14 December 2017
EMA/59447/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Taltz

International non-proprietary name: ixekizumab

Procedure No. EMEA/H/C/003943/II/0009

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Definition
ACR	American College of Rheumatology
ACR Core Set	Consists of 7 disease activity measurements: tender joint count, swollen joint count, Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, patient's assessment of physical function, and an acute-phase reactant value.
ACR Responder	**ACR20 Responder** A patient who had at least 20% improvement in both tender and swollen joint counts and at least 20% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or erythrocyte sedimentation rate). **ACR50 Responder** A patient who had at least 50% improvement in both tender and swollen joint counts and at least 50% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or erythrocyte sedimentation rate). **ACR70 Responder** A patient who had at least 70% improvement in both tender and swollen joint counts and at least 70% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or erythrocyte sedimentation rate).
ACR-N Responder Index	A continuous measure of clinical, laboratory, and functional measure in rheumatoid arthritis that characterizes the percentage of improvement from baseline in rheumatoid arthritis disease activity. This index is defined operationally as the lowest of either a) the percentage change in tender joint count, b) the percentage change in swollen joint count, or c) the median percentage change of the remaining 5 ACR core criteria. A patient with an ACR-N of X is a patient who has improvement of at least X% in both tender and swollen joint counts and a median improvement of at least X% in the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity,

Term	Definition
	patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or erythrocyte sedimentation rate).
ADAs	anti-drug antibodies
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase; formerly referred to as SGPT or serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase; formerly referred to as SGOT or serum glutamic oxaloacetic transaminase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARDs	biologic disease-modifying antirheumatic drugs (see also DMARDs); examples of biologics include—but are not limited to—etanercept (Enbrel®), adalimumab (Humira®), and infliximab (Remicade®)
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, *or* vice versa, *or* when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BQL	below the quantitation limit
BSA	body surface area, measured in 1% increments with area of patient's hand including palm, fingers and thumb = 1%

Term	Definition
CASPAR	Classification Criteria for Psoriatic Arthritis
cDMARD	conventional disease-modifying antirheumatic drugs
CEC	Clinical Events Committee
CI	confidence interval
clinical research physician	Individual at the sponsor company responsible for the medical conduct of the study. Responsibilities may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice requirements, and the applicable regulatory requirements.
COX-2	cyclooxygenase-2
CPDAI	Composite Psoriatic Disease Activity Index
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAS28-CRP	Disease Activity Score 28 diarthrodial joint count based on C-reactive protein
DLQI	Dermatology Life Quality Index
DMARDs	disease-modifying antirheumatic drugs; unless specifically referred to as bDMARDs (biologic DMARDs), this term refers to conventional DMARDs (cDMARDs) such as methotrexate, sulfasalazine, hydroxychloroquine, cyclosporine (ciclosporin) A, cyclophosphamide, azathioprine, etc.
DMC	Data Monitoring Committee, a group specifically established for interim safety monitoring
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form. Sometimes referred to as clinical report form: An electronic form for recording study participants' data during a clinical study, as required by the protocol.
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.

Term	Definition
end of study	End of study is the date of the last visit or last scheduled procedure shown in the Schedule of Events for the last active patient in the study.
enroll/randomize	Refers to a method of treatment assignment. The point of randomization in this study is the point at which treatment is assigned and the patient begins treatment; thus, patients who are randomized in the study are those who have been assigned to a treatment.
ENSEMBLE MDS	Enterprising Selective Multi-Instrument Blend for Heterogeneity-analysis Minimum Data Set
enter/consent	The act of obtaining informed consent for participation in a clinical study from patients deemed eligible or potentially eligible to participate in the clinical study. Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
enthesitis	Inflammation of tendons and ligaments that can manifest as localized pain and tenderness.
EQ-5D 5L	European Quality of Life-5 Dimensions 5 Level
ERB	ethical review board
ETV	Early Termination Visit
Fatigue NRS	Fatigue Severity Numeric Rating Scale
FEAE	follow-up–emergent adverse event
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBV	hepatitis B virus
hs-CRP	high sensitivity (assay) C-reactive protein
ICF	Informed consent form; potential study participants will sign ICFs directly or through their legally acceptable representatives prior to any study activities or data collection (even for screening)
ICH	International Conference on Harmonisation
Ig	immunoglobulin
	IgA immunoglobulin A
	IgG immunoglobulin G

Term	Definition
	IgG4 immunoglobulin G subclass 4
	IgM immunoglobulin M
IL	interleukin (for example, IL-17; a proinflammatory cytokine produced by Th17 cells)
Inadequate Responder (Week 16)	A patient who failed to meet defined criteria for improvement in tender and swollen joints at Week 16 and was administered rescue therapy.
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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB, ERB	Institutional Review Board or Ethical Review Board. A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ITT	Intent(ion)-to-Treat. Statistical analytical term; 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 patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients 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.
IV	intravenous
IVRS	interactive voice-response system
LDI-B	Leeds Dactylitis Index-Basic
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
LEI	Leeds Enthesitis Index
LLN	lower limit of normal
LLT	Lowest Level Term
LOCF	last observation carried forward
LS	least-squares

Term	Definition
LSS	Lilly safety system
mBOCF	modified baseline observation carried forward
MCS	Mental Component Summary
MDA	Minimum Disease Activity
MDA_{PASI}	Minimum Disease Activity including Psoriasis Area and Severity Index
MDA_{sPGA}	Minimum Disease Activity including static Physician Global Assessment of psoriasis
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effects models for repeated measures
mRNA	messenger ribonucleic acid
mSACRAH	modified Score for Assessment and Quantification of Chronic Rheumatoid Affections of the Hands
mTSS	modified Total Sharp Score
MTX	methotrexate
n	number of observations
NAb	neutralizing antibody
NAPSI	Nail Psoriasis Severity Index
NICE	National Institute for Health and Care Excellence
NK	natural killer
NRI	nonresponder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
	PASI 75 at least a 75% improvement in PASI score from baseline
	PASI 90 at least a 90% improvement in PASI score from baseline
	PASI 100 a 100% improvement in PASI score from baseline
PatGA	Patient's Global Assessment of Disease Activity

Term	Definition
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PBAC	Pharmaceutical Benefits Advisory Commission
PCS	Physical Component Summary
PGA	Physician's Global Assessment of Disease Activity
PI	principal investigator
PK/PD	pharmacokinetics/pharmacodynamics
pMI	placebo multiple imputation
PPD	purified protein derivative
PPS	Per Protocol Set
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritic Response Criteria
Q2W	every 2 weeks
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 items)
QTc	corrected QT
QTcF	corrected QT using Fridericia's correction factor
QTcLCTPB	corrected QT using a large clinical trial population based correction
RA	rheumatoid arthritis
RHAJ	I1F-MC-RHAJ
RHAK	I1F-MC-RHAK
SAE	Serious adverse event; specifically, an adverse event meeting criteria established by regulatory authorities requiring reporting of relevant data within certain timeframe because of potential threat to patient safety (see also AE).
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. In this study, screening involves invasive or diagnostic procedures and/or tests (for example,

Term	Definition
	diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	standard deviation
SEM	standard error of the mean
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SI	International System of Units
SJC	swollen joint count
SMQ	standardized Medical Dictionary for Regulatory Activities query
SOC	System Organ Class
sPGA	static Physician Global Assessment of psoriasis
TB	tuberculosis
TE-ADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event. Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with the treatment.
Th	T helper
TJC	tender joint count
TNF	tumor necrosis factor
UK	United Kingdom
ULN	upper limit of normal
USA	United States of America
VAS	visual analog scale
WPAI-SHP	Work Productivity and Activity Impairment–Specific Health Problem

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 22 May 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include Ixekizumab, alone or in combination with conventional disease-modifying anti-rheumatic drug (cDMARD), for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated to reflect the new safety and efficacy information. The Package Leaflet and RMP have been updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0233/2016 on the acceptance of a modification of a paediatric investigation plan (PIP) (EMEA-001050-PIP01-10M02) and a conclusion by PDCO of partially completed compliance.

At the time of submission of the application, the PIP P/0233/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The ixekizumab clinical development programme for PsA was informed by scientific advice from the Committee for Medicinal Products for Human Use (EMA/CHMP/SAWP/339078/2011).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Greg Markey

Timetable	Actual dates
Submission date	22 May 2017
Start of procedure:	17 June 2017
CHMP Co-Rapporteur Assessment Report	2 August 2017
CHMP Rapporteur Assessment Report	11 August 2017
PRAC Rapporteur Assessment Report	18 August 2017
PRAC members comments	23 August 2017
Updated PRAC Rapporteur Assessment Report	24 August 2017
PRAC Outcome	1 September 2017
CHMP members comments	4 September 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 September 2017
Request for supplementary information (RSI)	14 September 2017
CHMP Rapporteur Assessment Report	13 November 2017
PRAC Rapporteur Assessment Report	20 November 2017
PRAC members comments	22 November 2017
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur Assessment Report	7 December 2017
Opinion	14 December 2017

2. Scientific discussion

2.1. Introduction

Ixekizumab (Taltz) is a monoclonal antibody that selectively targets interleukin-17A (IL-17A). IL-17A is produced mainly by inflammatory Th17 cells, a subset of T helper cells, but also by other T cells,

neutrophils, and mast cells. Increased numbers of IL 17A producing cells are present in the peripheral blood, synovial tissue and fluid, and skin plaques of patients with psoriatic arthritis (PsA; Jandus et al. 2008; Kagami et al. 2010; Lin et al. 2011; Noordenbos et al. 2012; Menon et al. 2014; Leijten et al. 2015). Preclinical and clinical evidence has demonstrated the role of IL-17A signalling in the formation of psoriatic lesions, as well as in synovial inflammation, cartilage destruction, and bone erosion (Kotake et al. 1999; Koshy et al. 2002; Lee 2013; Lowes et al. 2013). Neutralisation of IL-17A has been shown to inhibit the aforementioned pathological cellular events, as well as mitigate disease activity in patients with PsA (Lee 2013; Lowes et al. 2013; Mease et al. 2014b, 2015b, 2017; McInnes et al. 2015).

Taltz is approved for the treatment of moderate-to-severe plaque psoriasis at a recommended dose of 160 mg by subcutaneous (SC) injection at Week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg every 4 weeks (Q4W) thereafter. The positive benefit-risk profile of ixekizumab for the treatment of moderate-to-severe plaque psoriasis was supported by superiority versus placebo and etanercept in achieving clear/almost clear skin and balanced with an acceptable safety profile.

This Type II variation application is for a proposed new indication and associated posology as follows:

Taltz, alone or in combination with a conventional disease-modifying antirheumatic drug (cDMARD), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have responded inadequately to or who are intolerant to one or more DMARD therapies.

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For PsA patients with concomitant moderate-to-severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis.

To support this variation, the efficacy and safety of ixekizumab in PsA were assessed in 2 pivotal, randomised, double-blind, placebo-controlled, Phase III studies (RHAP and RHBE); the placebo-controlled, double-blind treatment periods were 24 weeks in length. Each study included separate patient populations to address the efficacy and safety profile in bDMARD-naive patients (RHAP) and bDMARD-experienced patients (RHBE). Both studies included assessment of long-term efficacy through Week 52. This application includes data up to Week 52 for RHAP. The extension period of RHBE is ongoing, and the Week 52 data are anticipated to become available in August 2017.

In addition to RHAP and RHBE, a third Phase 3 study I1F-MC-RHBF (RHBF) with a randomised-withdrawal design is on-going to further evaluate maintenance of efficacy.

The ixekizumab clinical development programme for PsA was informed by scientific advice from the Committee for Medicinal Products for Human Use (EMA/CHMP/SAWP/339078/2011) and the CHMP 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis 2007'.

2.2. Non-clinical aspects

No new non- clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

The MAH submitted a justification for not submitting any ERA studies since the product is a human antibody. This is acceptable by CHMP.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Ixekizumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The clinical part of the application includes supportive safety and efficacy data from 2 pivotal Phase 3 studies in patients with active PsA (I1F-MC-RHAP [RHAP] and I1F-MC-RHBE [RHBE], Table 1), as well as safety data accrued in the ixekizumab global clinical development program for patients with PsA or with moderate-to-severe plaque psoriasis. To support characterize the clinical pharmacology for ixekizumab in patients with PsA, population pharmacokinetic (PK) and exposure-response modelling were conducted using serum drug concentration data from the 2 pivotal Phase 3 clinical studies in patients with PsA (RHAP and RHBE) in combination with data from 3 studies in patients with psoriasis from the initial MAA (I1F-MC-RHAG [RHAG], RHAJ, and I1F-MC-RHAZ [RHAZ]), along with safety and efficacy measures from RHAP and RHBE in patients with PsA.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 **Index of Studies and Analyses Supporting the Summary of Clinical Pharmacology for Ixekizumab in Patients with Psoriatic Arthritis**

Population	Report/Location	Objectives	Dosing Regimens[b]
PsA/psoriasis	Integrated Population PK/PD Report for Studies RHAP and RHBE / Section 5.3.3.5	Population PK[a], efficacy, safety, immunogenicity	**RHAP:** Ixekizumab • SC starting dose of 160 mg at Week 0 (Day 1) • SC 80 mg Q2W or Q4W up to 24 weeks (Double-Blind Treatment Period) • SC 80 mg Q2W or Q4W 24-52 weeks (Extension Period) SC 80 mg Q2W or Q4W 52-156 weeks (Long-Term Extension Period) Placebo • Patients who were inadequate responders at Week 16 were re-randomized (1:1) to ixekizumab (160 mg starting dose, then 80 mg Q2W or Q4W through Week 24). • Patients on placebo through Week 24 were re-randomized (1:1) to ixekizumab (160 mg followed by 80 mg Q2W or Q4W). Adalimumab SC 40 mg Q2W up to 24 weeks (Treatment): • Patients who were inadequate responders at Week 16 (and were re-randomized to treatment with ixekizumab and had completed 8-week placebo washout period) received 160 mg ixekizumab at Week 24, then 80 mg Q2W or Q4W. • Patients who remained on adalimumab through Week 24, were re-randomized (1:1) to ixekizumab 80 mg Q2W or Q4W (no 160 mg starting dose), and thereafter went through a placebo washout for the following 8 weeks (Week 26-Week 32) before beginning ixekizumab at Week 32.
			RHBE: Ixekizumab • SC starting dose of 160 mg at Week 0 (Day 1) • SC 80 mg Q2W or Q4W up to 24 weeks (Double-Blind Treatment Period) • SC 80 mg Q2W or Q4W 24-156 weeks (Extension Period) Placebo • Patients who were inadequate responders at Week 16, were re-randomized (1:1) to ixekizumab (160 mg starting dose, then 80 mg Q2W or Q4W through Week 24). • Patients on placebo through Week 24 were re-randomized (1:1) to ixekizumab 160 mg followed by 80 mg Q2W or Q4W.

Population	Report / Location	Objectives	Dosing Regimens[b]
			RHAG: Ixekizumab Q2W given on 3 occasions: • SC injection(s) of 5, 15, 50, and 150 mg or • IV infusion of 15 mg
			RHAJ (Part A): Ixekizumab • SC injection(s) of 10, 25, 75, and 150 mg at 0, 2,4, 8, 12, and 16 weeks
			RHAZ: Ixekizumab • SC starting dose of 160 mg • SC 80 mg Q2W or Q4W up to 12 weeks (Induction Dosing Period) • SC 80 mg Q4W or Q12W Weeks 12 to 60 (Maintenance Dosing Period)
Healthy adults	RHCA CSR[c] / Section 5.3.4.1	Immune response to vaccines; PK	• SC 160 mg at Week 0 (Day 1) • 80 mg at Week 2 (Day 15) • tetanus and pneumococcal vaccines at Week 2 (Day 15)

2.3.2. Analytical methods

Assay for Ixekizumab Serum Concentrations

Serum samples obtained during this study were analysed for ixekizumab (LY2439821) using a validated Enzyme Linked Immunosorbent Assay (ELISA) method. The lower limit of quantification was 7.5 ng/mL and the upper limit of quantification was 300.0 ng/mL for analysis. Samples above the limit of quantitation were diluted to yield results within the quantifiable range. Samples below the limit of quantitation and diluted were repeated at a lesser dilution to yield results within the quantifiable range. The inter-assay accuracy (% relative error [RE]) during validation ranged from -20.7% to 7.9%. The inter-assay precision (% CV) during validation ranged from 0.9% to2.0%. The intra-assay accuracy (% RE) during validation ranged from -4.5% to -3.6%. The intra-assay precision (% CV) during validation ranged from 0.7% to 1.6%. Ixekizumab was stable for up to 33 months when stored at approximately -70°C ± 10°C; all samples were assayed within 33 month stability.

Assays for Immunogenicity Screening and Neutralizing Antibody

Anti-Drug Antibody (ADA) assay

The acid capture and elution enzyme-linked immunosorbent assay (ACE-ELISA) is the same method employed as in the original application. The validation package was updated to re-evaluate a disease state patient population specific Tier 1 (screening) cut-point and Tier 2 (confirmatory) cut-point to better describe the performance of the method and to align with evolving regulatory expectations. The psoriatic arthritis cut-points was compared to the psoriasis cut points and were not found to be statistically different. Therefore, The Tier 1 cut point and Tier 2 % inhibition values of 0.169 OD and 65.9% were retained and was used for clinical testing of samples in this application (studies RHAP and RHBE) to detect anti-ixekizumab (anti-LY2439821).

Re-interpolation of the sensitivity and drug tolerance with the newly assigned cut point yield an assay sensitivity of 4.6 ng/mL and drug tolerance of 480.5 µg/mL ixekizumab for 500 ng/mL of affinity purified polyclonal anti-ixekicumab from hyper-immune monkey sera. Drug tolerance at additional levels of affinity purified polyclonal anti- ixekicumab from hyper-immune monkey sera, 8 ng/mL, 20 ng/mL, and 45 ng/mL, were also re-interpolated using the newly assigned cut point and yield of 0.5 µg/mL, 3.1 µg/mL, and 21.5 µg/mL of LY2439821, respectively.

Neutralising Anti-Drug Antibody (NAb) assay

The neutralising ADA assay is the same method employed as in the original application and was updated to re-establish neutralizing antibody inhibition cut point, drug tolerance and sensitivity based on disease specific (psoriatic arthritis) baseline patient samples to align with evolving regulatory expectations. The assay is based on electrochemiluminescence (ECL) detection using the Meso Scale Discovery (MSD) platform and detects NAbs by direct competition between the binding of the therapeutic target (IL-17) and binding of ADA at the active site of ixekizumab.

The disease state validation parameters re-established for psoriatic arthritis baseline patient samples were statistically different from the psoriasis disease parameters and the disease specific parameters were therefor used for the clinical testing in this application. The psoriatic arthritic cut point was found to be 10.2% inhibition. The psoriatic arthritic sensitivity established was 135.3 ng/mL and the drug tolerance was 1.8 µg/mL ixekizumab for 5000 ng/mL of affinity purified polyclonal anti-ixekicumab from hyper-immune monkey sera. The measured drug tolerance of the assay may not be sufficient for all samples collected at the dosing regimens in Phase 3 related to the expected trough ixekizumab

concentration (predicted 5th to 95th percentile C_{min}: 80 mg Q4W: 0.3 to 3 ug/ml). Given the polyclonal nature of the affinity purified surrogate control, it is likely that not all of the control material is neutralizing, and thus, the drug tolerance assessment is likely greater than indicated for the detection of NAb.

2.3.3. Pharmacokinetics

To describe ixekizumab PK in patients with PsA, ixekizumab concentration data from the PsA trials (Studies RHAP and RHBE) were integrated with the psoriasis PK dataset (Studies RHAG, RHAJ, and RHAZ, all available data). The characteristics for the PsA patients included in the PK analysis are summarized in Table 2. A total of 2966 concentrations from 657 patients were available in Studies RHAP and RHBE, of which 20 (0.67%) were below the detection limit of the PK assay. The total number of PK samples included in the PK analysis (all indications) is summarised in Table 3.

Table 2 Demographics at Study Entry for Patients Included in the Pharmacokinetic Analysis

Baseline Covariate	Overall (RHAP, RHBE, RHAG, RHAJ, RHAZ)	RHAP	RHBE	RHAG/RHAJ/RHAZ
Total Patient Count	2056	381	276	1399
Age (years)[a]	48 (17-88)	50 (19-76)	53 (18-86)	46 (17-88)
Body Weight (kg)[a]	87.3 (41.8-206)	83.1 (41.8-206)	87.6 (45.9-165)	88.9 (46.0-200)
Sex – Female (%)	38.9	53.8	52.5	32.2
Site/route of injection (%)[b]				
Abdomen - Subcutaneous	67.7	72.1	67.9	66.2
Arm - Subcutaneous	9.46	5.13	7.61	11.2
Buttock - Subcutaneous	0.465	0	0	0.688
Thigh - Subcutaneous	22.3	22.8	24.2	21.9
Intravenous	0.0504	0	0	0.0745
Not available	0.0233	0	0.224	0
Concomitant Methotrexate (%)				
≥ 85% of treatment duration	12.9	42.3	37.7	0
< 85% of treatment duration	2.92	11.8	5.43	0
Not at all	84.2	45.9	56.9	100
Previous Methotrexate (%)	30.7	75.3	88.4	7.22
Previous Adalimumab (%)	8.85	0 [c]	23.2	2.43

[a] Median (range).
[b] Site of injection might vary over time. Percentage reported for total number of injections across all patients. Unknown site of injection was replaced by the most common site of injection for that patient in Studies RHAG, RHAJ, and RHAZ.
[c] Per study protocol, a subset of patients were randomized to receive adalimumab who then switched to receive ixekizumab treatment after Week 24. These patients account for approximately 22% of the patients from Study RHAP in this PK dataset.

Table 3 Summary of Number of Pharmacokinetic Data by Study

Data included in PK Analysis					
Study	Number of PK Samples			Number of Patients	Average Number of PK Samples per Patient
	Total	BQL[a]	Measurable		
RHAP	1795	20	1775	381	4.66
RHBE	1171	0	1171	276	4.24
RHAG, RHAJ, RHAZ	6057	296	5761	1399	4.12
Overall (RHAP, RHBE, RHAG, RHAJ, RHAZ)	9023	316	8707	2056	4.23

Abbreviations: BQL = below quantification limit of assay; PK = pharmacokinetic.

[a] BQL PK that were included in analysis were samples collected at post-dose and from patients receiving at least one injection of ixekizumab treatment. BQL samples that were excluded from the analysis were collected prior to the first dose of ixekizumab or collected from patients receiving placebo.

All existing covariate relationships identified in the psoriasis analysis were retained in the new model, and the model parameters were re-estimated including the PsA data.

