician reported measures except for those assessments or fields that require joint manipulation, such as Joint Assessment, Enthesitis Assessment, Dactylitic Count, Physician's Global Assessment of Disease Activity, and Clinical Sacroiliitis
- Participant/Parent administered measures

Other alternative locations: Other procedures that may be done at an alternate location in exceptional circumstances are local draw labs, investigational product preparation and administration. This alternative location may count as an "on-site" visit with regard to the guidance in this appendix.

In the event that access to the site is not possible, and with approval from Lilly Medical, sites will follow the guidance in the table below.

Visit(s)	Guidance
V1-V2	If one of these visits cannot be accomplished at the site, then the visit should be postponed. Refer to Section "Screening Period Guidance" in this appendix for further screening guideline and Section "Adjustments to Visit Windows" in this appendix for visit window adjustments.
V7	This visit must be performed at site (Primary Outcome).

	Participants under Ixekizumab Arm	Participants under Adalimumab Arm
OLT Visits (V3-V6)	Use a combination of telephone/telemedicine with use of an acceptable alternative site for the safe administration of the ixekizumab injection and assessments performed by site personnel.	Use a combination of telephone/telemedicine with use of an acceptable alternative site for assessments performed by site personnel.
OLE Visits: **V8, V11,V14, V17, V20, V23, V26, V29**	Use a combination of telephone/telemedicine with use of an acceptable alternative site to perform the assessments required to be done by health care professional, and for the preparation and safe administration of the ixekizumab injection.	Use a combination of telephone/telemedicine with use of an acceptable alternative site to perform the assessments required to be done by health care professional and the delivery of treatment supplies for the actual visit and for the next 2 treatment-only visits (e.g., V8 + V9, V10).
Tx only visits: V9, V10, V12, V13, V15, V16, V18, V19, V21, V22, V24, V25, V27, V28	Use a combination of telephone/telemedicine for follow up with use of an acceptable alternative site for the safe administration of the injection for participants under ixekizumab treatment arm.	Telephone/telemedicine for follow up. Participants would have received additional treatment supplies in the previous regular visit.
LTE Visits: **V30, V31,**	Use a combination of telephone/telemedicine with use of an acceptable alternative site to	Use a combination of telephone/telemedicine with use of an acceptable alternative site to perform the

Visit(s)	Guidance	
V33, V36, V39, V42,V45, V48, V51, V54, V57, V60, V63, V66, V69	perform the assessments required to be done by health care professionals, and for the preparation and safe administration of the ixekizumab injection.	assessments required to be done by health care professionals and the delivery of treatment supplies for the actual visit and for the next 2 treatment-only visits (e.g., V31 + V32, V34).
LTE Tx Visits Only: **V32, V34, V35, V37, V38, V40, V41, V43, V44, V46, V47, V49, V50, V52, V53, V55, V56, V58, V59, V61, V62, V64, V65, V67, V68**		Telephone/telemedicine for follow up. Participants would have received additional treatment supplies in the previous regular visit.
ETV	Sites may use telephone/telemedicine.	Sites may use telephone/telemedicine.
Follow-up (V801-V803)	Telephone/telemedicine or use of an acceptable alternative site.	Telephone/telemedicine or use of an acceptable alternative site.

Abbreviations: ETV = early termination visit; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment; Tx = treatment; V = visit.

Any required procedures that cannot be conducted at that time should be conducted as soon as possible thereafter, using an unscheduled visit if necessary.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

2. Local Laboratory Testing Option

Preferred collection of labs is centrally, but if the participant is unable to attend the site, labs can be collected locally in lieu of central laboratory testing. For participants unable to access investigator sites, laboratory testing will be conducted locally approximately every 8 weeks through Week 16, and then approximately every 12 weeks. Failure to have labs collected within the described ranges above will result in participant termination from the study. The local laboratory must be qualified in accordance with applicable local regulations.