Additional covariate evaluation was conducted for the following covariates: PsA as an indication, concomitant use of MTX, and prior use of MTX or adalimumab, as these are factors associated with the patient population in Studies RHAP and RHBE. None of these factors were found to be significant, indicating they do not affect ixekizumab PK. The PK parameters from the final model are shown in Table 4 and visual predictive checks are displayed in Figure 1.

Table 4 **Pharmacokinetic and Covariate Parameters in the Final Population Pharmacokinetic Model Estimated by SAEM and IMP Algorithm with BQL Samples Included**

Parameter Description[a]	Population Estimate (95% CI, %RSE)[h]	Inter-Individual Variability (IIV) % (%RSE)
CL (L/h)[b]	0.0153 (0.0149 – 0.0156, 1.22%)	31.7 (4.38%)
Intercompartmental CL (Q) (L/h)[c,d]	0.0201 (0.0186 – 0.0570, 13.4%)	15.0 (Fixed)
Weight effect on CL and Q (allometric scaling)[b,c]	0.975 (0.902 – 1.04, 3.77%)	–
ADA titer on CL (fractional increase)[b]	0.0433 (0.0323 – 0.0499, 8.96%)	–
NAb on CL (fractional increase)[b]	0.464 (0.280 – 0.981, 10.9%)	–
Central Volume of Distribution (V_2) (L)[e]	2.19 (1.93 – 4.77, 11.4%)	68.6 (32.1%)
Peripheral Volume of Distribution (V_3) (L)[d,e]	3.89 (2.88 – 4.06, 4.60%)	15.0 (Fixed)
Weight effect on V_2 and V_3 (allometric scaling)[e]	0.614 (0.539 – 0.739, 7.62%)	–
F for RHAG and RHAJ[f]	0.575 (Fixed)	57.1 (Fixed)
F for RHAZ[f]	0.784 (Fixed)	57.1 (Fixed)
F for RHAP[f]	0.764 (Fixed)	57.1 (Fixed)
F for RHBE[f]	0.612 (Fixed)	57.1 (Fixed)
Increase in F for thigh injection site[g]	0.482 (0.32 – 0.65, 18.2%)	–
First order absorption rate constant (Ka) (h^{-1})[d]	0.00657 (0.00598 – 0.0162, 7.15%)	15.0 (Fixed)
Residual Error		
Proportional (%)	31.2% (1.00%)	

Abbreviations: ADA = anti-drug antibodies; BQL = below the quantifiable lower limit of the assay; CI = confidence interval; CL = clearance; CV= coefficient of variation calculated by: %CV = 100*SQRT(EXP(OMEGA(N))-1), where OMEGA(N) is the NONMEM output for the between-subject variability of the Nth parameter; F = bioavailability; IMP = importance sampling; NAb = neutralizing antibodies; PK = pharmacokinetic; RSE = relative standard error; SAEM = stochastic approximation expectation maximization.

a Model was concluded using first-order conditional estimation method with interaction (FOCEI) method with BQL samples excluded. Then the model was refitted by the SAEM method followed by IMP, where BQL samples were included. The parameters in the table reflect final results of the SAEM IMP algorithm.

b The table provides the population estimate. To obtain individual CL estimates, use the following equation: $CL_{individual}$ = CL*(bodyweight/89.9)$^{0.975}$*(1+0.0433*LOG(ADA titer))*(1+0.464*NAb), where NAb is 0 for negative/inconclusive NAb result and 1 for positive NAb result.

c $Q_{individual}$ = Q * (bodyweight/89.9)$^{0.975}$

d Variability fixed to 15% to optimize efficiency of SAEM algorithm (Nonlinear Mixed Effects Modeling Program [NONMEM] 7.3.0 user guide).

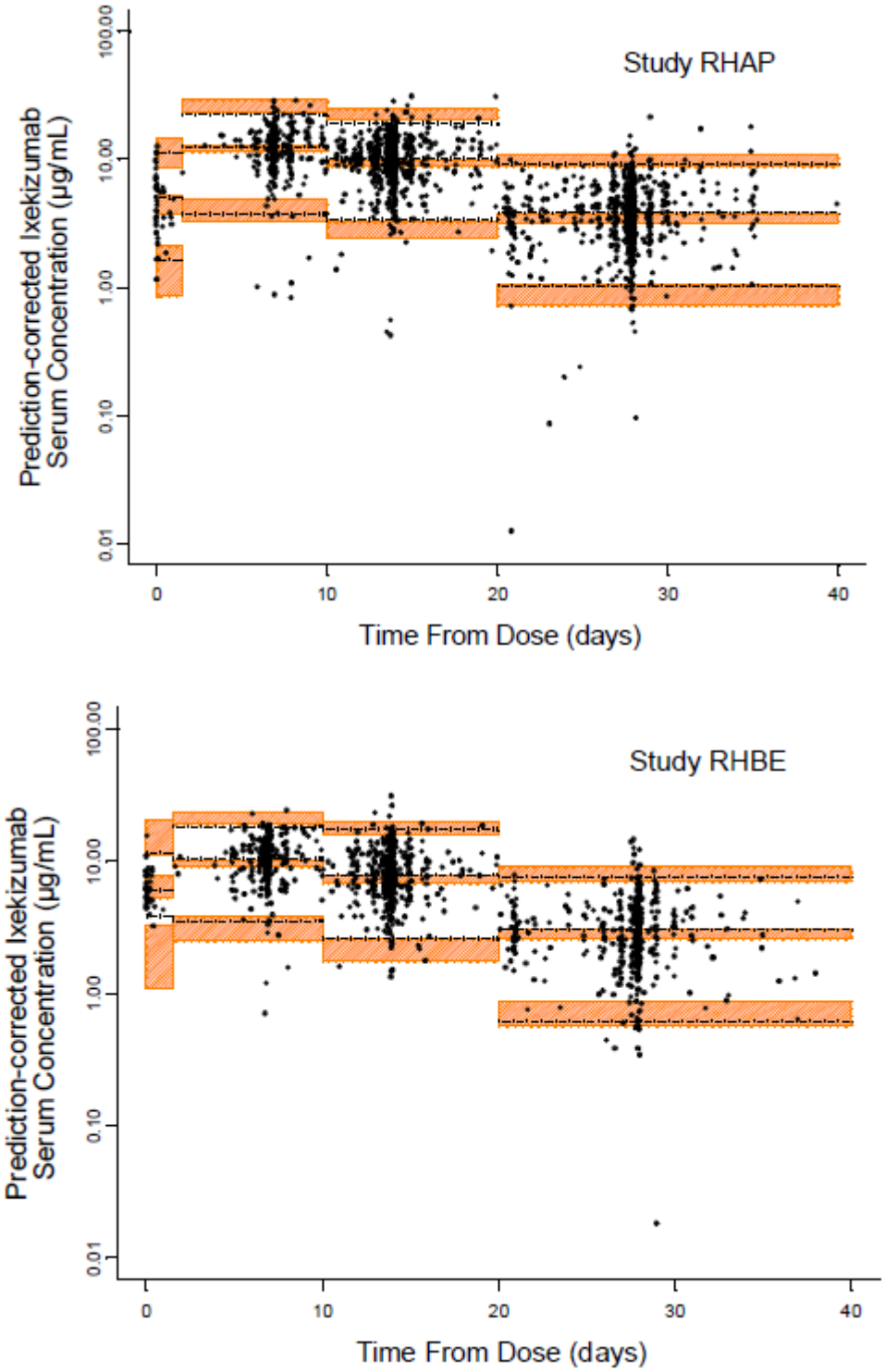
e $V_{2,individual}$ = V_2 * (bodyweight/89.9)$^{0.614}$, $V_{3,individual}$ = V_3 * (bodyweight/89.9)$^{0.614}$

f Estimate fixed to that from the FOCEI model where BQL data were not included. The 95% CI of F is 0.496 – 0.662 for Studies RHAG and RHAJ, 0.673 – 0.886 for Study RHAZ, 0.660 – 0.887 for Study RHAP, and 0.532 – 0.710 for Study RHBE.

g Estimate is on the logit parameter for F. This translates to an increase in F for the thigh injection site from 0.575 to 0.686 for Studies RHAG and RHAJ, from 0.784 to 0.855 for Study RHAZ, from 0.764 to 0.840 for Study RHAP, and from 0.612 to 0.719 for Study RHBE.

h The CI was estimated by bootstrap.

Figure 1 **Visual predictive check for final population pharmacokinetics model versus Study RHAP (top panel) and Study RHBE (lower panel) data.**



Both panels show prediction-corrected ixekizumab concentration versus time from the last dose. The black dots are observations. The dashed lines represent the observed median, 5th, and 95th percentiles, while orange shaded

areas represent simulated 95% confidence interval (CI) of the same. For clarity, the plots were truncated to Day 40, although there were few observations available after Day 40.

The majority of PK parameters estimated in the combined PsA/psoriasis PK model were similar to the psoriasis model indicating the consistency of PK between patients with PsA and psoriasis. Additionally, disease status (PsA versus psoriasis) was not significant when evaluated as an additional covariate. In addition, key PK parameters for patients with psoriasis and for patients with PsA from the respective models are summarized in Table 5 showing consistency between the 2 populations.

Table 5 Comparison of Model-Estimated Ixekizumab Pharmacokinetic Parameters Between Patients with Psoriatic Arthritis and Patients with Psoriasis

PK Parameter	Psoriasis PK Analysis[a]	PsA PK Analysis[b]
CL (L/hr)	0.0161 (37%)	0.0147 (33%)
V_{ss} (L)	7.11 (29%)	6.02 (18%)
$t_{1/2}$ (days)	13 (40%)	12 (32%)
%F (range)	60 to 90	61 to 84[c]

Abbreviations: CL = systemic clearance; F = bioavailability; PK = pharmacokinetics; PsA = psoriatic arthritis; $t_{1/2}$ = half-life, V_{ss} = volume of distribution at steady state

[a] Parameters estimated with data from 3 psoriasis studies (Population PK RHAG/RHAJ/RHAZ) for analysis (reported in the psoriasis submission). Data reported are Geometric mean (CV%).

[b] The data from the 2 PsA studies (RHAP and RHBE) were combined with data from 3 psoriasis studies (RHAG, RHAJ, and RHAZ) for analysis; parameters were calculated and summarized using post hoc values from patients in the 2 PsA studies. Data reported are Geometric mean (CV%).

[c] This includes the effect of site of injection on bioavailability. Population estimates from the model for subcutaneous injections via areas other than thigh were 61.2% for Study RHBE and 76.4% for Study RHAP.

The magnitude of the increase in CL due to being NAb positive was smaller in the current combined PsA/psoriasis PK analysis compared with the prior psoriasis only analysis due to the implementation of the new disease-specific cut point assay for determining NAb status.

The additional significant covariates included in the combined PsA/psoriasis PK model are shown below. The magnitudes of these effects on PK are comparable between the current combined PsA/psoriasis PK analysis and the original psoriasis analysis in the submission and are therefore not described further. None of these factors impacted the dosing regimen recommendations.

- Body weight: On parameters reflecting clearance (CL, Q) and volume (V2, V3), best described using an allometric relationship, showing that as body weight increases, both CL and V terms increase.
- Injection site: SC injection via the thigh resulted in higher bioavailability (F) compared with the other areas of the body (arm, abdomen, or buttock).
- Immunogenicity: Increasing anti-drug antibody (ADA) titer was associated with an increase in CL.

Overall, the present analysis suggests that ixekizumab PK are similar between patients with PsA and patients with psoriasis. Concomitant use of MTX or recent prior use of MTX or adalimumab does not change ixekizumab PK.

To further explore the impact of immunogenicity on CL in patients with PsA, the final population PK model, was modified such that the impact of ADA titre on CL was split (i.e., described by 2 parameters), 1 for patients with psoriasis and the other for patients with PsA. Similarly, 2 parameters were used to describe the impact of NAb on CL for patients with psoriasis and for patients with PsA, respectively. It was found that the CL–titre relationship in patients with PsA was still significant. However, the CL–NAb relationship was no longer significant for patients with PsA, likely due to the small number of NAb-positive samples in patients with PsA from the current studies.

2.3.4. PK/PD modelling

Relationships between Exposure and Efficacy

The exposure-response analyses were performed using the PsA dataset only (Studies RHAP and RHBE). Observed ACR20/50/70 response data at Week 24 and observed time-matched drug concentrations were used to develop the ACR static model. Observed PASI 50/75/90/100 response data at Week 12 and observed time-matched drug concentrations were used to develop the PASI static model. Observed ACR20/50/70 responses up to and including Week 24 data and model-predicted PK parameters based on available ixekizumab concentration data through Week 24 were used to develop the ACR time course model.

ACR Week 24 Static Model

The ACR static model was conducted based on observed ACR responses and time-matched ixekizumab serum concentrations at Week 24. The dataset includes 279 patients from Study RHAP and 310 patients from Study RHBE who were randomized to receive 1 of the 2 ixekizumab regimens or placebo, observed data is summarised in Table 6.

Table 6 **Observed Percentage of Patients Achieving Week 24 ACR Percent Improvements in Study RHAP and Study RHBE Based on the Exposure Response Analysis Dataset**

		N Responders/ Total N (%)		
	Week 24 ACR Response Rate	**Placebo**	**Q4W dosing**	**Q2W dosing**
Study RHAP	ACR20	32/91 (35.2)	62/98 (63.3)	65/97 (67.0)
	ACR50	16/91 (17.6)	43/98 (43.9)	48/97 (49.5)
	ACR70	6/91 (6.59)	25/98 (25.5)	35/97 (36.1)
Study RHBE	ACR20	36/97 (37.1)	68/112 (60.7)	62/108 (57.4)
	ACR50	13/97 (13.4)	43/112 (38.4)	41/108 (38.0)
	ACR70	2/97 (2.06)	27/112 (24.1)	15/108 (13.9)
Combined	ACR20	68/188 (36.2)	130/210 (61.9)	127/205 (62.0)
	ACR50	29/188 (15.4)	86/210 (41.0)	89/205 (43.4)
	ACR70	8/188 (4.26)	52/210 (24.8)	50/205 (24.4)

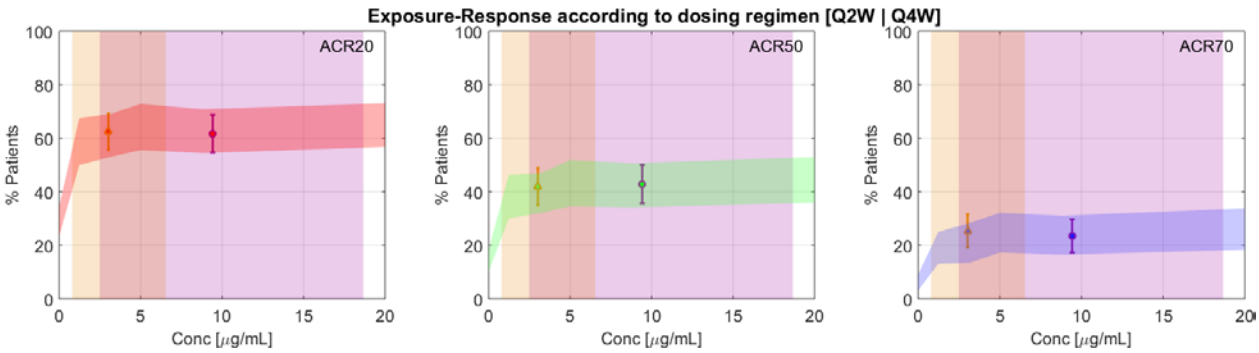
Abbreviations: ACR = American College of Rheumatology Responder Index; N = number of patients; Q2W = every 2 weeks; Q4W = every 4 weeks.

Data included in this table were from patients who had Week 24 ACR measurements. Among them 14 patients treated with ixekizumab did not have drug concentration records at Week 24 and were excluded from the ACR static model analysis.

Non-responder imputation (NRI) was conducted for placebo patients who were assessed to be inadequate responders (placebo-IR) and received ixekizumab treatment prior to Week 24, where their Week 24 ACR scores were set to represent not achieving ACR20 and their drug concentration values were set to 0. An ordered categorical model well described the exposure-response relationship of ACR20, ACR50, and ACR70 response rates simultaneously. Age and sex were found to be significant covariates on drug effect. Briefly, males tended to have higher response rates than females. For patients aged 55 years or older, ACR response rates were similar irrespective of age. For patients aged 55 or younger, ACR response rates tended to increase with decreasing age. Many additional covariates were tested (for example, body weight, immunogenicity, prior failure on anti-tumor necrosis factor [anti-TNF] treatment, concomitant MTX, and prior MTX treatment) but were not found to be significant and thus do not impact ACR responses. The final parameter estimates from the static ACR model are summarised below:

Figure 2 illustrates model-predicted ACR20/50/70 response rates over the concentration range observed following Q2W and Q4W dosing, which were overlaid with observed median ixekizumab concentrations and corresponding ACR response rates at Week 24 for each dosing regimen. Results indicated that rates of response are similar across dosing regimens despite the higher range of exposure achieved with the Q2W regimen.

Figure 2 **Observed (symbol) and predicted (horizontal color band) exposure response profile of ixekizumab showing the impact of dosing regimen on Week 24 ACR response rates.**



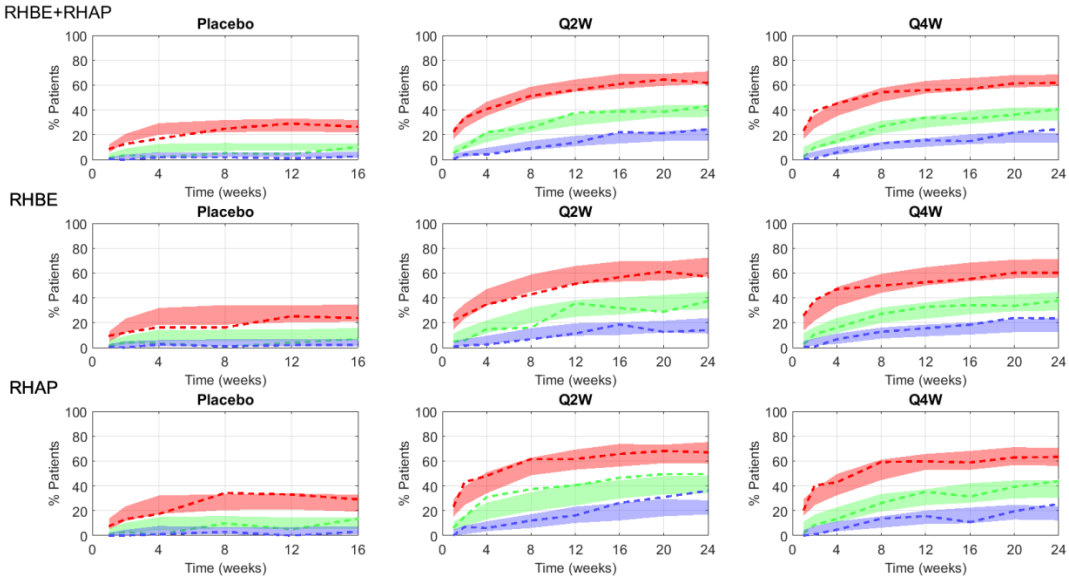
Abbreviations: CI = confidence interval; Q2W = every 2 weeks; Q4W = every 4 weeks; ACR = American College of Rheumatology Responder Index.

- The color shaded curve corresponds to the 90% predicted interval for ACR20 (red), ACR50 (green), and ACR70 (blue) based on the model simulations.
- The purple shaded area shows the range (5^{th} to 95^{th} percentile) of observed concentrations for Q2W dosing, part of which overlaps with the Q4W observed concentrations (overlap in exposures is indicated by the darker shaded area in the middle) at Week 24.
- The orange shaded area is the range (5^{th} to 95^{th} percentile) of observed concentrations for Q4W dosing, part of which overlaps with the Q2W observed concentrations (overlap in exposures is indicated by the darker shaded area in the middle).
- The triangles and circles are the observed percentage of patients achieving ACR20 (left), ACR50 (center) and ACR70 (right) response in Q4W and Q2W regimens, respectively, based on pooled Study RHAP and Study RHBE data from patients randomized to receive ixekizumab from the start of the studies, with the error bars representing the 95% confidence interval of the observed percentage response.
- The position of the observed data points and error bars on the x-axis occurs at the median observed exposure for the corresponding dosing regimen group.

ACR Time Course Model

A time course model was also developed to evaluate the exposure-response relationship for ACR scores over time, up to Week 24 (VPC plots shown in Figure 3). Covariate analysis was restricted to the 2 significant covariates (that is, age and sex) identified in the ACR static model in addition to prior experience with anti-TNF therapy, which differentiates the patient population between Studies RHAP (biologic disease-modifying anti-rheumatic drugs [bDMARDs]-naive) and RHBE (bDMARDs-experienced). Like the ACR static model, age and sex were identified as significant covariates on drug effect, whereas prior experience with anti-TNF therapy was not identified as a significant covariate in the ACR time course model.