When collecting local labs, sites should store/retain records from the labs including results, address, certification (College of American Pathologists/Clinical Laboratory Improvement Amendments [CAP/CLIA]) status, and reference ranges. The principal investigator/subinvestigator should document, sign, and date review of local labs per normal process and follow-up with the participant as needed. Local labs may be sent to the participant as this is standard process in clinical care.

These laboratory measures listed below are the minimum required to monitor participant safety and determine temporary or permanent discontinuation of investigational product. Additionally, investigators should include any symptom-based laboratory testing based on their interactions with their participants. As stated in the protocol, investigators are responsible for monitoring the overall health of their participants.

Because these participants have already successfully screened into the study (therefore have met all study inclusion/exclusion criteria for laboratory values), the investigators should request the following laboratory analyses for these select parameters:

1) ALT, AST, total bilirubin, INR
2) ALP
3) WBC
4) Neutrophil and lymphocyte count
5) hemoglobin
6) platelet count
7) Serum pregnancy tests (where

applicable) Notes:

Serum pregnancy is to ensure female participants do not become pregnant while participating in the study (in lieu of urine pregnancy testing at the study site).

Temporary interruption rules (see Protocol RHCG Section 8.1.2) must be followed where applicable. For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator the laboratory abnormality is due to intercurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when

the laboratory value meets resumption thresholds following the resolution of the intercurrent illness or other identified factor may the investigator restart investigational product after consultation with Lilly Medical.

In some circumstances, participants may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. See Protocol RHCG Section 9.4.5 for details regarding managing participants who test positive for TB at any time during the study.

3. Study Intervention and Ancillary Supplies

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and either receive study supplies or have injection administration from site staff without completion of a full visit,
- arranging delivery of study supplies, and
- working with the sponsor to determine how study intervention that is typically administered on-site will be administered to the participant at an alternate location.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of study supplies.
- When delivering supplies to a location other than the study site as an alternative site for the safe administration of the ixekizumab injection or the supply treatment for adalimumab. The investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

In addition, if study intervention will be administered to the participant at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer study intervention.
- Requirements and instructions for investigational product storage and dose preparation will be the same as stated in main protocol,

Pharmacy Binder and Ixekizumab Dosing Instructions Manual must be followed.

4. Screening Period Guidance

To ensure safety of study participants, laboratory values, and other eligibility assessments taken at screening visit are valid for a maximum of 42 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If paused for less than 42 days from screening to randomization visit: The participant will proceed to the next study visit per the usual Schedule of Activities, provided that randomization visit must be conducted within 7 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the CRF.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If paused for more than 42 days from screening to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen fail in the CRF with a reason of exceptional circumstance. This screen fail is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual Schedule of Activities should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

5. Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	**Tolerance**
Visit 3 through Visit 7 (OLT)	Within 14 days before intended date, or up to 14 days after the intended date

Visit 8 through Visit 29 (OLE)	Within 14 days before intended date, or up to 14 days after the intended date
Visit 30 through Visit 69 (LTE)	Within 14 days before intended date, or up to 14 days after the intended date
Visit 801 through Visit 802 (Visit 803)	Within 14 days before intended date, or up to 14 days after the intended date

Abbreviations: LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study, as well as to prevent dosing administration less than 21 days apart.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances.
- Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Appendix 9. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [b]: (21-Sep-2022)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants
- reliability and robustness of the data generated in the clinical study

Overall Rationale for the Amendment:

To include Long Term Extension Study information to determine long term efficacy and safety of LY2439821 in children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-related Arthritis (Including Juvenile-Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis.

Section # and Name	Description of Change	Brief Rationale
Title Page	• Adjusted to follow the harmonized template. • Deleted original title page.	For alignment of Legacy Protocol documents with the new harmonized template.
SOC Table	Protocol Amendment SOC table added.	For alignment with new harmonized template.
Section 1. Synopsis	LTE period data added.	For alignment.
Section 2. Schedule of Activities	• LTE tables added, andOLE adjusted. • Visit and week numbering adjusted. • Weight recording adjustedto 10th of a kilogram. • Deleted the Self-HarmFollow- up Form • Specified that the Global Assessment ofWell-Being must be completed by a caregiver until participant ≥14 years of age.	For alignment and accuracy.