Figure 3 **Visual predictive check of the final population ixekizumab exposure-response time course model for ACR20/50/70 in PsA patients.**

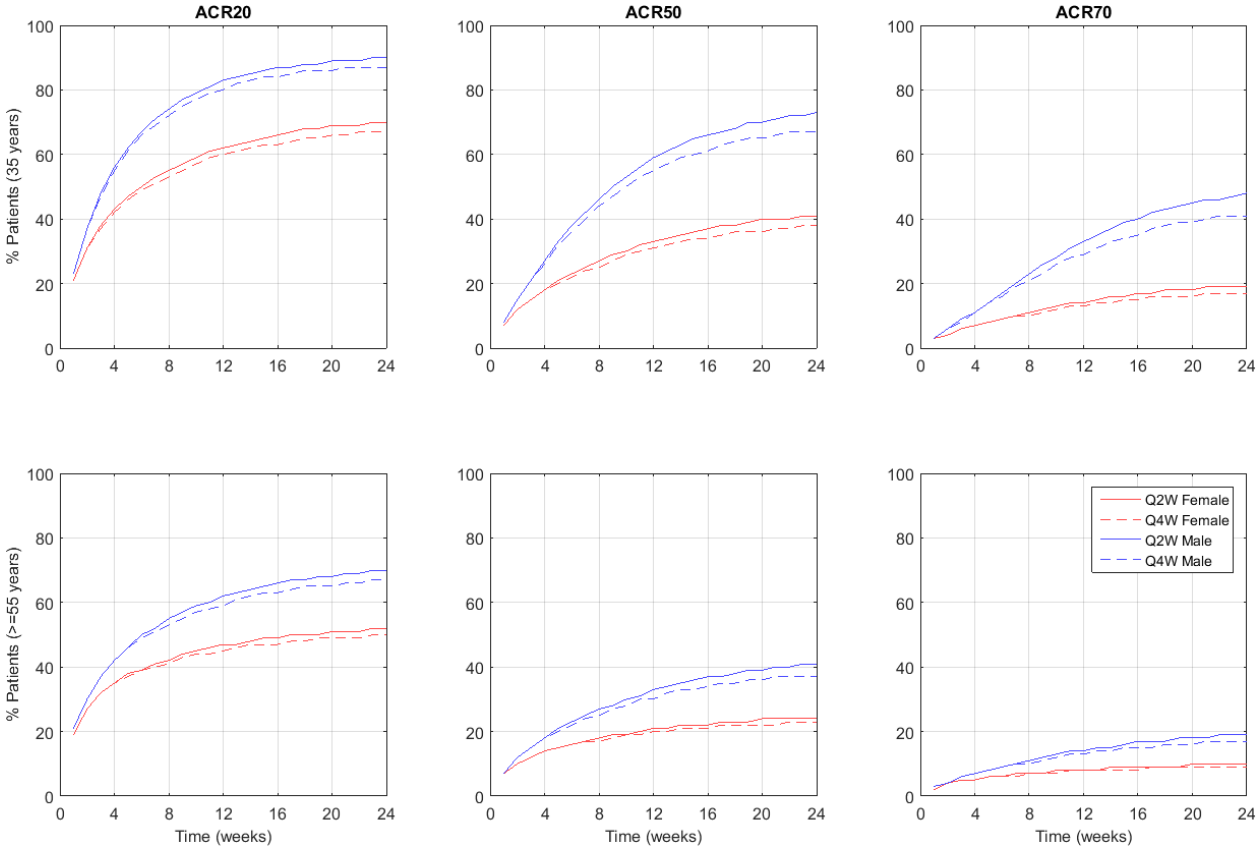


Abbreviations: ACR = American College of Rheumatology Responder Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

Dashed lines represent the observed percentage of patients achieving ACR20 (red), ACR50 (green), and ACR70 (blue) along time (weeks) for placebo patients (left), ixekizumab Q2W patients (center), and ixekizumab Q4W patients (right), respectively, through Week 24. Since placebo inadequate responder (IR) patients started to receive ixekizumab treatment at Week 16, the ACR response vs. time curves for placebo patients were plotted up to Week 16. The shaded area is the 90% confidence interval (CI) of the model prediction. Visual predictive check (VPC) for Studies RHAP and RHBE combined is shown in the first row, for Study RHBE in the second row, and for Study RHAP in the last row.

The ACR time course model was used to simulate scenarios that address multiple factors simultaneously, including differences in age, sex, and dosing regimen (Figure 4). The model does not account for any dropouts, so simulated results may appear somewhat higher than observed NRI results. Based on the model, both dosing regimens are predicted to result in similar rates of responses that plateau after approximately 16 weeks of treatment within the age and sex subgroups. The simulations indicate that younger males had a higher response rate compared with older females; however, there appeared to be no additional benefit on response predicted with the higher exposures associated with the Q2W dosing regimen relative to the Q4W dosing regimen in each of the age and sex subgroups, suggesting that increasing the dosing frequency from Q4W to Q2W would not be expected to offer additional efficacy based on ACR response that would be considered clinically meaningful in patients with active PsA.

Figure 4 **Effect of age, sex, and treatment regimens on ACR20, ACR50, and ACR70 response rates in female and male patients.**



Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% response rates; Q2W = every 2 weeks; Q4W = every 4 weeks.

Notes: ACR time course model was used to simulate the ACR response rates in male or female patients at age 35 or at and beyond 55 years old, using typical values of parameter estimates in the ACR model. The ixekizumab concentrations that drive the ACR responses were simulated with typical values of the final population pharmacokinetics (PK) model, assuming median body weight of Studies RHAP and RHBE (approximately 85 kg), subcutaneous injection via body areas other than thigh, and no development of anti-drug antibodies during treatment.

Solid lines represent Q2W treatment and dashed lines Q4W. Red color represents the response for females and blue for males. Column 1 = ACR20; Column 2 = ACR50; Column 3 = ACR70. Top row = % Patients (35 years): 35 years was the median of the lower tertile of the age in RHAP and RHBE patients. Second row = % Patients (≥55 years): 55 years was the median age of the RHAP and RHBE patients.

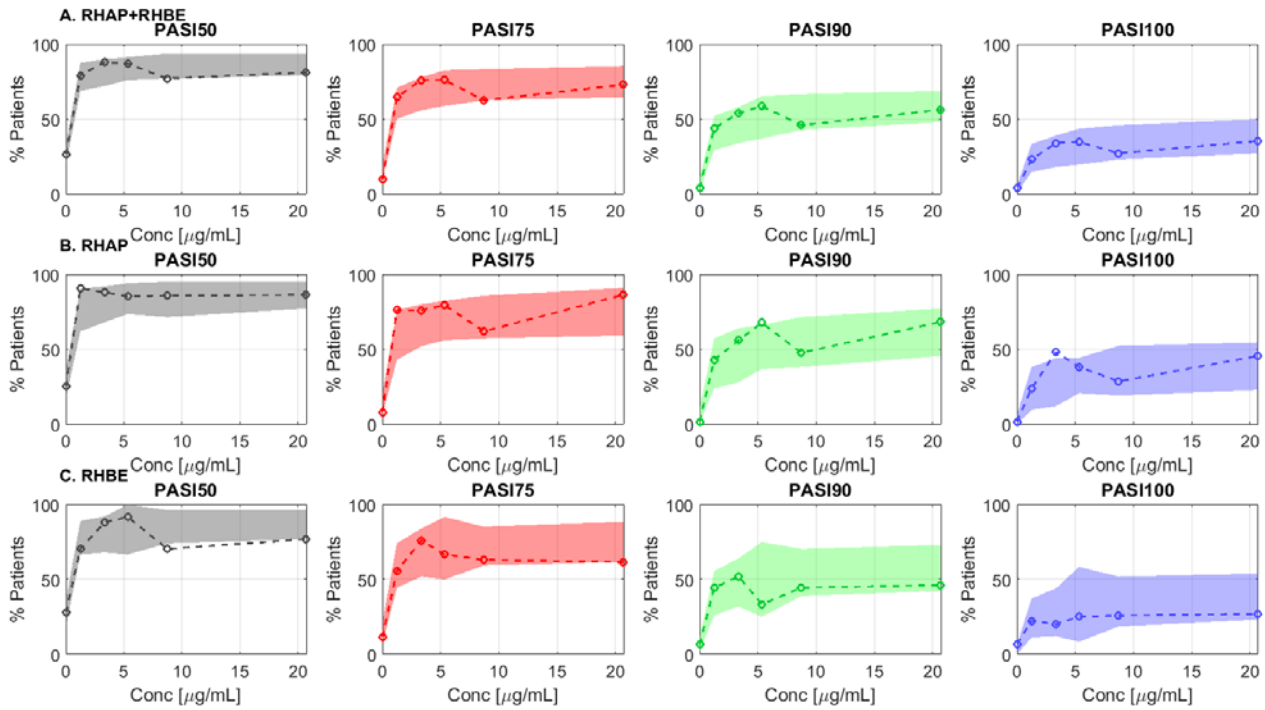
PASI Week 12 Static Model

Analyses with the PASI static model were conducted based on observed PASI responses (in patients from RHAP and RHBE with BSA ≥ 3% at baseline) and time-matched ixekizumab serum concentrations at Week 12. An ordered categorical model well described the exposure-response relationship for PASI 50, PASI 75, PASI 90, and PASI 100 response rates simultaneously (VPC plots shown in Figure 5). The factors evaluated as potential covariates were the same as those assessed in the ACR static model. No significant covariates were detected.

Figure 5 illustrates PsA PK model-predicted PASI 75/90/100 response rates over the concentration range observed following Q2W and Q4W dosing, which were overlaid with observed median ixekizumab

concentrations and corresponding PASI response rates at Week 12 for each dosing regimen. Overall, the Q2W regimen was associated with a higher predicted percentage response rate compared with the Q4W dosing regimen, especially for PASI 90 and PASI 100 responses. The higher range of observed concentrations for patients in the Q2W dosing regimen group (the purple-shaded areas) ensured the majority of patients were on the plateau of the exposure-response curve and thus were likely to achieve a response. This is compared with the Q4W dosing regimen group where the range of exposures (the orange-shaded areas) was lower and encompassed the slope of the curve resulting in fewer patients predicted to achieve a response.

Figure 5 Visual predictive check of Week 12 PASI final model.



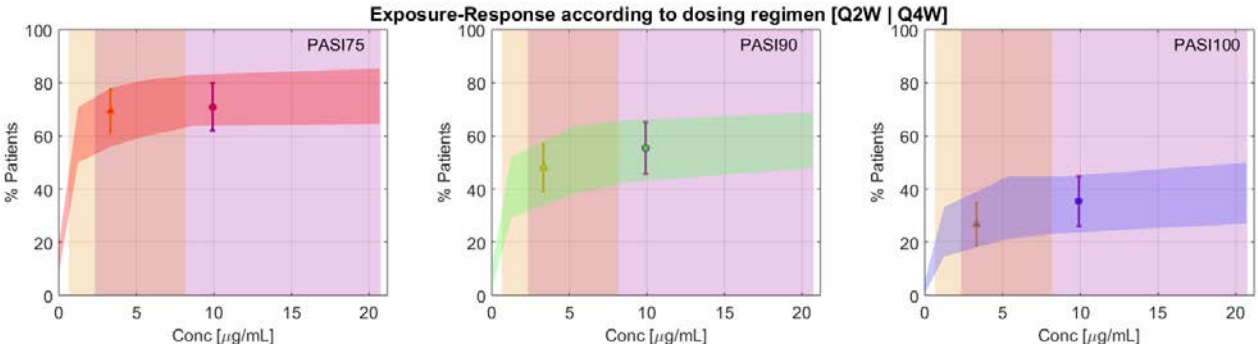
Abbreviations: Conc = concentration; PASI = Psoriasis Area and Severity Index.

The circles with dashed lines represent the observed percentage of patients with the relevant percentage of PASI improvement in each quartile of the Week 12 observed trough concentration or for placebo. The first point corresponds to the concentration of 0 representing observed response rate in placebo patients. The shaded area is the 95% confidence interval of the model prediction.

A. Visual predictive check (VPC) for Studies RHAP and RHBE studies combined; B. VPC for Study RHAP only; C. VPC for Study RHBE only.

Columns from left to right correspond to PASI 50 (grey), PASI 75 (red), PASI 90 (green), and PASI 100 (blue), respectively.

Figure 6 **Observed (symbol) and predicted (horizontal color band) exposure-response profile of ixekizumab showing the impact of dosing regimen on Week 12 PASI response rates.**



Abbreviations: Conc = concentration; Q2W = every 2 weeks; Q4W = every 4 weeks; PASI = Psoriasis Area and Severity Index.

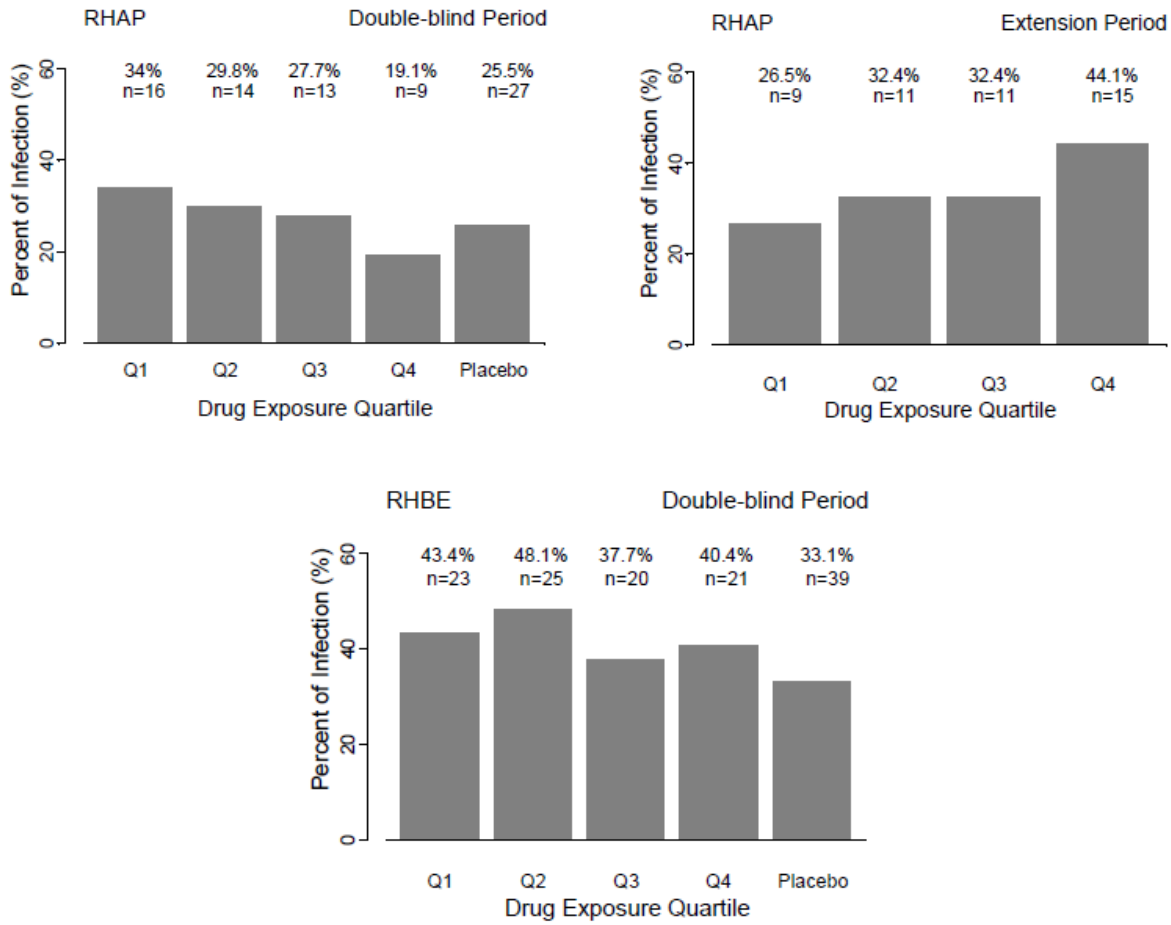
- The color shaded curve corresponds to the 90% predicted interval for PASI 75 (red), PASI 90 (green), and PASI 100 (blue) based on the model simulations.
- The purple-shaded area shows the range (5th to 95th percentile) of observed concentrations for Q2W dosing, part of which overlaps with the Q4W observed concentrations (overlap in exposures is indicated by the darker shaded area in the middle) at Week 12.
- The orange-shaded area is the range (5th to 95th percentile) of observed concentrations for Q4W dosing, part of which overlaps with the Q2W observed concentrations (overlap in exposures is indicated by the darker shaded area in the middle).
- The triangles and circles are the observed percentage of patients achieving PASI 75 (left), PASI 90 (center), and PASI 100 (right) response following Q4W and Q2W regimens, respectively, based on pooled Study RHAP and Study RHBE data from patients (with baseline psoriasis lesion involving ≥3% of the body surface area) who were randomized to receive ixekizumab from the start of the studies, with the error bars representing the 95% confidence interval of the observed percentage response.
- The position of the observed data points and error bars on the x-axis occurs at the median observed exposure for the corresponding dosing regimen group.

Relationships between Exposure and Safety

Ixekizumab serum concentrations used in the present analyses were observed trough concentrations (Ctrough) at Week 24 from patients who participated in the Double-Blind Treatment Period up to Week 24 (Studies RHAP and RHBE) and the observed Ctrough at Week 52 for those who participated in the Extension Period from Weeks 24 to 52 (Study RHAP). Placebo data were included in the comparison of the Double-Blind Treatment Period up to Week 24. Treatment-emergent adverse events evaluated were all infections and, specifically, infections due to Candida or staphylococcal and infection-related serious adverse events (SAEs), injection site reactions, hypersensitivity reactions, Crohn's disease, major adverse cerebrocardiovascular events (MACE), and neutropenia Grade 2 or higher.

When applicable, these TEAEs were summarized for each exposure quartile and evaluated visually for a trend of exposure-safety relationship. No apparent relationship to exposure was observed for all infections within the exposure range following the Q2W and Q4W regimen (Figure 7).

Figure 7 **Summary of infections by trough concentration quartile at Week 24 (for Double-Blind Period) and Week 52 (for Extension Period).**

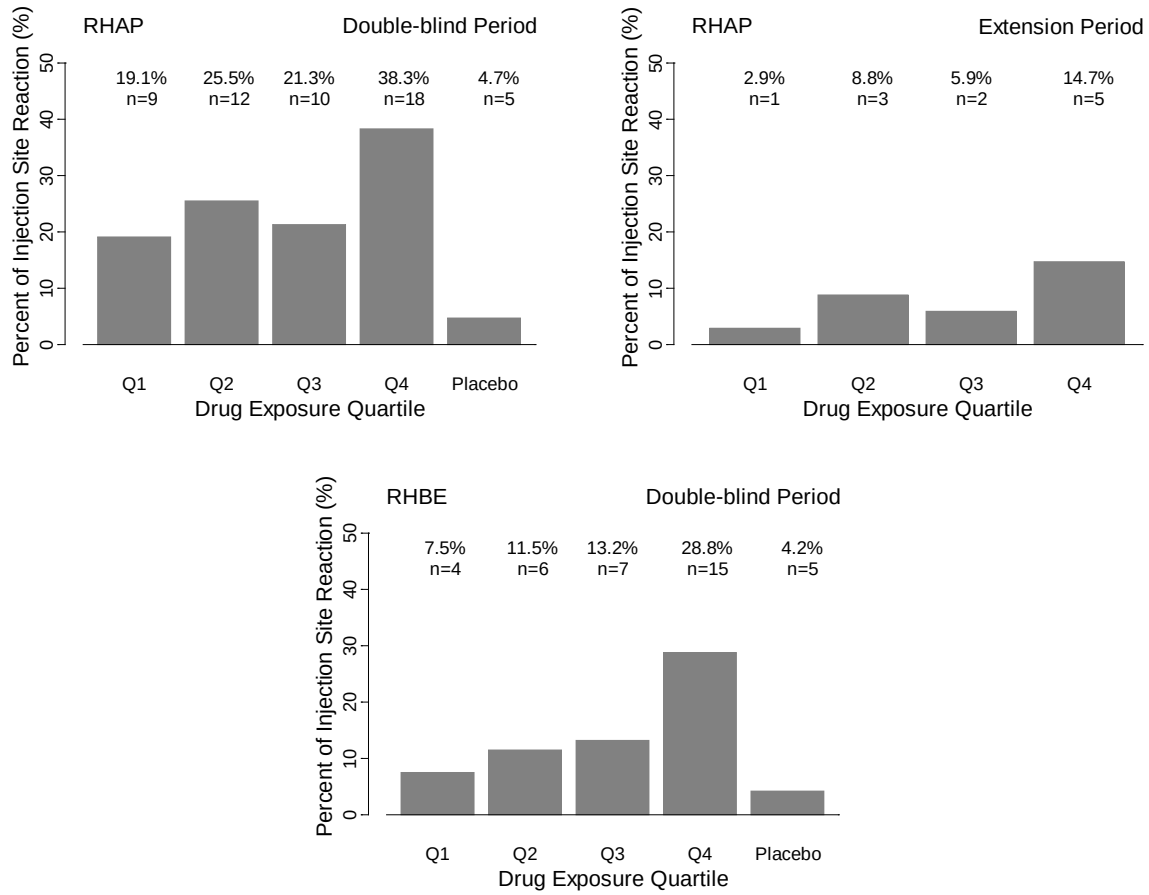


Abbreviations: n = number of patients who experienced that adverse event.
Study RHAP double-blind period: Q1: ≤ 3.39 µg/mL, Q2: 3.39 – 5.31 µg/mL, Q3: 5.31 – 10.2 µg/mL; Q4: > 10.2 µg/mL
Study RHAP extension period: Q1: ≤ 3.70 µg/mL, Q2: 3.70 – 5.85 µg/mL, Q3:5.85 - 10.8 µg/mL; Q4: > 10.8 µg/mL
Study RHBE double-blind period: Q1: ≤ 2.31 µg/mL, Q2: 2.31 – 4.61 µg/mL, Q3: 4.61 – 9.05 µg/mL; Q4: > 9.05 µg/mL

Exposure-response relationship was observed for injection site reactions only (Figure 8), in both the Double-Blind Treatment Period (up to Week 24) and the Extension Period (Weeks 24 through 52). Of note, the exposure-response relationship correlates the drug concentration in the blood circulation to the response of interest. When it is applied to injection site reactions, caution should be taken to interpret the finding because, if this is primarily due to a local reaction then an alternative relationship may exist between the number of SC injections with ixekizumab and the incidence rate. Per study protocols, patients under Q2W regimen should receive twice as many ixekizumab injections as those under Q4W regimen, and consequently will have higher drug concentrations in systemic circulation. In Figure 8, all patients reporting injection site reactions in the 4th drug concentration quartiles were treated with the Q2W regimen.

The exposure-response relationship for injection site reactions was similar between the PsA studies and the psoriasis studies as shown in the psoriasis submission.

Figure 8 **Summary of injection site reaction incidences by trough concentration quartile at Week 24 (for Double-Blind Period, RHAP and RHBE) and Week 52 (for Extension Period, RHAP).**



Abbreviations: n = number of patients who reported an adverse event; Q = quartile.
Study RHAP Double-Blind Period: Q1: ≤3.39 µg/mL, Q2: 3.39 – 5.31 µg/mL, Q3: 5.31 – 10.2 µg/mL, Q4: >10.2 µg/mL.
Study RHAP Extension Period: Q1: ≤3.70 µg/mL, Q2: 3.70 – 5.85 µg/mL, Q3: 5.85 – 10.8 µg/mL, Q4: >10.8 µg/mL.
Study RHBE Double-Blind Period: Q1: ≤2.31 µg/mL, Q2: 2.31 – 4.61 µg/mL, Q3: 4.61 – 9.05 µg/mL, Q4: >9.05 µg/mL.

2.3.5. Discussion on clinical pharmacology

Standard methods and software have been used in the development and evaluation of the population PK models. The goodness-of-fit graphs and visual predictive checks indicate that the population PK model fit adequately to the data. The level of detail of the visual predictive checks could have benefited from increased binning and representation on normal scale; however it is not expected to influence the overall conclusion on PK.

Body weight, ADAs and neutralizing antibodies were included as significant covariates on ixekizumab PK. The parameter estimates for the allometric scaling exponents are not in line with the theoretical values of 0.75 (CL) and 1 (V), although due to the indicated adequacy of the model the further investigation is not sought for. Graphical presentation of the body weight influence on PK display that a 120 kg patient receive approximately 2-fold decrease in plasma concentration compared to a 60 kg patient. Furthermore, simulations of the exposure-ACR relationship display that the difference in

exposure does not translate into differences in ACR response. Thus, dose adjustment for heavy weight patients is not required.