Section # and Name	Description of Change	Brief Rationale
Section 3.1 Study Rationale	Study Rationale for LTE period information added.	For accuracy.
Section 3.2 Background	IXORA-PEDS trial information added.	For alignment.
Section 4 Objectives and Endpoints	LTE O/E added.	For accuracy.
Section 5.1 Overall Design	• LTE information added. • LTE treatment period added. • Schema Adjusted to incorporate LTE information.	For alignment.
Section 5.1.3 Open-Label Extension Period	Sentence added to indicate participants switched over to ixekizumab will be treated in separate group.	For accuracy.
Section 5.1.4 Long-Term Extension Period	New section to depict LTE period of study.	For alignment.
Section 5.1.5 Post-Treatment Follow-up Period	LTE post follow up period clarified.	For alignment.
Section 5.3 End of Study Definition	LTE information added.	For alignment.
Section 5.4 Scientific Rationale for Study Design	• Added 3-year optionality wording. • Rationale for LTE added.	For accuracy.
Section 5.5 Justification for Dose	Wording added to clarify LTE dose.	For accuracy.
Section 6.1 Inclusion Criteria	Screening and baseline wording added to Inclusion Criterion #3	For clarification.
Section 6.4 Screen Failures	Wording on ICF/assent form added.	For alignment.
Section 7.1 Treatments Administered	• LTE information added to Table RHCG 7.1. • Wording added to Post- Administration Observation.	For alignment.
Section 7.2 Method of Treatment Assignment	Clarified that all participants who enter LTE will receive ixekizumab.	For clarification.
Section 7.4 Dosage Modification	Clarified dosing during LTE period.	For alignment.

Section # and Name	Description of Change	Brief Rationale
Section 7.7 Concomitant Therapy	• Clarified use of concomitant therapy in LTE period. • Wording on intra-articularjoint and bursal corticosteroid injections changed.	• For alignment. • For clarification.
Section 7.8.1 Study Extensions	Changed wording to include LTE in RHCG study.	For accuracy.
Section 7.8.2 Treatment After Study Completion	Clarified use of adalimumab in LTE period.	For alignment.
Section 8 Discontinuation Criteria	Sentence added to refer to Appendix 3 for discontinuation criteria.	For accuracy.
Section 8.1 Discontinuation from Study Treatment	Paragraph added to clarify permanent discontinuation.	For accuracy.
Section 8.1.1 Permanent Discontinuation from Study Treatment	Updated hepatic parameters for discontinuation and resumption of study drug.	As per updated safety requirements.
Section 8.1.3 Discontinuation of Inadvertently Enrolled Patients	Section removed.	As per new Lilly guidelines.
Section 9.1.3.1 Childhood Health Assessment Questionnaire (CHAQ)	Note added to state the CHAQ will be provided to participants.	For alignment.
Section 9.1.4.5 Morning Joint Stiffness Duration	Note added to state the morning stiffness will be assessed by participants.	For alignment.
Section 9.2.1 Timing and Mechanism, for Collecting Events	Adverse Event collecting events table added.	As per new harmonized template guidelines.
Section 9.3 Treatment Overdose	Updated treatment overdose information.	As per new harmonized template guidelines.
Section 9.4.11.1 Hepatic Safety Monitoring	Hepatic Safety information updated.	As per new safety guidelines.
Section 10.2 Population for Analyses	LTE information added.	For alignment.
Section 10.3.1 General Statistical Considerations	Clarified wording for OLT participants.	For clarification.