Based on the population estimates, an ADA in the moderate titer range (1:≥ 160 and 1:<1280) was associated with an increase in CL of approximately 20% to 30% and being NAb positive was associated with an increase in CL of 46% compared to in ADA negative patients. It is pointed out, however, that the combined PsA/psoriasis PK dataset is largely represented by the psoriasis population, where a higher number of NAb positive samples were associated with higher ADA titers compared to the PsA population. The effect of antibodies in patients with PsA has been determined. However there is insufficient data to inform on the effect of neutralising antibodies in PsA patients.

The population PK analysis indicate that the pharmacokinetics of ixekizumab is similar between PsA and psoriasis patients. Body weight, site of injection, study and immunogenicity were included as covariates on ixekizumab PK and were not deemed to warrant any dose adjustments. There were no apparent differences in CL after Q2W or Q4W treatment. Further, there was no significant effect of concomitant or prior recent use methotrexate or adalimumab on ixekizumab PK.

Exposure efficacy analysis

Adequate methods and software have been used in the development and evaluation of exposure-response relationships. The logistic regression models were used for the two static models and a latent variable response model was used for the ACR Time Course model.

At the lower exposure range (<2.5 µg/ml) it is indicated, across all exposure-response analyses, that there is somewhat lower effect and it seems as these concentrations are measured given a q4w dosing regimen. Although for a majority of the exposure range the maximum effect is reached which speaks in favour of the less frequent Q4W dosing regimen. Sex and age were identified as significant covariates for the effect. However, due to the flat exposure-response relationship there is no strong indication that a dose adjustment is warranted for females and elderly patients.

The ACR time course model indicates a similar response over time, up to 24 weeks, between the Q2W and Q4W regimen, and the model predictions does not indicate a faster response onset with a more frequent dosing (i.e. Q2W dosing).

The static PASI model was used to determine the exposure-response relationship at week 12. The response for PASI 75 seems to be close to maximum effect for the entire exposure range, for PASI 90 and PASI 100 exposure-response relationship was somewhat more pronounced and there was a tendency that the effect was slightly higher for concentrations given a Q2W dosing regimen.

Exposure-Safety analysis

A graphical analysis was performed for infections and injection site reactions versus ixekizumab exposure quartiles. The graphical analysis is deemed adequate although quartiles of exposure are a quite blunt grouping of the exposure range, it is not anticipated that a more detailed graphical display would reveal any hidden relationships. Further, all patients reporting injection site reactions in the 4th drug concentration quartiles were treated with the Q2W regimen. No overall exposure-infection relationship was detected, although a slight increase in infections versus exposure was apparent in the extension period of the RHAP study.

2.3.6. Conclusions on clinical pharmacology

The population PK analysis indicate that ixekizumab PK is similar in patients with psoriatic arthritis and moderate to severe psoriasis.

Overall, the established exposure-efficacy relationships for all investigated endpoints indicate that the maximum effect is reached for a majority of the studied exposure range. No significant difference was detected in response onset between Q2W and Q4W dosing regimen.

No overall exposure-infection relationship was detected, although a slight increase in infections versus exposure was apparent in the extension period of the RHAP study.

2.4. Clinical aspects

Introduction

The efficacy and safety of ixekizumab in PsA were assessed in 2 pivotal, randomised, double-blind, placebo-controlled, Phase III studies (RHAP and RHBE, Table 7); the placebo-controlled, double-blind treatment periods were 24 weeks in length. Each study included separate patient populations to address the efficacy and safety profile in bDMARD-naive patients (RHAP) and bDMARD-experienced patients (RHBE). The ixekizumab clinical development programme for PsA was informed by scientific advice from the Committee for Medicinal Products for Human Use (EMA/CHMP/SAWP/339078/2011) and the CHMP 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis 2007'.

Table 7 Summary of the Pivotal Phase III Trials Supporting the Psoriatic Arthritis Indication

Study	Description	N	Treatment	Primary Endpoint
I1F-MC-**RHAP**	Efficacy and safety in **bDMARD-naive** patients.	417	Ixekizumab: 160 mg at Week 0, then 80 mg Q2W or Q4W until Week 156. Placebo [a,b]: Q2W until Week 24. Adalimumab [c,d]: 40 mg Q2W until Week 24.	ACR20 at Week 24
I1F-MC-**RHBE**	Efficacy and safety in **bDMARD-experienced** patients.	363	Ixekizumab: 160 mg at Week 0, then 80 mg Q2W or Q4W until Week 156. Placebo [a,b]: Q2W until Week 24.	ACR20 at Week 24

Abbreviations: ACR20 = American College of Rheumatology 20% response rate; bDMARD = biologic disease-modifying antirheumatic drug; IR = inadequate responder (patient with <20% improvement from baseline in both tender joint count and swollen joint count at Week 16); N = number of patients in efficacy analysis (intent-to-treat population); Q2W = every 2 weeks; Q4W = every 4 weeks.

a Placebo IRs at Week 16 were re-randomised 1:1 to receive either ixekizumab 80 mg Q2W or Q4W dosing regimens, with a starting dose of 160 mg, beginning at Week 16.

b Placebo responders or nonresponders at Week 24 were re-randomised 1:1 to receive either ixekizumab 80 mg Q2W or Q4W dosing regimens, with a starting dose of 160 mg, beginning at Week 24.

c Adalimumab IRs at Week 16 were re-randomised 1:1 to receive either ixekizumab 80 mg Q2W or Q4W dosing regimens starting at Week 24, following an 8-week placebo washout period.

d Adalimumab responders or nonresponders at Week 24 were re-randomised 1:1 to receive either ixekizumab 80 mg Q2W or Q4W dosing regimens starting at Week 32, following an 8-week placebo washout period.

In line with CHMP scientific advice, RHAP (bDMARD-naive population) also included an adalimumab reference arm. The study was designed to evaluate the efficacy response of 2 separate dosing regimens of ixekizumab as compared to placebo in patients with PsA. Both studies included

assessment of long-term efficacy through Week 52. This application includes data up to Week 52 for RHAP. The extension period of RHBE is ongoing, and the Week 52 data are anticipated to become available in August 2017.
In addition to RHAP and RHBE, a third ongoing Phase III study I1F-MC-RHBF (RHBF) was designed to address CHMP scientific advice recommendation of employing a randomised-withdrawal design to further evaluate maintenance of efficacy. RHBF is a Phase III, multicentre study with a 36-week, initial, open-label treatment period, examining the effect of ixekizumab 80 mg every 2 weeks (Q2W) in patients with active PsA who are inadequate responders (IRs) to cDMARDs and are bDMARD-naive, followed by a randomised, double-blind withdrawal period from Week 36 to Week 104, examining the effect of ixekizumab 80 mg Q2W compared to placebo. The primary objective of the study is to compare ixekizumab 80 mg Q2W with placebo in the maintenance of treatment response, as measured by the time to relapse during the randomised, double-blind withdrawal period.

2.4.1. Dose response studies

The dosing regimens selected for the pivotal Phase III studies in PsA were based on the following:

- Dose-ranging data from bDMARD-naive and bDMARD-IR populations in I1F-MC-RHAK (RHAK) (Phase II rheumatoid arthritis [RA] study)
- Dose-ranging data from I1F-MC-RHAJ (RHAJ) (Phase II psoriasis study)
- Final dosing regimen selection for the pivotal Phase III studies in patients with moderate-to-severe plaque psoriasis.

The ixekizumab dosing regimens (80 mg Q2W and 80 mg Q4W) for the pivotal Phase III studies in PsA were designed to provide an assessment of the clinical safety and efficacy, as well as the associated benefit-risk profile in patients with PsA. A 160 mg starting dose was included for earlier attainment of steady-state concentrations and to allow a rapid onset of response. This starting dose was similar to the initial doses in the Phase II studies in RA (RHAK) and psoriasis (RHAJ) which showed early onset of ACR20 and at least a 75% improvement in Psoriasis Area and Severity Index score from baseline (PASI 75), respectively.

In CHMP scientific advice, CHMP was concerned on entering Phase III with dosing regimens that had not been evaluated in the target patient population. However, CHMP deemed it acceptable to extrapolate dose findings in RA and psoriasis to PsA, which is the approach that the MAH took.

2.4.2. Main studies

2.4.2.1. Introduction

The application for Taltz in psoriatic arthritis is supported by two pivotal phase III studies. Study RHAP is a Phase III, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient study in patients with active PsA who are bDMARD-naive. Study RHBE is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study in patients with active PsA who are cDMARD- and bDMARD-experienced and either inadequate responders (have discontinued at least 1 TNFi due to either an inadequate response [based on a minimum of 12 weeks on therapy]), or intolerant to, a TNFi.

Patients enrolled in the pivotal Phase III trials fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR); had active PsA, defined as the presence of at least 3/68 tender and at least 3/66 swollen joints; and had active psoriatic skin lesions or a documented personal history of plaque psoriasis.

Since RHAP evaluated radiographic joint damage, patients were required to have at screening either ≥1 disease-related hand or foot joint erosion on centrally read x-rays or C-reactive protein (CRP) >6 mg/L to further ensure a patient population with active PsA, include ng those with underlying erosive disease and a propensity for radiographic progression. RHAP enrolled patients who were naive to bDMARDs, regardless of past or present cDMARD use. Patients were then randomised in 1:1:1:1 ratio to placebo, adalimumab, ixekizumab 80 mg Q4W, or ixekizumab 80 mg Q2W. Randomisation was stratified by country and by prior/current/no use of cDMARDs. In line with CHMP scientific advice, RHAP included a separate analysis on the cDMARD-experienced population (past use or current use) to support the proposed indication for this application.

RHBE enrolled patients with prior treatment of ≥1 cDMARD and who had an inadequate response (lack of efficacy) to 1 or 2 TNFi or who were intolerant to a TNFi. Patients were randomised in 1:1:1 ratio to placebo, ixekizumab 80 mg Q4W, or ixekizumab 80 mg Q2W. Randomisation was stratified by country and TNFi experience; 56%, 35%, and 9% of patients had an inadequate response (lack of efficacy) to 1 TNFi, 2 TNFi, or were intolerant to TNFi, respectively. Consistent with CHMP scientific advice, both pivotal studies allowed concomitant background therapy (eg, MTX, corticosteroids), as long as the dose was stable prior to randomisation and remained unchanged during the Double-Blind Treatment Period. In RHAP and RHBE, 64% and 51%, respectively, were currently being treated with a cDMARD, of whom 85% and 81%, respectively, were receiving MTX.

The design of the studies is presented below.

Table 8 Design Features of Pivotal Phase III Studies RHAP and RHBE

Design Feature		RHAP N=417	RHBE N=363
Population	Medical history	• Active PsA of ≥6 months duration • Met CASPAR criteria • Active, or personal history of, plaque psoriasis	• Active PsA of ≥6 months duration • Met CASPAR criteria • Active, or personal history of, plaque psoriasis
	Previous treatment	• bDMARD-naive	• cDMARD and bDMARD-experienced • TNFi-experienced (non-responder or intolerance to a TNFi)a
	Treatment at entry	• Allowed stable doses of cDMARDs at entry	• Allowed stable doses of cDMARDs at entry
Disease Features		• ≥3/68 tender and ≥3/66 swollen joints; • ≥1 disease-related definite joint erosion on hand or foot radiographs OR CRP >6 mg/L at screening	• ≥3/68 tender and ≥3/66 swollen joints •
Stratification Factors		• Country • cDMARD experience (naive, past use, current use)	• Country • TNFi experience (inadequate response to 1 TNFi, inadequate response to 2 TNFi's, intolerance to a TNFi)
Treatment Administered	Double-Blind Treatment Period (Weeks 0-24)[a]	• Placebo, Q2W[b] • Adalimumab, 40 mg Q2W[c] • Ixekizumab, 80 mg Q2W[d] • Ixekizumab, 80 mg Q4W[d] (Randomization ratio: 1:1:1:1) • Inadequate responders to placebo or adalimumab at Week 16 were randomized (1:1) to one of the ixekizumab regimens	• Placebo, Q2W • Ixekizumab 80 mg Q2Wc • Ixekizumab 80 mg Q4Wc (Randomization ratio: 1:1:1) • Inadequate responders to placebo at Week 16 were randomized (1:1) to one of the ixekizumab regimens
	Extension Period(s) (Weeks 24-52 or 156)[e]	• Ixekizumab, 80 mg Q2W • Ixekizumab, 80 mg Q4W	• Ixekizumab, 80 mg Q2W • Ixekizumab, 80 mg Q4W
Objectives[f]	Primary Endpoint	• ACR20 at Week 24	• ACR20 at Week 24
	Major Secondary Endpoints (multiplicity-adjusted)	• mTSS at Week 24 • Change in HAQ-DI at Week 24 • ACR20 at Week 12 • PASI 75 at Week 12 • Change in LEI score at Week 12 • Change in Itch NRS at Week 12	• Change in HAQ-DI at Week 24 • ACR20 at Week 12 • PASI 75 at Week 12 • MDA at Week 24 • LEI resolution at Week 24
Design Feature		RHAP N=417	RHBE N=363
	Other Secondary Endpoints (nonmultiplicity-adjusted)	• Over52 weeks: o ACR20, ACR50, and ACR70 responses, o ACR Core Set, ACR-N (change from baseline) o DAS28-CRP (change from	• Over 24 weeks: o ACR20, ACR50, and ACR70 responses, o ACR Core Set (change from baseline) o BASDAI (change from baseline)

Design Feature	RHAP N=417	RHBE N=363
	baseline) o HAQ-DI (change from baseline and MCID) o PsARC response o LEI (change from baseline, ≥1 site resolved) o LDI-B (change from baseline, ≥1 digit resolved) o PASI 75, PASI 90, PASI 100 response o sPGA (0,1) response o BSA involvement of psoriasis (percent) o NAPSI (change from baseline) o BASDAI (change from baseline) o Itch NRS (change from baseline) o Fatigue NRS (change from baseline) o SF-36 (change from baseline) • Throughout study: o mTSS at Weeks 16 and 24 (change from baseline, non-progression) o mTSS at Weeks 52, 108, and up to 3 years (change from baseline) o PK/PD relationship o Immunogenicity	o Fatigue NRS (change from baseline) o SF-36 (change from baseline) • Over 52 weeks: o ACR20, ACR50, and ACR70 responses, • Throughout the study: o PK/PD relationship o Immunogenicity

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% response rate; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drugs; BSA = body surface area; CASPAR = Classification Criteria for Psoriatic Arthritis; cDMARD = conventional disease-modifying antirheumatic drugs; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score (28 diarthrodial joint count) based on C-Reactive Protein; HAQ-DI = Health Assessment Questionnaire—Disability Index; IVRS = interactive voice-response system; IWRS = interactive web-response system; LDI-B = Leeds dactylitis index – basic; LEI = Leeds enthesitis index; MDA = minimal disease activity; mTSS = modified total Sharp score; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI 75/90/100 = psoriasis area and severity index 75%/90%/100% improvement; PD = pharmacodynamics; PK = pharmacokinetics; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritic Response Criteria; Q2W = every 2 weeks, Q4W = every 4 weeks; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; SJC = swollen joint count; sPGA = static Physician Global Assessment of psoriasis; TJC = tender joint count; TNFi = tumor necrosis factor inhibitor;

a After 16 weeks of treatment, patients who failed to meet predefined criteria for change in TJC and SJC (<20% improvement from baseline in both TJC and SJC) were classified as inadequate responders and administered rescue therapy. Inadequate responders were identified at Week 16 by the IVRS/IWRS system to investigators who were required to make modifications to the patient's background therapy as rescue therapy at this visit, which was maintained for the remainder of the Double-Blind Treatment Period (unless change was required for safety reasons). The inadequate response criteria were blinded to investigators, study personnel, and patients (the criteria were described to ethics review boards (ERBs) via an ERB supplement to the study protocol).

b Inadequate responders to placebo at Week 16 were re-randomized (1:1) to one of the ixekizumab regimens. They received a 160 mg starting dose at Week 16 and their assigned ixekizumab regimen thereafter.

c Approved dose and regimen of adalimumab (Humira®; AbbVie, Inc). Inadequate responders to adalimumab at Week 16 were re-randomized (1:1) to one of the ixekizumab regimens, but first underwent an 8-week washout period, receiving their assigned ixekizumab regimen from Week 24. The study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab.

d At Week 0, patients were administered a 160 mg starting dose. Inadequate responders to ixekizumab at Week 16 remained on their

originally assigned ixekizumab regimen.

e Extension Period was double-blind until all patients had completed Week 24. This report includes data for RHAP through 52 weeks and data for RHBE through 24 weeks. Patients receiving an ixekizumab regimen at the completion of the Double-Blind Treatment Period remained on the same dose regimen during the Extension Period. Patients who were on placebo at the end of the Double-Blind Treatment Period received a 160 mg starting dose of ixekizumab at Week 24, then were re-randomized (1:1) to an ixekizumab regimen. Patients who were on adalimumab at the end of the Double-Blind Treatment Period underwent an 8-week washout period, received their initial 80 mg dose of ixekizumab at Week 32, then were re-randomized (1:1) to an ixekizumab regimen.

f Statistical analyses for the primary and major secondary endpoints were controlled for multiplicity. Major Secondary Endpoints are listed in the order of testing. For patients who were inadequate responders at Week 16, only data up to the Week 16 injections were included in the double-blind treatment analyses.

2.4.2.2. Study RHAP (bDMARD-naive patients)

Study RHAP was a Phase III, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient study in patients with active PsA who were bDMARD-naive. The study was conducted by 118 investigators, all rheumatologists or dermatologists, at 115 study sites in 15 countries.

Methods

Study participants

The patients enrolled in this trial fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR); had active PsA, defined as the presence of at least 3/68 tender and at least 3/66 swollen joints; and had active psoriatic skin lesions or a documented personal history of plaque psoriasis.

Since RHAP evaluated radiographic joint damage, patients were required to have at screening either ≥1 disease-related hand or foot joint erosion on centrally read x-rays or C-reactive protein (CRP) >6 mg/L to further ensure a patient population with active PsA, including those with underlying erosive disease and a propensity for radiographic progression. RHAP enrolled patients who were naive to bDMARDs, regardless of past or present cDMARD use.

Key inclusion criteria

Patients included in this trial were male or female patients who were 18 years or older, with an established diagnosis of PsA (of at least 6 months duration) and currently met the Classification Criteria for Psoriatic Arthritis (CASPAR).

Patients were also required to have the following:

1. active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints, as determined by the Tender and Swollen Joint Count Assessment Form at Visit 1 (Screening) and Visit 2 (Week 0, baseline)

2. at least 1 disease-related definite joint erosion on hand or foot x-rays as determined by the central reader OR a C-reactive protein (CRP) >6 mg/L at screening

3. active psoriatic skin lesions (plaque) or a documented history of plaque psoriasis

Exclusion criteria

Patients were excluded from the study if they were receiving or had received medication or therapy that could confound the interpretation of the study results or be a safety risk if taken concomitantly with the study drug. Examples of these included:

- received any prior, or were currently receiving, treatment with any bDMARD therapy for PsA or biologic therapy for psoriasis, including investigational therapies (such as a TNF inhibitor, IL-1, IL-6, IL-12/23p40, T cell, or B cell targeted therapies) or had received denosumab
- used cDMARDs other than MTX, leflunomide, sulfasalazine, or hydroxychloroquine in the 8 weeks prior to baseline (Week 0, Visit 2), or concurrently used more than 1 cDMARD at entry to the study
- used oral corticosteroids at average daily doses of >10 mg/day of prednisone or its equivalent, or used variable doses of any oral corticosteroids, within 4 weeks prior to baseline
- received any parenteral glucocorticoid administered by intra-articular, intramuscular, or intravenous (IV) injection within 6 weeks prior to baseline, or for whom a parenteral injection of glucocorticosteroids was anticipated during the Double-Blind Treatment Period (Period 2) of the study
- concomitantly used NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, unless the patient was on a stable dose for at least 2 weeks prior to baseline
- used any opiate analgesic at average daily doses of >30 mg/day of morphine or its equivalent or used variable doses of any opiate analgesic within 6 weeks prior to baseline
- had received systemic non-biologic psoriasis therapy other than MTX or corticosteroids as above or phototherapy within 4 weeks prior to baseline (Week 0, Visit 2);
  OR had topical psoriasis treatment within the previous 2 weeks prior to baseline (Week 0, Visit 2)
- had ever received natalizumab or other agents that target alpha-4-integrin

Patients were also excluded if they had a history of drug-induced psoriasis.

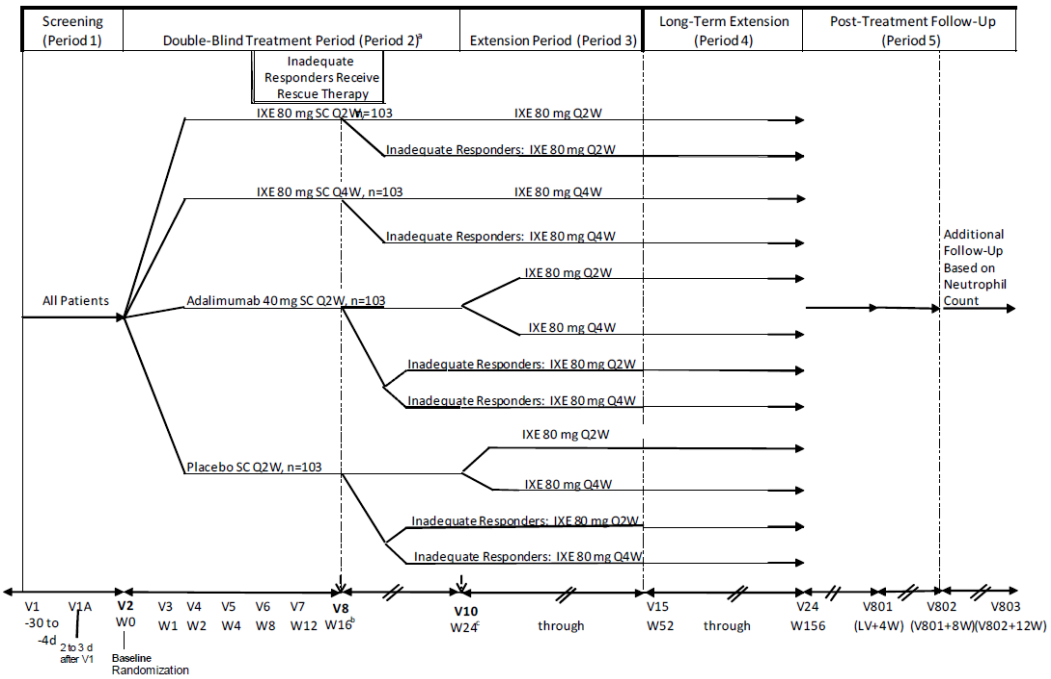
Treatments

The study design is presented in **Figure 9**.

Patients were randomized at a 1:1:1:1 ratio to 1 of 4 treatment groups:

- ixekizumab 80 mg Q2W SC (with a starting dose of 160 mg ixekizumab)
- ixekizumab 80 mg Q4W SC (with a starting dose of 160 mg ixekizumab)
- placebo
- adalimumab (Humira®; Abbott Laboratories) 40 mg Q2W SC.

Figure 9 RHAP Study design



Abbreviations: d = day(s); IXE = ixekizumab; LV = date of last visit; n = number of patients; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week.

a The study remained blinded until the last patient completed Week 24 and the reporting database was locked.

b Inadequate Responders at Week 16 (as defined by blinded tender joint count and swollen joint count criteria) received rescue therapy starting at Week 16. In addition, all Inadequate Responders at Week 16 who were initially randomized to placebo were re-randomized to either ixekizumab dose regimen and receive 2 SC injections of ixekizumab (160 mg total) and, therefore, all patients received 3 SC injections of blinded investigational product at this time point to maintain the study blind. All Inadequate Responders at Week 16 who were initially randomized to adalimumab and re-randomized to either ixekizumab dose regimen received a final dose of adalimumab at Week 16 and placebo for 8 weeks (thus from after Week 16 until Week 24) as a washout procedure before beginning ixekizumab with a starting dose of 160 mg (given as 2 injections) at Week 24.

c At Week 24, all patients still receiving placebo from the placebo group were re-randomized to ixekizumab and received 2 SC injections of ixekizumab (160 mg total). All patients received 3 SC injections of blinded investigational product at this time point to maintain the study blind. Also at Week 24, all patients still receiving adalimumab received a final dose of adalimumab at Week 24 but were re-randomized to either ixekizumab dose regimen and thereafter went through a placebo washout for the following 8 weeks (Week 26 until Week 32) before beginning ixekizumab at Week 32. Patients are to be discontinued from the study if they do not meet the defined response criteria at Week 32 and any subsequent visit during the study.

Patients in each treatment group who were Inadequate Responders (IRs) at Week 16, defined as patients who failed to meet defined criteria for improvement in tender joint count (TJC) and swollen joint count (SJC) at Week 16, received rescue therapy (changes to concomitant medications). IRs at Week 16 who had been assigned to placebo or adalimumab were also re-randomized (1:1) to either ixekizumab dose regimen at that time. Patients who were originally randomized to adalimumab went through a blinded placebo washout phase for 8 weeks (from after Week 16 until Week 24) before starting ixekizumab.

Patients commenced the study in the active- and placebo-controlled Double-Blind Period (Weeks 0 to 24). Patients who completed the Double-Blind Treatment Period entered the Extension Period (Weeks 24 to 52). Following the Extension Period is a 2-year Long-Term Extension Period (open-label once last patient in study completed Week 24). At the date of data cutoff, all patients had completed the Double-Blind Treatment Period and the Extension Period. The Long-Term Extension Period is ongoing.

For the purposes of safety monitoring, all patients who received ≥1 dose of ixekizumab entered the Post-Treatment Follow-Up (PTFU) Period following either treatment discontinuation or their last scheduled visit. Patients participated in the PTFU Period for a minimum of 12 weeks; for patients who

required continued monitoring for neutropenia or other safety reasons, participation in this period was extended as necessary.

Patients who were inadequate responders at Week 16 received rescue therapy. For patients randomised to placebo or adalimumab, this meant re-randomisation to either ixekizumab dose. Patients initially randomised to ixekizumab received modification of the concomitant therapy. This could be either modification of DMARD dose (up to maximum 25 mg MTX, 400 mg hydroxychloroquine, 20 mg leflunomide or 3 g sulfasalazine/day), introduction of new DMARD, adjustment of oral corticosteroid dose up to 10 mg/day of prednisone or equivalent, intra-articular injection of a corticosteroid.

Objectives

The primary objective of the study was to assess whether ixekizumab 80 mg Q2W or 80 mg Q4W was superior to placebo in the treatment of bDMARD-naive patients with active PsA, as measured by the proportion of patients achieving ACR20 response at Week 24.

The major secondary objectives of the study were to assess whether ixekizumab 80 mg Q2W or 80 mg Q4W was superior to placebo in the treatment of patients with PsA who are bDMARD naive on the following measures:

- change from baseline to Week 24 in Health Assessment Questionnaire-Disability Index (HAQ-DI) scores
- change from baseline to Week 24 in modified Total Sharp Score (mTSS) on hand and foot x-rays
- proportion of patients achieving ACR20 response at Week 12
- proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 (at least a 75% improvement in PASI score from baseline) response at Week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥ 3% body surface area [BSA])
- change from baseline to Week 12 in Leeds Enthesitis Index (LEI) in patients with enthesitis at baseline
- change from baseline to Week 12 in itching severity using the Itch Numeric Rating Scale (NRS) (restricted to patients with baseline psoriatic lesion(s) involving ≥ 3% BSA)

Outcomes / endpoints

The primary efficacy endpoint was the American College of Rheumatology 20% response rate (ACR20) at Week 24.

The major secondary efficacy endpoints were:

- mTSS at Week 24
- Change in HAQ-DI at Week 24
- ACR20 at Week 12
- PASI 75 at Week 12

- Change in LEI score at Week 12
- Change in Itch NRS at Week 12

A description of the endpoints used in the phase III program follows below.

Health Assessment Questionnaire—Disability Index (HAQ-DI)
One of the ACR core domains, the HAQ-DI consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities (Fries et al. 1980,1982).

The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do), covering the 8 domains. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains were averaged to calculate the functional disability index. A threshold for minimal clinically important difference (MCID) of ≥0.35 was set for the categorical analysis of this endpoint (Mease et al. 2011).

Van der Heijde Modified Total Sharp Score (mTSS) for PsA
Structural progression in the peripheral joints was measured using the mTSS for PsA (van der Heijde 2005), and the major secondary endpoint was mTSS change from baseline at Week 24.

This mTSS methodology quantifies the extent of bone erosions (20 locations per hand/wrist and 12 locations per foot) and joint space narrowing (JSN; 20 locations per hand/wrist and 6 locations per foot), with higher scores representing greater damage. The total mTSS at a time point is the sum of the erosion (maximum of 320) and JSN (maximum of 208) scores for a maximum total score achievable per patient of 528. The 24-week efficacy endpoint in mTSS was chosen to allow adequate time to demonstrate inhibition of structural joint damage from treatment with ixekizumab, while minimizing the duration of treatment with placebo.

During screening, all patients meeting entry criteria had a single postero-anterior radiographic assessment of the left and right hand/wrist and a single dorso-plantar radiographic image taken of the left and right foot. These images were reviewed and assessed centrally by 1 of 5 qualified readers for evidence of erosive bone change(s). The initial radiographs obtained at screening served as the baseline radiographs for analyses.

The independent read of radiographs was performed centrally by 2 primary readers, and 1 adjudicator when necessary, based on predefined criteria. The 2 primary readers each read 100% of radiographic images from the study patients, blinded to the chronologic order of the images and the patient's identity or treatment group. To check if a consistent read was applied by the independent readers, an inter/intra reader variability assessment was included in the central imaging core laboratory independent read. Images were read in 2 "campaigns." In Campaign 1, images from Weeks 0, 16, and 24 were read. Campaign 1 images were used for the analysis during the Double-Blind Treatment Period (Weeks 0 to 24). In Campaign 2, images from Weeks 0 and 24 were re-read, alongside images from Week 52. Campaign 2 images were used for the analysis during the Extension Period only.

Psoriasis Area and Severity Index (PASI)
The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for

the most severe disease (Fredriksson and Pettersson 1978). Patients achieving PASI 75, 90, or 100 are defined as having an improvement of at least 75%, 90%, or 100%, respectively, in the PASI compared to baseline.

Leeds Enthesitis Index (LEI)

The LEI has been developed specifically for use in PsA. It measures enthesitis at 6 sites (lateral epicondyle, left and right, medial femoral condyle, left and right, Achilles tendon insertion, left and right) (Healy and Helliwell 2008). Each site 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).

Itch Numeric Rating Scale (NRS)

The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching from psoriasis is indicated by circling the number that best describes the worst level of itching in the past 24 hours.

Minimal Disease Activity (MDA)

Minimal Disease Activity is a stringent composite endpoint that was developed as a treatment goal specifically for PsA. This measure of near-remission relies upon 7 key outcome measures encompassing most domains of PsA (Coates et al. 2010a; Coates and Helliwell 2010). A White Paper, located in Module 5.3.5.3, provides an overview of the scientific evidence demonstrating that MDA is a suitable measure for evaluating treatment effect on health status.

Patients are classified as achieving MDA if they fulfill 5 of the 7 outcome measures: TJC ≤1; SJC ≤1; PASI total score ≤1 or BSA ≤3; patient pain VAS score of ≤15; patient global disease activity VAS score of ≤20; HAQ-DI score ≤0.5; and tender entheseal points ≤1. These criteria for MDA were validated in observational cohorts as well as in pharmacologic clinical trials of PsA where it was shown to predict improvements in physical function and radiographic progression (Coates and Helliwell 2010b; Coates et al. 2010b; Kavanaugh et al. 2016).

MDA was also evaluated using static Physician Global Assessment (sPGA) instead of PASI to assess skin involvement; however, unless otherwise specified, this report summarizes MDA using PASI (as described above).

American College of Rheumatology (ACR) Response Criteria – ACR50 and ACR70

ACR50 and ACR70 represent improvements of at least 50% and 70%, respectively, in the multiple disease assessment ACR criteria, and are calculated in the same manner as ACR20.

Psoriatic Arthritic Response Criteria (PsARC)

The PsARC is a composite measure reported in terms of the percentage of patients achieving response according to the following endpoints: TJC, SJC, Physician Global Assessment of Disease Activity VAS, and Patient Global Assessment of Disease Activity VAS. Overall response is defined by improvement from baseline assessment in 2 of 4 criteria, 1 of which must be a joint count, and there must not be worsening in any of the 4 criteria. A modified version of the PsARC was used in RHAP and RHBE to reflect that the patient's and physician's global assessments each used a 100-mm VAS) (instead of the 5-point Likert scale in the original criteria [Clegg et al. 1996]):

At least 30% reduction in TJC

At least 30% reduction in SJC

At least a 20-mm reduction in physician's assessment

At least a 20-mm reduction in patient's assessment.

Disease Activity Score–C-Reactive Protein (DAS28-CRP)

The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score utilizing the following variables: TJC, SJC, CRP (measured in mg/L), and the Patient's Global Assessment of Disease Activity VAS.

For DAS28-CRP, the 28 joints to be examined and assessed for TJC and SJC are a subset of those assessed for the ACR response criteria, and include 14 joints on each side of the patient's body: the 2 shoulders, the 2 elbows, the 2 wrists, the 10 metacarpophalangeal joints, the 2 interphalangeal joints of the thumb, the 8 proximal interphalangeal joints, and the 2 knees (Smolen et al. 1995).

Composite Psoriatic Disease Activity Index (CPDAI)

The CPDAI is a validated instrument intended to assess composite psoriatic disease activity and response to therapy (Mumtaz et al. 2010). This instrument assesses individual domains involved as well as the global effect of disease in all dimensions by which each patient may be affected. Domains include peripheral arthritis as assessed by the number of tender and swollen joints and the HAQ-DI, skin as assessed by the PASI and the DLQI, enthesitis as assessed by the number of sites with enthesitis and the HAQ-DI, dactylitis as assessed by the number of digits affected and the HAQ-DI, and spinal disease as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life (ASQoL). Scores range from 0 to 15 for assessment including spinal disease (BASDAI), and 0 to 12 for assessment excluding spinal disease, with a higher score indicating higher disease activity.

The ASQoL was not collected in Study RHAP, so the CPDAI was modified to include BASDAI only, giving a score range of 0 to 14. The ASQoL was collected in RHBE, so the CPDAI was analyzed in 2 ways for this study: the original way (as described by Mumtaz et al. [2010]), and then without the axial domain (neither BASDAI nor ASQoL).

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is a self-administered VAS (100 mm) used to answer 6 questions pertaining to the 5 major symptoms of axial activity: 1) fatigue; 2) neck, back, or hip pain; 3) joint pain/swelling other than neck, back, or hips; 4) areas of localized tenderness; 5) overall level of morning stiffness; and 6) duration of morning stiffness (Garrett et al. 1994). To give each symptom equal weighting, the mean of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score.

Spondyloarthritis Research Consortium of Canada Criteria (SPARCC)

The SPARCC enthesitis index evaluates tenderness in a total of 16 enthesitis sites: the greater trochanter (right/left [R/L]), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L), and the supraspinatus insertion (R/L) (Mease 2011). Tenderness at each site is quantified on a dichotomous basis: 0 = non-tender and 1 = tender. The results from each site are then added to produce a total score (range 0 to 16).

The SPARCC was administered by an independent assessor to minimize bias. The assessor was not involved in patient care and was asked not to discuss disease activity or treatment with patients or principal investigator. The SPARCC was only collected in RHBE.

Leeds Dactylitis Index–Basic (LDI-B)

If the patient had dactylitis, the LDI-B was administered. The LDI-B was developed to measure the severity of dactylitis (Helliwell et al. 2005; Healy and Helliwell 2007). The LDI-B total score is based on the presence of dactylitis in a digit(s). For each digit that is dactylitic, as defined by a minimum increase of 10% in circumference of the dactylitic digit (A) over the contra-lateral digit (B), the ratio (A/B) of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured. If the same digits on each hand or foot are thought to be involved, the clinician refers to a table of normative values (provided to investigative sites) for a value which will be used to provide the comparison; this concept is also applied if there is a contralateral missing finger or toe.

The calculated ratio (A/B) is then subtracted by 1, multiplied by 100, and then multiplied by a tenderness score (C) of 0 (not tender) or 1 (tender). The results of each digit are then added to produce the LDI-B total score.

*LDI-B total score = sum ((((A/B)-1)*100)*C)*

The LDI-B was administered by an independent assessor to minimize bias. The assessor was not involved in patient care and was asked not to discuss disease activity or treatment with patients or principal investigator.

Static Physician Global Assessment (sPGA)

The sPGA is the physician's determination of the patient's psoriatic lesions overall at a given time point. The sPGA is recommended as an endpoint to assess efficacy in the treatment of psoriasis (European Medicines Agency [EMEA] 2004). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

Percentage of Body Surface Area (BSA) Involvement of Psoriasis

The BSA is the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% = no involvement to 100% = full involvement, where 1% corresponds to the size of the patient's handprint including the palm, fingers, and thumb (National Psoriasis Foundation 2009).

Nail Psoriasis Severity Index (NAPSI)

The NAPSI is a numeric, reproducible, objective tool for evaluation of nail psoriasis (Rich and Scher 2003). This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit.

The nail is divided with imaginary horizontal and longitudinal lines into quadrants. Each nail is given a score for nail bed psoriasis (0 to 4) and nail matrix psoriasis (0 to 4), depending on the presence (1) or absence (0) of any of the features of nail psoriasis in each quadrant. The NAPSI score of a nail is the sum of scores in nail bed and nail matrix from each quadrant (thus a maximum of 8). Each nail is evaluated, and the sum of all the nails is the total NAPSI score. Thus, the sum of the scores from all nails is 0 to 80, or 0 to 160 if toenails are included (Rich and Scher 2003). In RHAP and RHBE, only fingernail involvement was assessed.

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)

The SF-36 is a 36-item patient-administered measure designed to be a short, multi-purpose assessment of health in the areas (or domains) of physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the mental component summary (MCS)

and physical component summary (PCS) scores. The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health.

A White Paper and a Patient-Reported Outcomes (PRO) Dossier, providing an overview of the scientific evidence demonstrating SF-36 as a suitable measure for evaluating treatment effect on health status, are provided in Module 5.3.5.3.

Fatigue Severity Numeric Rating Scale (Fatigue NRS)

The Fatigue NRS is a patient-administered, single-item, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine." Patients use this tool, developed for Study RHAP, to rate their fatigue (feeling tired or worn out) by selecting the one number that describes their worst level of fatigue during the past 24 hours.

Dermatology Life Quality Index (DLQI)

The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as 0. The recall period is "over the last week" and totals range from 0 to 30 (less to more impairment), and a 5-point change from baseline is considered clinically relevant (Basra et al. 2008). The DLQI was assessed in patients with baseline psoriatic lesion(s) involving ≥3% BSA.

DLQI total scores were interpreted as: 0 to 1 no effect; 2 to 5 small effect; 6 to 10 moderate effect; 11 to 20 very large effect; and 21 to 30 extremely large effect.

European Quality of Life–5 Dimensions 5 Level (EQ-5D 5L)

The EQ-5D 5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 100-mm VAS. The descriptive system comprises: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by marking the box associated with the most appropriate statement in each of the 5 dimensions.

The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)." This information can be used as a quantitative measure of health outcome. The EQ-5D 5L health states, defined by the EQ-5D 5L descriptive system, may be converted into a single summary index by applying a formula that attaches values to each of the levels in each dimension (EuroQol Group [WWW]).

Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP)

The WPAI-SHP consists of 6 questions to determine employment status, hours missed from work due to PsA, hours missed from work for other reasons, hours actually worked, the degree to which PsA affected work productivity while at work, and the degree to which PsA affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment (Reilly Associates Health Outcomes Research [WWW]).

Quick Inventory of Depressive Symptomatology–Self Report (16 items) (QIDS-SR16)

The QIDS-SR16 is a self-administered 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity.

The ACR20 has been used as the primary endpoint in multiple registration studies of PsA treatments, and is recommended in EMA Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis (CHMP/EWP/438/04). The ACR20 takes into consideration 7 components relating to disease activity and severity which are listed below. The ACR20 is defined as having at least a 20% improvement in:

- Tender joint count (TJC) – 68 joint count. A positive response for pressure, movement, or both was translated into a single tender/nontender dichotomy.
- Swollen joint count (SJC) – 66 joint count. Joints were classified as either swollen or not swollen, defined as palpable fluctuating synovitis of the joint.

And, at least a 20% improvement in ≥3 of the following criteria:

- Patient's assessment of pain visual analog scale (VAS) – Patient marked their level of joint pain on a VAS; results expressed in millimeters (higher numbers equal greater pain).
- Patient's global assessment of disease activity VAS – Higher numbers represent more active disease.
- Physician's global assessment of disease activity VAS
- Patient's assessment of physical function Health Assessment Questionnaire—Disability Index (HAQ-DI)
- Acute phase reactant as measured by C-reactive protein (CRP).

The primary and major secondary efficacy variables covers relevant aspects of the disease, and are overall endorsed. In the background information to the advice sought from the CHMP, the primary endpoint was originally intended to be ACR20 at Week 12. As stated by the applicant, *"The 24-week efficacy endpoint for ACR20 response was chosen because steady-state exposure is expected to be reached by this time point, and it is likely that a maximal clinical effect will be observed within this timeframe in both ixekizumab dosing regimens, based on previous studies with ixekizumab in patients with RA and Ps".* ACR20 at 24 Weeks is the same primary endpoint as used in the phase III program for Cosentyx and is considered acceptable.

The primary endpoint is based on subjective assessment by the patient and the clinician. The primary endpoint is as advised by the Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis, CHMP/EWP/438/04, Dec 2006 and so is acceptable.

Each VAS was a 10cm line on to which the patient placed a mark to indicate severity.

The company does not appear to have provided examples of the various VAS tools (other than a written description) or instructions on how to use. This was clarified during the assessment.

The company has submitted a published description of the HAQ though does not appear to have submitted the HAQ tool as used in the current study.

LEI is a relevant outcome measure that has been specifically developed for use in PsA and it has been used in several PsA clinical trials on certolizumab, secukinumab and clazakizumab (Mease et al. 2017). The NRS was developed and validated based on a study with baricitinib, and three Phase III ixekizumab studies on skin psoriasis. MDA has been shown in one study to be predictive of less structural degradation and has been validated as a treatment target (Coates et al. 2015)

The company has submitted results of very many clinical outcome assessment tools. It is appreciated that the ACR, mTSS, PsARC, PASI and SF-36 are described in CHMP guidelines yet the company does not appear to have qualified these tools for use in the current submission for psoriatic arthritis. For other tools, the company seems to rely on published manuscripts unrelated to the current development programme as evidence of content validity, reliability, ability to detect change and interpretability.

Overall, a number of secondary outcomes are included in the study, including measures of peripheral arthritis, axial symptoms, dactylitis, skin and nail engagement, enthesitis, composite disease activity scores and health outcome measures. Since psoriasis is a heterogenous disorder with either a peripheral joint disease or an axial disease, both with concomitant enthesitis, dactylitis and skin/nail engagement, it can be necessary to provide several outcome measures with such diverse outcome measures and this is thereby endorsed.

Sample size

The total planned sample size for the study was 412 patients randomized at 1:1:1:1 ratio to 4 treatment groups in the Double-Blind Treatment Period: ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab 40 mg Q2W, and placebo. To account for multiple testing for the 2 ixekizumab groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. With 103 patients per treatment group, this study had >99% power to test the superiority of each ixekizumab dose regimen to placebo for ACR20 response at Week 24 (Visit 10), assuming ACR20 response rate at Week 24 was 48% for each ixekizumab group and 15% for the placebo group. It was estimated that approximately 75% of the total sample size had cDMARD experience at study baseline, which was approximately 77 patients per treatment group; this sample size would provide approximately 97% power to test the difference between each ixekizumab dose regimen and placebo in the cDMARD-experienced subpopulation, assuming ACR20 response rate was 46% for each ixekizumab group and 15% for the placebo group. With 103 patients per treatment group, this study had approximately 90% power to test the superiority of each ixekizumab dose regimen compared with placebo for change from baseline in mTSS at Week 24 (Visit 10) using a 2-sided t test at the 0.025 level. This assumed a difference of 0.59 in change from baseline mTSS between placebo and ixekizumab, and an SD of 1.19.

The split of α given the two ixekizumab groups is endorsed by CHMP. The sample size was seemingly determined to provide sufficient power to show a difference (versus placebo) with regard to the major secondary mTSS endpoint. For the primary analyses the power was >99% implying a high power also in the subpopulation of cDMARD-experienced patients since expected to comprise approximately 75% of the total sample size. This was to be a subset of the Intent-to-treat Population defined as all randomised patients who had conventional DMARD experience (i.e. past or current use) at baseline for which a number of analyses, besides analyses of the primary endpoint, were pre-planned.