Section # and Name	Description of Change	Brief Rationale
Section 10.3.1.2 General Considerations for OLE Period	• Visit 8 changed to Visit 7. • Adalimumab wording added.	For accuracy.
Section 10.3.1.3 General Considerations for LTE Period	New section added to incorporate general considerations for the LTE period.	For alignment.
Section 10.3.2.1 Participant Disposition	LTE and PTFU wording added.	For accuracy.
Section 10.3.3.2 Secondary Analyses	• Adjusted Table RHCG.10.2 to incorporate LTE period information. • New LTE period Table RHCG.10.5 added.	For alignment.
Appendix 2. Clinical Laboratory Tests	Updated wording added and outdated wording removed.	As per new harmonized template guidelines.
Appendix 3. Study Governance Considerations	Updated wording added and outdated wording removed.	As per new harmonized template guidelines.
Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality	Hepatic Safety information updated.	As per new safety guidelines.
Appendix 5. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow- up, and Reporting	Updated wording added and outdated wording removed.	As per new harmonized template guidelines.
Appendix 6. Contraceptive Guidance and Collection of Pregnancy Information	Updated contraceptive language.	As per new safety guidelines.
Appendix 7. I1F-MC-RHCG Blood Volume Prioritization Tool	• Pages updated. • Blood volumes updated.	For accuracy.
Appendix 8 Provisions for Changes in Study Conduct During Exceptional Circumstances	Updated language for LTE period added.	To follow new guidelines.
Appendix 9 Protocol Amendment I1F-MC-RHCG(a)	• Title removed. • Approval date added.	For alignment.

Section # and Name	Description of Change	Brief Rationale
All Sections	Minor editorial/formatting made throughout, including changing patient wording to participant where applicable.	For accuracy.

Abbreviations: ICF = informed consent form; LTE = long-term extension; O/E = Objectives/Endpoints; OLE = open label extension; OLT = open label treatment; PTFU = post-treatment follow up; SOC = summary of changes.

Amendment [a]: (06-Nov-2020)

Overview

Protocol I1F-MC-RHCG, Multicenter, Open-label, Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Subcutaneous Ixekizumab with Adalimumab Reference Arm, in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-related Arthritis (Including Juvenile-Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis, has been amended.

Overall Rationale for the Amendment:

The overall changes and rationale for changes made to this protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Amendment Summary for Protocol I1F MC RHCG Amendment (a) 06-Nov-2020

Section #	Description of Change	Brief Rationale
Section 1, Synopsis	Updated status of ixekizumab to approved for plaque psoriasis in adult and pediatric participants, adult psoriatic arthritis, radiographic axial spondyloarthritis (r-axSpA), and non-radiographic axSpA with objective signs of inflammation. Removed Week 16 as a timepoint for PK analysis and relationship between exposure, efficacy, and immunogenicity.	Updated to be consistent with the label. Clarification
Section 2, Schedule of Activities	Extended Screening period from -42 to -14 days to -42 to -7 days.	Correction to standard minimum window for randomization
	For Tanner Stage Scale, added the clarification, "Once the participant reaches the score of 5 on this scale, no further assessments are needed."	Clarification
	Clarified reading PPD was to be performed locally.	Minor clarification
	Combined HBV DNA row with HBV antibody row.	
	Added the word "site" to administration of study treatment at treatment visits (TV).	
	Deleted TB testing after screening	
	Added urine pregnancy test at every visit starting at Visit 8. Added tests are to be performed locally. Added clarification for testing during instances of delayed menstruation.	In response to Competent Authority request
	Added, "Includes an assessment of rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA." to clinical chemistry.	Clarification
	Added, "V803 is an additional follow-up based on neutrophil count (Section 5.1.4)." as a clarification.	Clarification to be consistent with other ixekizumab studies.
	Added "or ETV" to LV at each follow-up visit.	Clarification