Randomisation

At Week 0 (baseline, Visit 2), patients who met all criteria for enrolment at Visit 1, Visit 1A, and Visit 2 were randomly assigned in a 1:1:1:1 ratio to treatments arms with randomisation being stratified by

country and cDMARD experience (naive, past use, and current use). Inadequate Responders at Week 16 receiving placebo or adalimumab were re-randomised (1:1) to ixekizumab 80 mg Q2W or 80 mg Q4W (those receiving adalimumab were to complete a placebo washout phase until Week 24) and received rescue therapy. Inadequate responders at Week 16 in the ixekizumab groups continued receiving ixekizumab to both maintain the blind and allow additional response time in case of slow-responders in this group.

At Week 24 (Visit 10), patients remaining in the placebo and adalimumab treatment groups at the completion of Double-Blind Treatment Period (Period 2) were re-randomized (1:1) to ixekizumab 80 mg Q2W or Q4W; those receiving adalimumab completed a placebo washout phase until Week 32 after having received their final dose of adalimumab at Week 24.

The stratification factors are endorsed by CHMP. Regarding the re-randomisation of inadequate responders in the placebo and adalimumab arm, outcomes of comparisons between treatments at week 16 will be valuable in support of primary outcomes at week 24.

Blinding (masking)

This was a double-blind study; patients, study site personnel, and sponsor study team were blinded to study drug, including re-randomisations at Week 16 and Week 24, until all patients completed Week 24 (Visit 10) or had discontinued from the study (moved into Period 5) and the reporting database through Week 24 had been locked. Blinding was achieved by the use of double-dummy technique with placebo for ixekizumab and placebo for adalimumab. At Week 16 (Visit 8), patients were classified as a responder or non-responder according to blinded criteria defined in the IRB Supplement to the study protocol; these criteria were to remain blinded to investigators, study personnel, and patients.

Statistical methods

Comparisons between each ixekizumab 80 mg regimen (Q2W or Q4W) and placebo were performed for all analyses in Period 2 as were comparisons between adalimumab and placebo. There were no statistical comparisons between each ixekizumab dose regimen and adalimumab or between ixekizumab dose regimens.

Unless otherwise specified, analyses were conducted on the Intent-To-Treat (ITT) Population. The ITT Population was defined as all randomised patients analysed according to the treatment to which they were assigned. For patients who were inadequate responders at Week 16, only data up to Week 16 were included in the Double-Blind Treatment Period analyses.

Treatment comparisons of categorical efficacy variables, including the primary endpoint proportion of patients with ACR20 response at Week 24, were made using a logistic regression analysis with treatment, geographic region, and conventional DMARD experience at baseline (naive, past use, and current use) in the model. The proportions and 95% confidence interval were reported. Missing data were handled using a non-responder imputation (NRI).

The primary analyses were repeated using the Per Protocol Set (PPS); a subset of the ITT Population defined as all randomised patients who were compliant with therapy, who did not have significant protocol violations, and whose investigator's site did not have significant GCP issues. For patients eligible for rescue therapy at Week 16 to be included in the PPS, the above requirements only applied up to Week 16. In addition, the primary, major secondary and some other non-gated important secondary efficacy (ACR20/50/70, DAS28-CRP, HAQ-DI ≥0.35) and health outcome (Quick Inventory of Depressive Symptomatology-Self Report (16 Items) [QIDS-SR16] total score) endpoints were analysed using the Conventional DMARD-experienced Population. This was a subset of the Intent-to-

treat Population defined as all randomised patients who had conventional DMARD experience (i.e. past or current use) at baseline.

The primary analyses for all continuous gated outcome variables were based on a mixed-effects model for repeated measures (MMRM) method. The model included treatment, geographic region (Europe and ROW), baseline score, conventional DMARD experience at baseline (naive, past use, and current use), visit, and the interaction of treatment-by-visit as fixed factors.

The secondary approach to the analysis of the structural progression data after MMRM was the linear extrapolation method, which assumes that individual patients would continue to accrue structural damage in their joints at the same rate that was observed at their time of last observation. As a third approach a multiple imputation (MI) approach was used for the Week 24 analyses of mTSS, bone erosion score (ES), and joint space narrowing (JSN). A set of Bayesian regressions using SAS Proc MI were utilized for the imputation of missing values due to dropout, rescue or treatment reassignment, unevaluable images, or otherwise missing data such as surgically modified (for example, joint replacement or other surgery).

As supportive analyses of continuous gated efficacy variables (except mTSS) were performed using analysis of covariance (ANCOVA) with treatment, geographic region, baseline value, and conventional DMARD experience at baseline (naive, past use, and current use) in the model. To handle missing data a modified baseline observation carried forward (mBOCF) approach was used. For patients eligible for rescue therapy at Week 16, their last non-missing observation prior to initiation of rescue therapy will be carried forward. For patients discontinuing investigational product due to an AE, the baseline observation were carried forward. For patients discontinuing investigational product for any other reason, the last non-missing observation before discontinuation were carried forward. Randomized patients without at least 1 post-baseline observation were excluded with the exception of patients discontinuing study treatment due to an AE.

In addition, sensitivity analyses using LOCF were performed. This approach was identical to the mBOCF approach, with one exception: for patients discontinuing investigational product due to an AE, the last non-missing post-baseline observation before discontinuation was carried forward to the corresponding endpoint for evaluation. Randomised patients without at least one post-baseline observation were excluded for evaluation. A third approach for the analysis of major continuous endpoints at Visit 10 (Week 24) was the Placebo Multiple Imputation (pMI) method. Placebo Multiple Imputation assumes that the statistical behaviour of drug- and placebo- treated patients after discontinuing study medication becomes that of placebo-treated patients.

A graphical approach to multiplicity control was used to control the family-wise type I error rate at a 2-sided alpha level of 0.05 and allow simultaneous inference of the primary and all major secondary endpoints (Bretz et al. 2009, 2011; Alosh et al. 2014). The total α was initially split equally between the ixekizumab 80 mg Q2W and 80 mg Q4W dose regimen; the primary hypothesis (ACR20) for these 2 doses were allocated a type I error of $\alpha/2$ (of 0.025) and all other hypotheses are allocated $\alpha = 0$. All the primary and secondary endpoints within a dose regimen were to be tested in a sequential manner; each test for a particular dose was to be performed only if all prior tests at that dose were significant. For each dose schedule, if a test was not significant, all subsequent tests were not significant. If all the hypotheses for a dose regimen had been rejected at $\alpha/2$ (or 0.025 level) then the hypotheses related to other dose regimen could be tested at level α (or 0.05 level).

Subgroup analyses were planned for ACR20 response rate at Week 24 and change from baseline to Week 24 in mTSS using the ITT population.

CHMP comments :

The statistical analysis plan for Study RHAP is overall acceptable with some remarks. In all analyses, data collected after start of rescue/week 16 were ignored. Although this is an acceptable primary approach, sensitivity/supportive analyses including data post-rescue should have been planned as discussed within the scientific advice procedure 2011 (EMA/CHMP/SAWP/339078/2011). Categorical endpoints, including the primary endpoint, were analysed using logistic regression with missing data handled using a non-responder imputation. For the analysis of the primary endpoint (and other categorical endpoints) this implied that patients with inadequate response week 16 were treated as non-responders.

For continuous endpoints the primary analysis approach was MMRM. Considering the missing at random assumption, sensitivity/supportive analyses will be valuable.

Sensitivity analyses for major categorical endpoints were seemingly not pre-planned. Additional analyses based on e.g. categorical MMRM have however been performed; whether pre-planned or not, with the primary approach considered to be acceptable, additional analyses for assessment of robustness were further discussed.

For major continuous endpoints except mTSS analyses were repeated using ANCOVA and a modified baseline-observation-carried-forward (mBOCF) approach and last-observation-carried-forward (LOCF) respectively as well as MMRM using pMI. The mBOCF implied that the baseline observation was carried forward only for patients discontinuing study treatment due to an AE, for other reasons, the last non-missing observation before discontinuation were carried forward. In all cases except treatment discontinuation due to an AE, a post-baseline observation was used for imputation. The difference between analyses using mBOCF and analyses using LOCF may hence be small. For mTSS at least two additional analysis approaches were planned and have been performed including an ANCOVA using linear extrapolation that initially was considered primary.

Regarding the definition of the Safety Population, patients were to be analysed according to the treatment to which they were assigned at Week 0. Generally, and more appropriate, patients should be analysed according to the actual treatment received. However, during the double-blind period all patients seemingly received their assigned treatment but for one (who had a dosing error at Week 8, in which the patient took ixekizumab 80 mg after receiving 6 weeks of adalimumab).

A number of post hoc analyses were performed after database lock and unblinding including a sensitivity analysis on ACR20 response rates at Week 24 based on the PPS and excluding all patients from one Site which was closed for persistent GCP noncompliance. Considered to be for check of robustness or for clarifying/exploratory purposes, no concern is raised.

Treating patients with completely missing data as non-responders is agreed to be an appropriate approach, especially considering that the majority of the missing data at week 24 was created by the study design and was those patients with an inadequate response at week 16.

Results

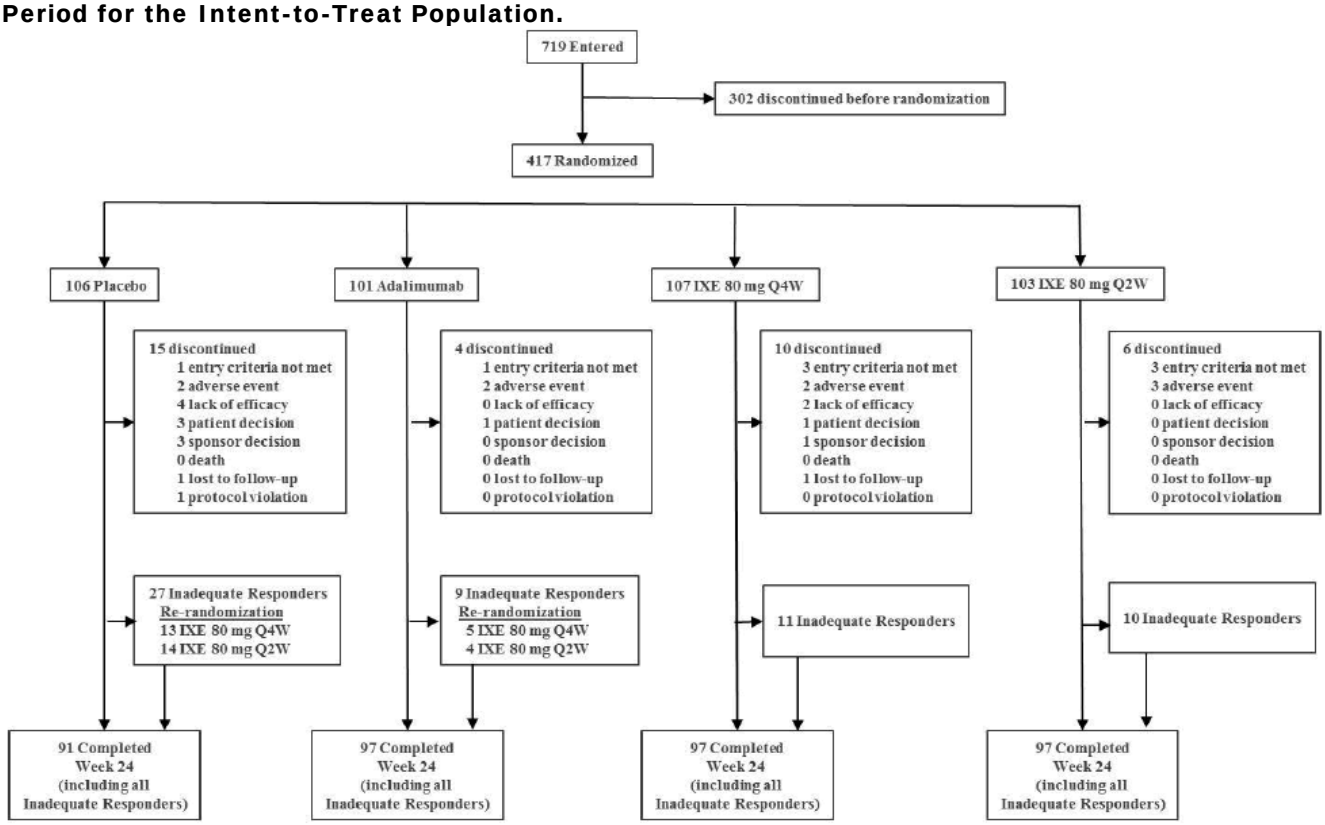
Study RHAP (bDMARD-naive patients)

Participant flow

A total of 719 patients entered the study. Prior to randomization at Week 0, 302 patients discontinued from the study. In total, 417 patients were randomized to 1 of 4 treatment groups as the ITT

Population: 107 to ixekizumab 80 mg Q4W, 103 to ixekizumab 80 mg Q2W, 101 to adalimumab 40 mg Q2W, and 106 to placebo (Table 11). A total of 91.6% of randomized patients completed the Double-Blind Treatment Period; greater percentages of patients in the ixekizumab groups (Q4W, 90.7%; Q2W, 94.2%) completed the Double-Blind Treatment Period compared with the placebo group (85.8%). One patient in the ixekizumab 80 mg Q4W group was reported as ongoing in the Double-Blind Treatment Period at the time of database lock. The patient was actually lost to follow-up after Visit 8 (Week 16) and should have been reported as discontinued during the Double-Blind Treatment Period. This data was entered after database lock, causing the status of this patient to display as ongoing. Patient disposition and reasons for discontinuation is shown in Figure 11 and Table 9 below.

Figure 10 Patient disposition from study treatment during the Double-Blind Treatment Period for the Intent-to-Treat Population.



Abbreviations: IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

a Patients randomized to adalimumab at Week 0 who were Inadequate Responders at Week 16 were re-randomized (1:1) to receive either IXE 80 mg Q2W or Q4W but went through a blinded placebo washout phase for 8 weeks (from after Week 16 until Week 24) before starting IXE.

Table 9 Patient Completion and Disposition from Study Treatment, Intent-to-Treat Population, Double-Blind Treatment Period

	RHAP n (%)				
	Placebo (N = 106)	**ADA (N = 101)**	**IXEQ4W (N = 107)**	**IXEQ2W (N = 103)**	**Total (N = 417)**
Number of Patients (%)					
Randomized at Week 0	106	101	107	103	417
Inadequate Responders (Week 16)	27 (25.5)	9 (8.9)	11 (10.3)	10 (9.7)	57 (13.7)
Completed Week 24	91 (85.8)	**97 (96.0)**[a]	97 (90.7)	97 (94.2)	382 (91.6)
Reason for Treatment Discontinuation (Double-Blind					

	RHAP n (%)				
	Placebo (N = 106)	ADA (N = 101)	IXEQ4W (N = 107)	IXEQ2W (N = 103)	Total (N = 417)
Treatment Period)					
Adverse Event	2 (1.9)	2 (2.0)	2 (1.9)	3 (2.9)	9 (2.2)
Lack of Efficacy	4 (3.8)	0	2 (1.9)	0	6 (1.4)
Patient Decision	3 (2.8)	1 (1.0)	1 (0.9)	0	5 (1.2)
Entry Criteria not Met	1 (0.9)	1 (1.0)	3 (2.8)	3 (2.9)	8 (1.9)
Lost to Follow-Up	1 (0.9)	0	0	0	1 (0.2)
Sponsor Decision	3 (2.8)	0	1 (0.9)	0	4 (1.0)
(Other) Protocol Violation	1 (0.9)	0	0	0	1 (0.2)
Death	0	0	0	0	0
Clinical Relapse	0	0	0	0	0
Physician Decision	0	0	0	0	0
Caregiver Decision	0	0	0	0	0

Abbreviation: ADA = adalimumab; ITT = intent-to-treat; IXEQ2W = ixekizumab 80 mg Q2W; IXEQ4W = ixekizumab 80 mg Q4W

Note: Significant comparisons (p<.05) are highlighted in bold text

a p<.05 versus placebo

Reasons for discontinuation from study drug for the ITT Population during the Double-Blind Treatment Period were similar across treatment groups. It is noted that there were (about) 3 times the number of inadequate responders in the placebo arm versus the three 'active' arms. The most common reasons for study drug discontinuation among patients in the placebo group were lack of efficacy, patient decision, and sponsor decision. One patient in the placebo group was lost to follow-up. One patient in the ixekizumab 80 mg Q4W group was lost to follow-up during the Double-Blind Treatment Period, but due to a data error, the patient was recorded as ongoing in the Double-Blind Treatment Period at the time of database lock. For the total ixekizumab group, the most common reasons for study drug discontinuation were entry criteria not met and adverse event.

Recruitment

First patient enrolled (assigned to therapy): 09 January 2013

Last patient completed Week 52 Visit (Extension Period): 15 June 2015

Date of database lock: 04 September 2015

Conduct of the study

There was one protocol amendment and 1 protocol addendum, and 2 protocol addendum amendments. The first patient was enrolled after implementation of the amendments and addendum, with the exception of the second protocol addendum amendment, which was implemented after all patients had enrolled.

In the first addendum, chest x-rays were added at the end of the Extension Period, at the end of study, and at early termination. Also, instructions were added regarding the proper injection of the study drug, caregiver administration of the study drug, and recording details of the injection in the injection log. Beta-D-Glucan, KL-6, and HBV testing was added.

In the second (global) amendment (12 Nov 2012), following feedback from the FDA, the most important changes were:

- At Week 16, all Inadequate Responders were rescued through modification or addition of background therapy, including cDMARDs, NSAIDs, analgesics, and/or corticosteroids. Placebo Inadequate Responders received ixekizumab in a blinded manner in addition to these treatments.
- Patient-level discontinuation criteria for signs and symptoms were applied at Week 32 and beyond.
- The total study duration was shortened from 5 to 3 years.

Two addendums (Japan) was approved at 10 Dec 2012 and 10 Feb 2016, concerning minimum dose of MTX at study entry and increased dose of ixekizumab from 80 mg every 4 weeks (Q4W) to 80 mg every 2 weeks (Q2W) during the Long-Term Extension Period, at the investigor's discretion.

In summary, the amendments were done prior to the first patient enrolled, and should have no impact on the result of the study. The addendum approved after study start did not affect the double-blind part of the study.

Baseline data

The mean age of patients in the ITT Population was 49.5 years. The majority of patients were female (54.0%) and white (94.0%). The patient demographics are detailed in Table 10 below.

Table 10 Patient demographics and Baseline Characteristics

	RHAP (N=417)				
	Placebo (N = 106)	**ADA (N = 101)**	**IXEQ4W (N = 107)**	**IXEQ2W (N = 103)**	**Total (N = 417)**
Demographics					
Age (Years)					
Mean (SD)	50.6 (12.32)	48.6 (12.43)	49.1 (10.07)	49.8 (12.62)	49.5 (11.87)
Median	52.0	48.0	50.0	50.0	50.0
Sex, n (%)					
Male	48 (45.3)	51 (50.5)	45 (42.1)	48 (46.6)	192 (46.0)
Female	58 (54.7)	50 (49.5)	62 (57.9)	55 (53.4)	225 (54.0)
Race, n (%)					
American Indian or Alaska Native	2 (1.9)	3 (3.0)	2 (1.9)	2 (1.9)	9 (2.2)
Asian	5 (4.7)	3 (3.0)	2 (1.9)	5 (4.9)	15 (3.6)
Black or African American	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	99 (93.4)	95 (94.1)	102 (95.3)	96 (93.2)	392 (94.0)
Multiple	0	0	1 (0.9)	0	1 (0.2)
Geographic Region, n (%)					
Europe	76 (71.7)	73 (72.3)	80 (74.8)	77 (74.8)	306 (73.4)
United States	22 (20.8)	21 (20.8)	20 (18.7)	20 (19.4)	83 (19.9)
Rest of the World	8 (7.5)	7 (6.9)	7 (6.5)	6 (5.8)	28 (6.7)
Weight (kg)					
Mean (SD)	83.8 (19.62)	91.6 (21.93)	85.5 (22.98)	81.6 (17.47)	85.6 (20.87)
Median	82.7	88.0	84.0	79.5	83.8
BMI, (kg/m^2)					

	RHAP (N=417)				
	Placebo (N = 106)	**ADA (N = 101)**	**IXEQ4W (N = 107)**	**IXEQ2W (N = 103)**	**Total (N = 417)**
Mean (SD)	29.2 (6.34)	32.1 (11.37)	30.2 (8.38)	28.6 (6.56)	30.0 (8.46)
Median	27.9	30.4	28.6	27.7	28.7
Previous Therapy					
Baseline Methotrexate Use at Randomization, n (%)					
Yes	59 (55.7)	57 (56.4)	57 (53.3)	53 (51.5)	226 (54.2)
No	47 (44.3)	44 (43.6)	50 (46.7)	50 (48.5)	191 (45.8)
Background Therapy, n (%)					
cDMARD naive	13 (12.3)	14 (13.9)	17 (15.9)	17 (16.5)	61 (14.6)
cDMARD past use	24 (22.6)	20 (19.8)	22 (20.6)	23 (22.3)	89 (21.3)
cDMARD current use	69 (65.1)	67 (66.3)	68 (63.6)	63 (61.2)	267 (64.0)
Background Therapy, n (%)					
Inadequate responder to 1 TNFi			NA		
Inadequate responder to 2 TNFi			NA		
Intolerance to a TNFi			NA		
Disease Characteristics					
CASPAR Total Score					
Mean (SD)	4.7 (0.93)	4.7 (0.97)	4.6 (0.99)	4.7 (0.93)	4.7 (0.95)
Median	5.0	5.0	5.0	5.0	5.0
Moll and Wright Classification, n (%)					
DIP joint only	5 (4.7)	3 (3.0)	3 (2.8)	3 (2.9)	14 (3.4)
Asymmetrical Oligoarthritis	11 (10.4)	15 (14.9)	17 (16.0)	12 (11.7)	55 (13.2)
Polyarthritis	85 (80.2)	81 (80.2)	77 (72.6)	84 (81.6)	327 (78.6)
Spondylitis	3 (2.8)	1 (1.0)	2 (1.9)	2 (1.9)	8 (1.9)
Arthritis Mutilans	2 (1.9)	1 (1.0)	7 (6.6)	2 (1.9)	12 (2.9)
Time Since PsA Onset (years)					
Mean (SD)	10.4 (8.82)	9.2 (7.93)	10.0 (9.51)	10.8 (10.80)	10.1 (9.31)
Median	8.3	6.3	6.3	7.1	7.2
Time Since PsA Diagnosis (years)					
Mean (SD)	6.3 (6.86)	6.9 (7.54)	6.2 (6.42)	7.2 (8.04)	6.7 (7.21)
Median	4.1	4.3	4.2	4.1	4.1
Time Since Ps Onset (years)					
Mean (SD)	18.8 (13.41)	17.2 (12.51)	18.7 (13.41)	19.7 (14.20)	18.6 (13.38)
Median	15.4	14.1	15.1	17.5	15.2
Time Since Ps Diagnosis (years)					
Mean (SD)	16.0 (13.79)	15.7 (12.67)	16.5 (13.76)	17.0 (14.01)	16.3 (13.54)
Median	13.5	12.0	12.9	14.1	13.2
Enthesitis[a]					
Yes	57 (53.8)	56 (55.4)	70 (65.4)	59 (57.3)	242 (58.0)
No	49 (46.2)	45 (44.6)	37 (34.6)	44 (42.7)	175 (42.0)
LEI score[b]					
Mean (SD)	2.9 (1.68)	3.0 (1.62)	2.7 (1.61)	3.1 (1.78)	2.9 (1.67)
Median	3.0	3.0	2.0	3.0	3.0
Dactylitis[c]					
Yes	39 (36.8)	23 (22.8)	54 (50.5)	41 (39.8)	157 (37.6)
No	67 (63.2)	78 (77.2)	53 (49.5)	62 (60.2)	260 (62.4)
LDI-B score[d]					
Mean (SD)	46.2 (65.47)	93.9 (111.90)	58.1 (96.70)	40.6 (54.57)	55.8 (83.61)
Median	26.0	47.3	25.2	22.2	26.7