Section #	Description of Change	Brief Rationale
Section 3.2 Background	Updated background information for ixekizumab	Updated to include current study results and indications
Section 4 Objectives and Endpoints	Removed Week 16 as a PK analysis time point Removed Week 16 as an analysis time point for the relationship between exposure, efficacy, and immunogenicity	Clarification Clarification
Section 5.1 Overall Design	Updated screening period and designation of follow-up visits.	For consistency with revisions made to Schedule of Activities
Section 5.1.3 Open-Label Extension Period	Added requirements for participants switching from adalimumab to ixekizumab. A requirement to capture the reasons for switching was also added.	In response to Competent Authority request
Section 5.5 Justification for Dose	Added requirements for participants switching from adalimumab to ixekizumab.	In response to Competent Authority request
Section 6.1 Inclusion Criteria	Added statement, "Participants and their partners of childbearing potential must agree to use contraception for 5 months after the last dose of adalimumab." to criterion [5].	In response to Competent Authority request
Section 6.2 Exclusion Criteria	Added statement, "Participants with moderate to severe heart failure [NYHA class III/IV] are not eligible for the study." to criterion[21].	In response to Competent Authority request
Section 7.1 Treatments Administered	Reorganized section by showing the dose level table at the beginning and adding subsections for Dosing and Post-Administration Observation. Added instructions for participants with a body weight of 10.0 kg to 15 kg.	Clarification In response to Competent Authority request
Section 7.7 Concomitant Therapy	Corrected the maximum dose of SSZ to be 3 g/day instead of 3 mg/day. Clarified the conditions for stable use of concomitant medications extend through the OLT period. Added footnote: Dose adjustments may only be made for safety reasons during OLT period (until Week 16).	Typo error Clarification Clarification
Section 8.1.1 Permanent Discontinuation	Revised consultation with Lilly-designated medical monitor to consultation with Lilly Medical.	Clarification on terms

Section #	Description of Change	Brief Rationale
from Study Treatment	Removed criterion of hemoglobin <6.5 g/dL from discontinuation criteria. Corrected typos.	In response to Competent Authority request
Section 8.1.3 Discontinuation of Inadvertently Enrolled Participants	Revised wording	To update to the current harmonized template language
Section 9 Study Assessments and Procedures	Deleted language about 60-day retention period for samples. Removed "Investigators should assess and monitor physical pain and distress at each visit."	To update to the current harmonized template language Statement did not belong in this section and it was not specific enough for site staff to interpret.
Section 9.2.1.2 Adverse Events of Special Interest	Added sentence, "In the case of suspected IBD, the participant should be referred to a gastroenterologist (preferably pediatric gastroenterologist) for evaluation and management."	In response to Competent Authority request
Section 9.4 Safety	Added sentence "These events will also be considered as an AE if the event does not result in a diagnosis but is considered clinically significant by the investigator."	In response to Competent Authority request.
Section 9.4.4 Laboratory Tests	Added mention of the Blood Volume Prioritization Tool as a new appendix.	In response to Competent Authority request
Section 9.4.4.1 Pregnancy Testing	Added section regarding pregnancy testing	To update to the current harmonized template language
Section 10.3.5 Pharmacokinetic/ Pharmacodynamic Analyses	Removed Week 16 as an analysis timepoint	Clarification
Section 10.3.8 Interim Analyses	Removed PK data as an interim analysis	Clarification
Section 10.3.9 Adjudication Committee	Corrected IBD charter to CEC charter	Terminology update
Appendix 2. Clinical Laboratory Tests	Added Neutrophils, juvenile (bands) Added footnote d clarifying urinalysis testing Added clarification for testing during instances of delayed menstruation to serum pregnancy testing footnote. Added clarification about when TB testing is required and add that it is to be performed locally.	Clarification Clarification In response to Competent Authority request Clarification
Appendix 3 Study Governance Considerations	Added for competent authority to approve Updated language according to the most current template	In response to Competent Authority request Updating per protocol template
Appendix 7. I1F-MC-RHCG Blood Volume	Added new appendix	In response to Competent Authority request

Section #	Description of Change	Brief Rationale
Prioritization Tool		
Appendix 8. Provisions for Changes in Study Conduct During Exceptional Circumstances	Added new appendix	In response to Competent Authority request

Signature Page for VV-CLIN-126448 v2.0

Approval	PPD Statistician 30-Nov-2023 16:13:47 GMT+0000

Approval	PPD Medical 01-Dec-2023 15:53:21 GMT+0000

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