	RHAP (N=417)				
	Placebo (N = 106)	**ADA (N = 101)**	**IXEQ4W (N = 107)**	**IXEQ2W (N = 103)**	**Total (N = 417)**
Individual Components of ACR Core Set					
Baseline TJC (68 joints)					
Mean (SD)	19.2 (12.98)	19.3 (12.97)	20.5 (13.68)	21.5 (14.08)	20.1 (13.42)
Median	17.0	16.0	17.0	19.0	17.0
Baseline SJC (66 joints)					
Mean (SD)	10.6 (7.26)	9.9 (6.48)	11.4 (8.21)	12.1 (7.23)	11.0 (7.35)
Median	8.0	8.0	10.0	10.0	9.0
Physician global assessment of disease activity (mm)					
Mean (SD)	55.9 (19.26)	55.4 (18.65)	57.6 (18.70)	58.5 (18.96)	56.9 (18.87)
Median	60.0	57.0	61.5	61.0	60.0
Patient global assessment of disease activity (mm)					
Mean (SD)	61.1 (22.67)	59.1 (19.10)	62.7 (19.07)	62.5 (19.94)	61.4 (20.25)
Median	59.0	57.0	63.0	61.0	60.0
Patient's assessment of joint pain (mm)					
Mean (SD)	58.5 (22.96)	58.7 (19.73)	60.1 (19.42)	58.4 (21.66)	58.9 (20.94)
Median	62.0	61.0	65.0	61.0	62.0
HAQ-DI Total Score					
Mean (SD)	1.2 (0.60)	1.1 (0.59)	1.2 (0.54)	1.2 (0.57)	1.2 (0.58)
Median	1.13	1.06	1.25	1.25	1.13
CRP (mg/L), n (%)					
>6	65 (61.3)	62 (61.4)	69 (64.5)	54 (52.4)	250 (60.0)
≤6	41 (38.7)	39 (38.6)	38 (35.5)	49 (47.6)	167 (40.0)
CRP (mg/L)					
Mean (SD)	15.1 (23.60)	13.2 (19.12)	12.8 (16.37)	15.1 (25.91)	14.1 (21.50)
Median	7.6	8.5	7.7	6.1	7.4
Baseline Severity					
DAS28-CRP					
Mean (SD)	4.9 (1.04)	4.9 (0.98)	5.0 (1.00)	5.0 (1.06)	4.9 (1.02)
Median	4.9	4.7	5.0	5.0	4.9
PASI total score[e]					
Mean (SD)	6.2 (7.52)	5.5 (6.46)	6.9 (6.61)	6.0 (7.04)	6.1 (6.91)
Median	3.1	3.4	4.7	3.2	3.5
PASI total score, n (%)[e]					
≥12	16 (15.8)	10 (10.3)	18 (18.0)	13 (13.8)	57 (14.5)
<12	85 (84.2)	87 (89.7)	82 (82.0)	81 (86.2)	335 (85.5)
sPGA score, n (%)[f]					
≥3	41 (40.2)	37 (38.1)	52 (52.0)	41 (43.6)	171 (43.5)
<3	61 (59.8)	60 (61.9)	48 (48.0)	53 (56.4)	222 (56.5)
BSA ≥3%, n (%)[f]					
Yes	67 (67.7)	68 (72.3)	73 (73.0)	59 (64.8)	267 (69.5)
No	32 (32.3)	26 (27.7)	27 (27.0)	32 (35.2)	117 (30.5)
Itch NRS score[e]					
Mean (SD)	4.2 (2.57)	4.1 (2.66)	4.3 (2.59)	4.3 (2.79)	4.2 (2.64)
Median	4.0	4.0	5.0	4.0	4.0
NAPSI total score[g]					
Mean (SD)	19.8 (17.17)	20.9 (17.46)	21.3 (18.91)	25.0 (21.15)	21.8 (18.76)
Median	16.0	17.0	16.0	20.0	17.0
SF-36 PCS score					
Mean (SD)	34.0 (8.33)	33.9 (8.85)	32.4 (10.09)	34.2 (8.68)	33.6 (9.01)

	RHAP (N=417)				
	Placebo (N = 106)	**ADA (N = 101)**	**IXEQ4W (N = 107)**	**IXEQ2W (N = 103)**	**Total (N = 417)**
Median	33.2	33.3	32.7	33.5	33.1
SF-36 MCS score					
Mean (SD)	47.4 (12.46)	46.6 (11.74)	46.5 (13.38)	48.0 (9.77)	47.1 (11.90)
Median	49.7	48.5	48.3	49.5	49.0
Van der Heijde mTSS					
Mean (SD)	17.6 (28.62)	15.9 (27.37)	19.2 (32.68)	15.2 (28.86)	17.0 (29.42)
Median	7.0	5.5	6.3	5.5	6.0

a Investigator-reported enthesitis

b In patients who have baseline enthesitis (LEI >0)

c Investigator-reported dactylitis

d In patients who have baseline dactylitis (LDI-B >0)

e In patients with baseline BSA ≥3%

f In patients who have baseline investigator-reported plaque psoriasis

g In patients with baseline fingernail involvement

Patients in the pivotal phase III trials fulfilled the CASPAR criteria for psoriatic arthritis. To be classified as psoriatic arthritis according to these criteria, patients must have inflammatory articular disease (joint, spine or entheseal) and ≥3 points from the following categories: Current psoriasis (2p) or personal or family history of psoriasis (1p), psoriatic nail dystrophy on current examination (1p), negative rheumatic factor (1p), dactylitis (current or on history as recorded by rheumatologist, 1p) or radiographic evidence of juxtaarticular new-bone formation (1p) (Tillett et al, J Rheumatology 2012). The CASPAR classification criteria are validated and have been used in several clinical studies and are considered acceptable. The patients must have an active disease, defined as at least 3 tender and swollen joints. The EMA PsA guideline does not provide definite classification criteria or definition of disease activity, but these criteria of active disease are identical to the ones used in the secukinumab trials, which is a relevant comparator.

To permit evaluation of radiographic outcome, patients with erosive disease or patients at risk of joint destruction (defined as laboratory signs of inflammatory activity) were enrolled in the study.

Concomitant treatment with analgesics and NSAIDs, including COX-2 inhibitors, were allowed to the maximum recommended doses for pain. DMARDs were allowed, but alteration of DMARD dose and/or introduction of a new DMARD were not permitted during the double-blind period. Oral corticosteroids was allowed up to 10 mg/day of prednisone or its equivalent.

In advice given by the CHMP (EMA/CHMP/SAWP/339078/2011), the company was discouraged to include patients naive to conventional DMARDs, since this would lead to a heterogenous study population with a combination of DMARD-naive and DMARD-experienced patients. The study was not powered to draw conclusions on the DMARD naive subpopulation. In this study, there is however a small proportion (14.6 %) of patients naive to DMARD therapy included. The sought indication is based on the DMARD-experienced population, as it follows *"Taltz, alone or in combination with conventional disease-modifying anti-rheumatic drug (cDMARD), is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies (see section 5.1)"*

Table 11. Concomitant Therapy Safety Population Double-Blind Treatment Period of study RHAP

ATC 4 Term Preferred Term	PBO (1) (N=106) n (%)	ADA40Q2W (2) (N=101) n (%)	IXE80Q4W (3) (N=107) n (%)	IXE80Q2W (4) (N=102) n (%)	Total IXE (N=209) n (%)	Total (N=416) n (%)	P-value Overall	2 vs. 1	3 vs. 1	4 vs. 1
Patients with >= 1 Concomitant Therapy	103 (97.2)	100 (99.0)	104 (97.2)	101 (99.0)	205 (98.1)	408 (98.1)	.647	.622	>.999	.622
OTHER SPECIFIC ANTIRHEUMATIC AGENTS	59 (55.7)	58 (57.4)	57 (53.3)	54 (52.9)	111 (53.1)	228 (54.8)	.908	.889	.784	.781
METHOTREXATE	55 (51.9)	50 (49.5)	54 (50.5)	51 (50.0)	105 (50.2)	210 (50.5)	.991	.782	.891	.890
METHOTREXATE SODIUM	4 (3.8)	8 (7.9)	3 (2.8)	3 (2.9)	6 (2.9)	18 (4.3)	.300	.243	.721	>.999
AMINOSALICYLIC ACID AND SIMILAR AGENTS	3 (2.8)	4 (4.0)	9 (8.4)	6 (5.9)	15 (7.2)	22 (5.3)	.314	.716	.135	.325
SULFASALAZINE	3 (2.8)	4 (4.0)	9 (8.4)	5 (4.9)	14 (6.7)	21 (5.0)	.329	.716	.135	.492
MESALAZINE	0	0	0	1 (1.0)	1 (0.5)	1 (0.2)	.488			.490
SELECTIVE IMMUNOSUPPRESSANTS	8 (7.5)	6 (5.9)	5 (4.7)	6 (5.9)	11 (5.3)	25 (6.0)	.856	.784	.408	.784
LEFLUNOMIDE	8 (7.5)	6 (5.9)	5 (4.7)	6 (5.9)	11 (5.3)	25 (6.0)	.856	.784	.408	.784

The majority of the patients on cDMARD therapy was on MTX. Only a minority was treated with other cDMARDs, for example sulfasalazine or leflunomide. (refer to discussion later in relation to the indication)

Numbers analysed

All the efficacy and health outcome endpoints were conducted on the ITT Population. The primary endpoint analysis of ACR20 response rate at Week 24 was repeated using the PPS. The primary, major secondary, and some important other secondary and health outcome analyses were also conducted using the cDMARD-Experienced Population. This dataset covered 355 patients with prior or current treatment with MTX, leflunomide, sulfasalazine, or cyclosporine randomised to either placebo (n=93), adalimumab (n=87), IXE80Q4W (n=90) or IXE80Q2W (n=85). Efficacy analyses were also conducted on the Inadequate Responder Population.

Outcomes and estimation

The primary efficacy variable ACR20 response using non-responder imputation for the ITT at Week 24 is shown in Table 12 and Figure 12. A higher proportion of patients in the ixekimumab 80 mg Q4W group and ixekimumab 80 mg Q2W group, compared to placebo, reached ACR20 response and the primary endpoint was thus met. The proportion of ACR20 responders in the IXE80Q4W group was similar to the proportion in the adalimumab group (57.9% and 57.4 %), and the response rate was slightly higher in the IXE80Q2W group (62.1 %). The ACR20 response rates for ixekizumab were different to placebo already at Week 12 (57%/60.2% vs 31.1 % in placebo).

Table 12 Key Outcomes from RHAP – Double-Blind Period

	PBO	ADA		IXE80Q4W		IXE80Q2W	
	Result	Result	Difference vs PBO[a]	Result	Difference vs PBO[a]	Result	Difference vs PBO[a]
ACR response rate, n(%)							
ACR20, Week 12	33 (31.1%)	52 (51.5%)	20.4% (7.2, 33.5) **p=.003**	61 (57.0%)	25.9% (13.0, 38.7) **p<.001**	62 (60.2%)	29.1% (16.1, 42.0) **p<.001**
ACR20, Week 24[b]	32 (30.2%)	58 (57.4%)	27.2% (14.2, 40.3) **p<.001**	62 (57.9%)	27.8% (15.0, 40.6) **p<.001**	64 (62.1%)	31.9% (19.1, 44.8) **p<.001**
ACR50, Week 12	5 (4.7%)	30 (29.7%)	25.0% (15.2, 34.8) **p<.001**	36 (33.6%)	28.9% (19.1, 38.7) **p<.001**	41 (39.8%)	35.1% (24.8, 45.4) **p<.001**
ACR50, Week 24	16 (15.1%)	39 (38.6%)	23.5% (11.8, 35.2) **p<.001**	43 (40.2%)	25.1% (13.6, 36.6) **p<.001**	48 (46.6%)	31.5% (19.7, 43.3) **p<.001**
ACR70, Week 12	0	18 (17.8%)	17.8% (10.4, 25.3) **p<.001**	16 (15.0%)	15.0% (8.2, 21.7) **p<.001**	17 (16.5%)	16.5% (9.3, 23.7) **p<.001**
ACR70, Week 24	6 (5.7%)	26 (25.7%)	20.1% (10.5, 29.7) **p<.001**	25 (23.4%)	17.7% (8.6, 26.8) **p<.001**	35 (34.0%)	28.3% (18.2, 38.5) **p<.001**
HAQ-DI							
Change from baseline, Week 12, LSM (95% CI)	-0.13 (-0.22,-0.04)	-0.35 (-0.44,-0.26)	-0.22 (-0.35, -0.09) **p<.001**	-0.37 (-0.46,-0.28)	-0.24 (-0.36,-0.12) **p<.001**	-0.47 (-0.56,-0.38)	-0.34 (-0.47,-0.21) **p<.001**
Change from baseline, Week 24, LSM (95% CI)	-0.18 (-0.28,-0.08)	-0.37 (-0.47,-0.27)	-0.19 (-0.33, -0.05) **p=.007**	-0.44 (-0.54,-0.34)	-0.26 (-0.40,-0.12) **p<.001**	-0.50 (-0.60,-0.40)	-0.32 (-0.46,-0.18) **p<.001**
≥0.35 response[c], Week 12, n(%)	27 (29.3%)	44 (49.4%)	20.1% (6.1, 34.0) **p=.006**	49 (49.0%)	19.7% (6.1, 33.2) **p=.008**	58 (64.4%)	35.1% (21.5, 48.7) **p<.001**
≥0.35 response[c], Week 24, n(%)	24 (26.1%)	44 (49.4%)	23.4% (9.6, 37.1) **p=.001**	49 (49.0%)	22.9% (9.6, 36.2) **p=.002**	52 (57.8%)	31.7% (18.1, 45.3) **p<.001**
MDA response rate, n (%)							
Week 12	5 (4.7%)	30 (29.7%)	25.0% (15.2, 34.8) **p<.001**	22 (20.6%)	15.8% (7.2, 24.5) **p<.001**	34 (33.0%)	28.3% (18.4, 38.2) **p<.001**
Week 24	16 (15.1%)	32 (31.7%)	16.6% (5.2, 27.9) **p=.005**	32 (29.9%)	14.8% (3.8, 25.8) **p=.013**	42 (40.8%)	25.7% (14.0, 37.4) **p<.001**
DAS28-CRP, Change from baseline, LSM (95% CI)							
Week 12	-0.6 (-0.8, -0.3)	-1.6 (-1.8, -1.3)	-1.0 (-1.3, -0.7) **p<.001**	-1.6 (-1.9, -1.4)	-1.1 (-1.4, -0.8) **p<.001**	-1.7 (-1.4, -1.4)	-1.1 (-1.4, -0.8) **p<.001**
Week 24	-0.8 (-1.1, -0.6)	-1.7 (-2.0, -1.5)	-0.9 (-1.3, -0.6) **p<.001**	-2.0 (-2.2, -1.7)	-1.1 (-1.5, -0.8) **p<.001**	-2.0 (-2.3, -1.8)	-1.2 (-1.5, -0.9) **p<.001**
LEI							
Change from baseline, Week 12[d], LSM (95% CI)	-0.8 (-1.3, -0.3)	-0.8 (-1.2, -0.3)	0.0 (-0.6, 0.7) p=.879	-0.9 (-1.3, -0.4)	0.0 (-0.7,0.6) p=.884	-1.5 (-2.0, -1.0)	-0.7 (-1.3,-0.0) p=.038
Change from baseline, Week 24[d], LSM (95% CI)	-0.8 (-1.4, -0.3)	-0.9 (-1.3, -0.4)	0.0 (-0.7, 0.6) p=.912	-1.3 (-1.7, -0.9)	-0.5 (-1.1,0.2) p=.151	-1.4 (-1.9, -0.9)	-0.6 (-1.2,0.1) p=.099
LEI (0)[e], Week 12, n (%)	16 (28.1%)	19 (35.2%)	7.1% (-10.2, 24.4) p=.540	19 (27.9%)	-0.1% (-15.9,15.7) p>.999	27 (47.4%)	19.3% (1.9, 36.7) p=.053

	PBO	ADA		IXE80Q4W		IXE80Q2W	
	Result	Result	Difference vs PBO[a]	Result	Difference vs PBO[a]	Result	Difference vs PBO[a]
LEI (0)[e], Week 24, n (%)	11 (19.3%)	18 (33.3%)	14.0% (-2.2, 30.3) p=.130	29 (42.6%)	23.3% (7.8, 38.9) **p=.007**	22 (38.6%)	19.3% (3.0, 35.6) **p=.038**
LDI-B[f]							
Change from baseline, Week 12, LSM (95% CI)	-26.8 (-40.8,-12.9)	-46.0 (-63.3,-28.6)	-19.1 (-40.2, 1.9) p=.075	-54.7 (-67.1,-42.3)	-27.9 (-44.9,-10.8) **p=.002**	-47.5 (-61.3, -33.7)	-20.7 (-38.6,-2.7) **p=.024**
Change from baseline, Week 24, LSM (95% CI)	-25.4 (-38.4,-12.5)	-57.1 (-72.7,-41.6)	-31.7 (-50.6, -12.7) **p=.001**	-57.1 (-68.4,-45.9)	-31.7 (-47.1,-16.3) **p<.001**	-48.3 (-60.9, -35.8)	-22.9 (-39.1,-6.7) **p=.006**
LDI-B (0), Week 12, n (%)	15 (53.6%)	11 (61.1%)	7.5% (-21.6, 36.7) p=.763	29 (74.4%)	20.8% (-2.2, 43.8) p=.117	18 (69.2%)	15.7% (-10.0, 41.3) p=.275
LDI-B (0), Week 24, n (%)	7 (25.0%)	14 (77.8%)	52.8% (27.8, 77.8) **p<.001**	31 (79.5%)	54.5% (34.0, 74.9) **p<.001**	20 (76.9%)	51.9% (29.1, 74.7) **p<.001**
mTSS, Change from baseline, LSM (95% CI)							
Week 16	0.36 (0.21, 0.50)	0.12 (-0.03, 0.26)	-0.24 (-0.43, -0.05) **p=.015**	0.13 (-0.02, 0.27)	-0.23 (-0.42,-0.04) **p=.018**	0.06 (-0.09, 0.20)	-0.30 (-0.49,-0.11) **p=.002**
Week 24	0.49 (0.32, 0.66)	0.10 (-0.06, 0.27)	-0.39 (-0.61, -0.16) **p<.001**	0.17 (0.00, 0.33)	-0.33 (-0.55,-0.10) **p=.004**	0.08 (-0.08, 0.24)	-0.41 (-0.63,-0.19) **p<.001**
SF-36, Change from baseline, LSM (95% CI)							
SF-36 PCS, Week 12	2.3 (0.7, 3.8)	5.7 (4.1, 7.3)	3.4 (1.4, 5.5) **p=.001**	5.8 (4.2, 7.3)	3.5 (1.4, 5.6) **p=.001**	7.6 (6.1, 9.2)	5.4 (3.3, 7.5) **p<.001**
SF-36 PCS, Week 24	2.9 (1.1, 4.8)	6.8 (5.0, 8.6)	3.8 (1.4, 6.3) **p=.002**	7.5 (5.7, 9.2)	4.5 (2.0, 7.0) **p<.001**	8.2 (6.5, 10.0)	5.3 (2.8, 7.8) **p<.001**
SF-36 MCS, Week 12	2.0 (0.3, 3.8)	3.6 (1.8, 5.4)	1.6 (-0.8, 3.9) p=.187	2.8 (1.0, 4.5)	0.7 (-1.6, 3.0) p=.541	3.4 (1.7, 5.2)	1.4 (-0.9, 3.7) p=.240
SF-36 MCS, Week 24	2.7 (0.7, 4.7)	4.2 (2.4, 6.1)	1.6 (-1.0, 4.1) p=.236	4.9 (3.0, 6.7)	2.2 (-0.4, 4.8) p=.096	3.4 (1.6, 5.2)	0.7 (-1.9, 3.3) p=.581
PASI response rate, n (%)[g]							
PASI 75, Week 12	5 (7.5%)	23 (33.8%)	26.4% (13.5, 39.2) **p<.001**	55 (75.3%)	67.9% (56.2, 79.6) **p<.001**	41 (69.5%)	62.0% (48.7, 75.4) **p<.001**
PASI 75, Week 24	7 (10.4%)	37 (54.4%)	44.0% (30.0, 57.9) **p<.001**	52 (71.2%)	60.8% (48.1, 73.5) **p<.001**	47 (79.7%)	69.2% (56.6, 81.8) **p<.001**
PASI 90, Week 12	1 (1.5%)	15 (22.1%)	20.6 (10.3, 30.8) **p<.001**	38 (52.1%)	50.6 (38.7, 62.4) **p<.001**	34 (57.6%)	56.1 (43.2, 69.1) **p<.001**
PASI 90, Week 24	4 (6.0%)	25 (36.8%)	30.8 (18.0, 43.6) **p<.001**	41 (56.2%)	50.2 (37.5, 62.9) **p<.001**	40 (67.8%)	61.8 (48.6, 75.0) **p<.001**
PASI 100, Week 12	1 (1.5%)	10 (14.7)	13.2 (4.3, 22.1) **p=.009**	23 (31.5)	30.0 (19.0, 41.1) **p<.001**	24 (40.7)	39.2 (26.3, 52.1) **p<.001**
PASI 100, Week 24	2 (3.0%)	16 (23.5)	20.5 (9.7, 31.4) **p<.001**	31 (42.5)	39.5 (27.4, 51.5) **p<.001**	31 (52.5)	49.6 (36.2, 62.9) **p<.001**
Itch NRS, Change from baseline, LSM (95% CI)[g]							
Week 12	0.2 (-0.3, 0.8)	-1.4 (-1.9, -0.8)	-1.6 (-2.4, -0.9) **p<.001**	-2.6 (-3.1,-2.1)	-2.8 (-3.6,-2.1) p<.001[h]	-2.8 (-3.4,-2.2)	-3.1 (-3.8,-2.3) p<.001[h]

	PBO	ADA		IXE80Q4W		IXE80Q2W	
	Result	**Result**	**Difference vs PBO[a]**	**Result**	**Difference vs PBO[a]**	**Result**	**Difference vs PBO[a]**
Week 24	-0.3 (-1.0, 0.3)	-1.7 (-2.3, -1.2)	-1.4 (-2.2, -0.6) **p<.001**	-2.9 (-3.4,-2.3)	-2.5 (-3.4,-1.7) **p<.001**	-2.8 (-3.4,-2.2)	-2.5 (-3.3,-1.6) **p<.001**

a Difference (IXE - PBO), (95% CI)

b Primary objective

c Intent-to-Treat Population with Baseline HAQ-DI ≥0.35

d Intent-to-Treat Population with enthesitis at baseline

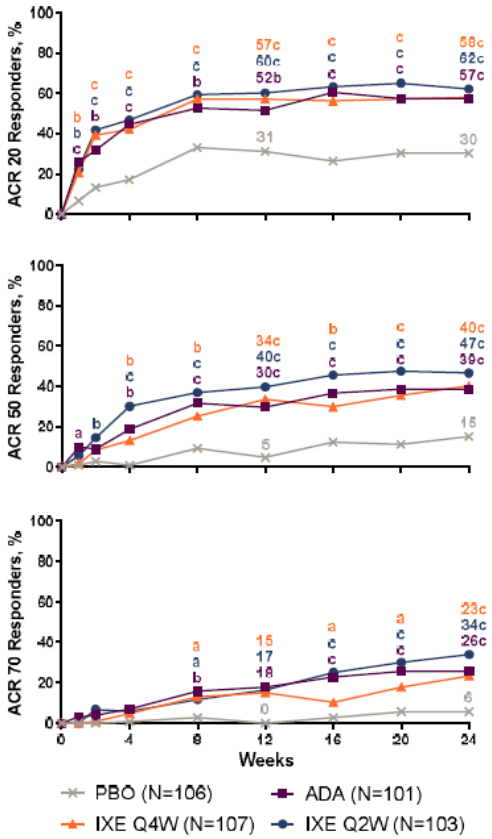
e Intent-to-Treat Population with baseline LEI >0

f Intent-to-Treat Population with LDI-B >0 at baseline

g Intent-to-Treat Population with baseline psoriatic lesions involving ≥3% BSA

h Per multiple testing procedure, this is considered not significant as the preceding endpoint (Change in LEI) was not significant (p<.025)

Figure 11. ACR20/50/70 response rates at each postbaseline visit (NRI), Intent-to-Treat Population, Double-Blind Treatment Period



Secondary efficacy results

Using multiplicity-controlled (gated) analyses, statistically significant differences for the ixekizumab 80 mg Q2W group, compared with the placebo group, and for the ixekizumab 80 mg Q4W group, compared with the placebo group, were observed for all major secondary endpoints with the exception of change from baseline to Week 12 in LEI (p>.025) and change from baseline to Week 12 in Itch NRS (not tested because of the multiplicity control strategy) (Table 13 and Table 14).

Table 13. Analysis for Primary and Gated Major Secondary Endpoints for Ixekizumab 80 mg Q2W Intent-to-Treat Population Double-Blind Treatment Period

Endpoint (IXE80Q2W vs. PBO)	LSMD or Odds Ratio (Nominal 95% CI)	Raw P-value	Adjusted Alpha	Adjusted P-value
Test 1: Proportion of patients achieving ACR20 response at Week 24 NRI[1]	3.88 (2.175, 6.913)	<0.001	.025	<0.001
Test 2: Change from baseline to Week 24 in HAQ-DI[2]	-0.317 (-0.4563, -0.1770)	<0.001	.025	<0.001
Test 3: Change from baseline to Week 24 in mTSS[2]	-0.410 (-0.6347, -0.1859)	<0.001	.025	<0.001
Test 4: Proportion of patients achieving ACR20 response at Week 12 NRI[1]	3.32 (1.876, 5.892)	<0.001	.025	<0.001
Test 5: Proportion of patients achieving PASI 75 response at Week 12 NRI, in patients with	29.06 (9.873, 85.532)	<0.001	.025	<0.001
Test 6: Change from baseline to Week 12 in LEI in patients with enthesitis at baseline[2]	-0.676 (-1.3164, -0.0366)	.038	.025	.038
Test 7: Change from baseline to Week 12 in Itch NRS, in patients with >= 3 % BSA[2]	-3.062 (-3.8211, -2.3024)	<0.001		

CI = Confidence Interval; LSMD = least squares mean difference; NRI = Non-responder Imputation.

Table 14. Analysis for Primary and Gated Major Secondary Endpoints for Ixekizumab 80 mg Q4W Intent-to-Treat Population Double-Blind Treatment Period

Endpoint (IXE80Q4W vs. PBO)	LSMD or Odds Ratio (Nominal 95% CI)	Raw P-value	Adjusted Alpha	Adjusted P-value
Test 1: Proportion of patients achieving ACR20 response at Week 24 NRI[1]	3.24 (1.837, 5.721)	<0.001	.025	<0.001
Test 2: Change from baseline to Week 24 in HAQ-DI[2]	-0.263 (-0.4024, -0.1245)	<0.001	.025	<0.001
Test 3: Change from baseline to Week 24 in mTSS[2]	-0.326 (-0.5490, -0.1036)	.004	.025	.004
Test 4: Proportion of patients achieving ACR20 response at Week 12 NRI[1]	2.92 (1.663, 5.138)	<0.001	.025	<0.001
Test 5: Proportion of patients achieving PASI 75 response at Week 12 NRI, in patients with	38.80 (13.359, 112.721)	<0.001	.025	<0.001
Test 6: Change from baseline to Week 12 in LEI in patients with enthesitis at baseline[2]	-0.045 (-0.6485, 0.5589)	.884	.025	.884
Test 7: Change from baseline to Week 12 in Itch NRS, in patients with >= 3 % BSA[2]	-2.835 (-3.5542, -2.1167)	<0.001		

CI = Confidence Interval; LSMD = least squares mean difference; NRI = Non-responder Imputation.

Analyses of the other secondary endpoints were not multiplicity controlled. Statistical significance when referring to a non- multiplicity-controlled analysis was based on a nominal p-value <.05.

Both ixekizumab groups differed from placebo (based on nominal p<.05) in the other secondary efficacy measures (ACR50/70, ACR-N, individual components of the ACR Core Set, DAS28-CRP, MDAsPGA, MDAPASI, PsARC, BASDAI, LDI-B, improvement in enthesitis and dactylitis, sPGA, percentage of BSA involvement of psoriasis, and NAPSI) and the secondary health outcomes endpoints of change from baseline in Itch NRS (except at Week 12 using multiplicity-controlled analyses), Fatigue NRS, health-related quality-of-life (as assessed by the SF-36 PCS), and depressive symptomology (as assessed by the QIDS-SR16 [Q2W only]).

Study RHAP met its primary outcome; ixekizumab 80 mg Q4W and 80 mg Q2W provided superior ACR20 responses at Week 24 compared to placebo. ACR20 responses were seen already at Week 12 and were maintained over time. There were numerically higher ACR20/50 response rates for Ixekizumab than for adalimumab. Ixekizumab was superior to placebo in inhibition of bone destruction, as measured by the mTSS at Week 24. As stated in the advice given by the CHMP, 24 weeks is a very short time to evaluate joint destruction. In the scientific advice, it was asked for descriptive evidence of joint structure preservation 12 and 24 months after baseline. In this application, only 12 month data are presented. In line with the results presented in the application for treatment in skin psoriasis, ixekizumab was superior to placebo based on the proportion of patients achieving PASI 75.

The proportion of patients classified as Inadequate Responders in each of the ixekizumab groups were smaller (Q4W, 11 patients [10.3%]; Q2W, 10 patients [9.7%]) compared with the placebo group (27 patients [25.5%]). This is considered to support the efficacy of ixekizumab. In the primary analysis data collected post-rescue were ignored and patients with inadequate response week 16 were treated as non-responders. This approach is acceptable. However, the company was requested by CHMP to provide the analysis of the primary endpoint taking all data collected up to week 24 into account irrespective of whether a patient received rescue or not, using a conservative approach. In the submitted analysis where observed data after Week 16 for Week 16 inadequate responders was included, the difference in ACR20 response rate at Week 24 between IXE80Q4W and IXE80Q2W respectively and placebo was smaller than in the primary analysis, due to a higher placebo response rate. The difference between treatment arms were however still statistically significant irrespective of comparison.

Results of the "other" secondary endpoints must be interpreted with knowledge of the absence of multiple-testing correction. Taken this into account, ixekixumab was superior to placebo in axial symptoms (change from baseline in BASDAI in the subset with baseline BASDAI>4, N=295).

The population for the LEI is a subpopulation of the ITT. Any apparent improvement at week 12 was not maintained.

Analysis in cDMARD-Experienced Population

For the cDMARD-Experienced Population, there were a statistically significantly higher percentage of patients who achieved ACR20 response at Week 24 for each of the ixekizumab groups compared with the placebo group. The ACR20 response rates at Week 24 (NRI) were 60.0% and 62.4% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 31.2% for the placebo group.

Table 15. ACR20, ACR50, and PASI 75 Response Rates at Weeks 12 and 24 (NRI); Comparison of cDMARD-Experienced and ITT Populations Double-Blind Treatment Period of RHAP

		PBO	ADA	IXE80Q4W	IXE80Q2W
ACR20 response rate at Week 12					
cDMARD-Experienced	n/N (%)	28/93 (30.1)	47/87 (54.0)	53/90 (58.9)	50/85 (58.8)
	Diff vs. PBO, % (95% CI)		**23.9 (9.9, 37.9)[b]**	**28.8 (15.0, 42.6)[c]**	**28.7 (14.7, 42.7)[c]**
ITT Population	n/N (%)	33/106 (31.1)	52/101 (51.5)	61/107 (57.0)	62/103 (60.2)
	Diff vs. PBO, % (95% CI)		**20.4 (7.2, 33.5)[b]**	**25.9 (13.0, 38.7)[c]**	**29.1 (16.1, 42.0)[c]**
ACR20 response rate at Week 24					
cDMARD-Experienced	n/N (%)	29/93 (31.2)	53/87 (60.9)	54/90 (60.0)	53/85 (62.4)
	Diff vs. PBO, % (95% CI)		**29.7 (15.8, 43.7)[c]**	**28.8 (15.0, 42.6)[c]**	**31.2 (17.2, 45.1)[c]**
ITT Population	n/N (%)	32/106 (30.2)	58/101 (57.4)	62/107 (57.9)	64/103 (62.1)
	Diff vs. PBO, % (95% CI)		**27.2 (14.2, 40.3)[c]**	**27.8 (15.0, 40.6)[c]**	**31.9 (19.1, 44.8)[c]**
ACR50 response rate at Week 12					
cDMARD-Experienced	n/N (%)	5/93 (5.4)	27/87 (31.0)	30/90 (33.3)	35/85 (41.2)
	Diff vs. PBO, % (95% CI)		**25.7 (14.9, 36.4)[c]**	**28.0 (17.2, 38.7)[c]**	**35.8 (24.4, 47.2)[c]**
ITT Population	n/N (%)	5/106 (4.7)	30/101 (29.7)	36/107 (33.6)	41/103 (39.8)
	Diff vs. PBO, % (95% CI)		**25.0 (15.2, 34.8)[c]**	**28.9 (19.1, 38.7)[c]**	**35.1 (24.8, 45.4)[c]**
ACR50 response rate at Week 24					
cDMARD-Experienced	n/N (%)	15/93 (16.1)	35/87 (40.2)	36/90 (40.0)	42/85 (49.4)
	Diff vs. PBO, % (95% CI)		**24.1 (11.4, 36.8)[c]**	**23.9 (11.3, 36.5)[c]**	**33.3 (20.3, 46.3)[c]**
ITT Population	n/N (%)	16/106 (15.1)	39/101 (38.6)	43/107 (40.2)	48/103 (46.6)
	Diff vs. PBO, % (95% CI)		**23.5 (11.8, 35.2)[c]**	**25.1 (13.6, 36.6)[c]**	**31.5 (19.7, 43.3)[c]**

		PBO	ADA	IXE80Q4W	IXE80Q2W
ACR70 response rate at Week 12					
cDMARD-Experienced	n/N (%)	0	17/87 (19.5)	13/90 (14.4)	15/85 (17.6)
	Diff vs. PBO, % (95% CI)		**19.5 (11.2, 27.9)[c]**	**14.4 (7.2, 21.7)[c]**	**17.6 (9.5, 25.8)[c]**
ITT Population	n/N (%)	0	18/101 (17.8)	16/107 (15.0)	17/103 (16.5)
	Diff vs. PBO, % (95% CI)		**17.8 (10.4, 25.3)[c]**	**15.0 (8.2, 21.7)[c]**	**16.5 (9.3, 23.7)[c]**
ACR70 response rate at Week 24					
cDMARD-Experienced	n/N (%)	6/93 (6.5)	23/87 (26.4)	21/90 (23.3)	30/85 (35.3)
	Diff vs. PBO, % (95% CI)		**20.0 (9.5, 30.5)[c]**	**16.9 (6.8, 26.9)[b]**	**28.8 (17.5, 40.2)[c]**
ITT Population	n/N (%)	6/106 (5.7)	26/101 (25.7)	25/107 (23.4)	35/103 (34.0)
	Diff vs. PBO, % (95% CI)		**20.1 (10.5, 29.7)[c]**	**17.7 (8.6, 26.8)[c]**	**28.3 (18.2, 38.5)[c]**
PASI 75 response rate at Week 12[d]					
cDMARD-Experienced	n/N (%)	5/59 (8.5)	21/59 (35.6)	49/64 (76.6)	36/50 (72.0)
	Diff vs. PBO, % (95% CI)		**27.1 (13.0, 41.3)[c]**	**68.1 (55.5, 80.7)[c]**	**63.5 (49.2, 77.9)[c]**
ITT Population	n/N (%)	5/67 (7.5)	23/68 (33.8)	55/73 (75.3)	41/59 (69.5)
	Diff vs. PBO, % (95% CI)		**26.4 (13.5, 39.2)[c]**	**67.9 (56.2, 79.6)[c]**	**62.0 (48.7, 75.4)[c]**
PASI 75 response rate at Week 24[d]					
cDMARD-Experienced	n/N (%)	7/59 (11.9)	32/59 (54.2)	47/64 (73.4)	40/50 (80.0)
	Diff vs. PBO, % (95% CI)		**42.4 (27.2, 57.5)[c]**	**61.6 (48.0, 75.2)[c]**	**68.1 (54.3, 82.0)[c]**
ITT Population	n/N (%)	7/67 (10.4)	37/68 (54.4)	52/73 (71.2)	47/59 (79.7)
	Diff vs. PBO, % (95% CI)		**44.0 (30.0, 57.9)[c]**	**60.8 (48.1, 73.5)[c]**	**69.2 (56.6, 81.8)[c]**

a p<.05; b p<.01; c p<.001

d Assessed in patients with baseline BSA ≥3%

Overall, the results in the cDMARD-experienced population are similar to the results in the ITT population.

Persistance of efficacy

ACR20/50/70 response rates from Weeks 0 through 52 for patients randomised to ixekizumab at Week 0 are shown in **Figure 13**. Among patients who achieved an ACR20/50/70 response at Week 24, approximately 80% maintained that response at Week 52 for both dosing regimens.

Figure 12. ACR20/50/70 response rates at each postbaseline visit (NRI), Intent-to-Treat Population – ixekizumab-treated patients, Double-Blind Treatment and Extension Periods, Study RHAP Maintenance Secondary Analysis Set.

The ACR responses were maintained over time. For ACR20, there were similar responses for ixekizumab 80 mgQ2W and 80 mg Q4W. For ACR50 and 70, response rates were numerically higher (and at some time points even statistically significantly higher) for ixekizumab 80 mg Q2W.

For the other major secondary endpoints, sustained therapeutic effect was observed for HAQ-DI and PASI75. For the radiographic endpoint mTSS, the change from baseline in mTSS was numerically higher in the IXE80Q4W group (mean 0.54) compared to the IXE80Q2W group (**Table 16**).

Table 16. Modified Total Sharp Score, Change from Baseline to Week 52, Extension Period Population

	PBO/IXEQ4W	PBO/IXEQ2W	ADA/IXEQ4W	ADA/IXEQ2W	IXE80Q4W/IXE80Q4W	IXE80Q2W/IXE80Q2W
mTSS change from baseline at Week 52 (Linear Extrapolation)						
n (N)	31 (45)	37 (46)	36 (49)	34 (48)	80 (97)	80 (96)
Mean (SD)	0.27 (0.844)	0.41 (0.810)	0.32 (1.015)	-0.03 (0.388)	0.54 (2.120)	0.09 (0.953)
mTSS change from baseline at Week 52 (LOCF)						
n (N)	43 (45)	44 (46)	47 (49)	45 (48)	93 (97)	95 (96)
Mean (SD)	0.18 (0.610)	0.45 (0.869)	0.24 (0.896)	0.06 (0.535)	0.42 (1.906)	0.10 (0.774)

	PBO / IXEQ4W	PBO / IXEQ2W	ADA / IXEQ4W	ADA / IXEQ2W	IXE80Q4W / IXE80Q4W	IXE80Q2W / IXE80Q2W
mTSS change from baseline at Week 52 (Observed)[a]						
n (N)	33 (33)	34 (34)	40 (40)	35 (35)	78 (78)	82 (82)
Mean (SD)	0.17 (0.645)	0.47 (0.888)	0.29 (0.967)	0.07 (0.607)	0.44 (2.068)	0.12 (0.801)
mTSS change from baseline at Week 52 (Linear Extrapolation with Delayed Radiograph Interpolation)[a,b]						
n (N)	43 (45)	44 (46)	47 (49)	45 (48)	93 (97)	95 (96)
Mean (SD)	0.15 (0.537)	0.32 (0.773)	0.14 (0.643)	0.03 (0.659)	0.21 (0.977)	0.10 (0.605)

a Extension Period Population with non-missing mTSS at Week s0, 24, and 52.

b Includes patients whose radiograph was delayed (obtained more than 1 day after Week 52)

2.4.2.3. Study RHBE (inadequate responders to, or intolerant to, a TNFi)

Study RHBE was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study in patients with active PsA who were cDMARD- and bDMARD-experienced and either inadequate responders (have discontinued at least 1 TNFi due to either an inadequate response [based on a minimum of 12 weeks on therapy]), or intolerant to, a TNFi. The study was conducted in 109 sites across 10 countries.

Study participants

The study population included patients aged 18 years or older who were cDMARD-experienced, previously treated with at least 1 tumor necrosis factor α inhibitor (TNFi) (discontinued due to inadequate response or intolerance), had an established diagnosis of PsA (of at least 6 months and currently met the Classification Criteria for Psoriatic Arthritis), had a least 3/68 tender and 3/66 swollen joints, and had active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis.

Inclusion criteria

Male or female patients who were 18 years or older, with an established diagnosis of PsA (of at least 6 months duration) and currently met the Classification Criteria for Psoriatic Arthritis (CASPAR) were enrolled in the study. Patients were also required to have the following:

1) active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints, as determined by the Tender and Swollen Joint Count Assessment Form at Visit 1 (Screening) and Visit 2 (Week 0, baseline)
2) prior treatment with 1 or more cDMARDs (MTX, sulfasalazine, leflunomide, or hydroxychloroquine)
3) prior treatment with at least 1 and not more than 2 TNFi, discontinued due to either an inadequate response (based on a minimum of 12 weeks on therapy) or documented intolerance
4) active psoriatic skin lesions (plaque) or a documented history of plaque psoriasis

Main exclusion criteria

Patients were excluded from the study if they were receiving or had received medication or therapy that could confound the interpretation of the study results or be a safety risk if taken concomitantly with the study drug. Examples of these prohibited medications or therapies included the following:

- any biologic or small molecule therapy for PsA or psoriasis, including investigational therapies
- concurrent or recent use of any biologic agent within the following washout periods: etanercept <28 days; infliximab, adalimumab, certolizumab pegol, or alefacept <60 days; golimumab <90 days; rituximab <12 months; or any other biologic agent or small molecule <5 half-lives prior to baseline (Week 0; Visit 2)
- used DMARDs other than MTX, leflunomide, sulfasalazine, or hydroxychloroquine (for example, gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents) in the 8 weeks prior to baseline (Week 0, Visit 2)

a. discontinued MTX or sulfasalazine within the 8 weeks prior to baseline, or hydroxychloroquine within 12 weeks prior to baseline

b. if taking MTX, leflunomide, sulfasalazine, or hydroxychloroquine must have been treated for at least 12 weeks prior to baseline and on a stable dose for at least 8 weeks prior to baseline, as follows: oral or parenteral MTX = 10 to 25 mg/week, leflunomide = 20 mg/day, sulfasalazine = up to 3 g/day, or hydroxychloroquine = up to 400 mg/day 6)

- received treatment with more than 1 conventional DMARD (MTX, leflunomide, sulfasalazine, or hydroxychloroquine) at study entry
- discontinued leflunomide within 4 weeks prior to baseline or received leflunomide from 4 to 12 weeks prior to baseline (Week 0, Visit 2) and had not undergone a drug elimination procedure
- used oral corticosteroids at average daily doses of >10 mg/day of prednisone or its equivalent, or used variable doses of any oral corticosteroids, within 4 weeks prior to baseline (Week 0, Visit 2)
- any parenteral glucocorticoid administered by intra-articular, intramuscular, or intravenous (IV) injection within 6 weeks prior to baseline (Week 0, Visit 2), or for whom a parenteral injection of glucocorticosteroids was anticipated during the Double-Blind Treatment Period (Period 2) of the study
- concomitantly used NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, unless the patient was on a stable dose for at least 2 weeks prior to baseline (Week 0, Visit 2)
- used any opiate analgesic at average daily doses of >30 mg/day of morphine or its equivalent or used variable doses of any opiate analgesic within 6 weeks prior to baseline (Week 0, Visit 2)
- received systemic nonbiologic psoriasis therapy other than DMARDs or corticosteroids as indicated above (including, but not limited to, oral psoralens and ultraviolet A [PUVA] light therapy, oral retinoids, thioguanine, hydroxyurea, fumaric acid derivatives, or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA, ultraviolet B [UVB] or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to baseline (Week 0, Visit 2); OR had topical psoriasis treatment within the previous 2 weeks prior to baseline (Week 0, Visit 2)

- had ever received natalizumab or other agents that target α-4-integrin

Patients were also excluded if they were identified to have a history of drug-induced psoriasis.

Treatments

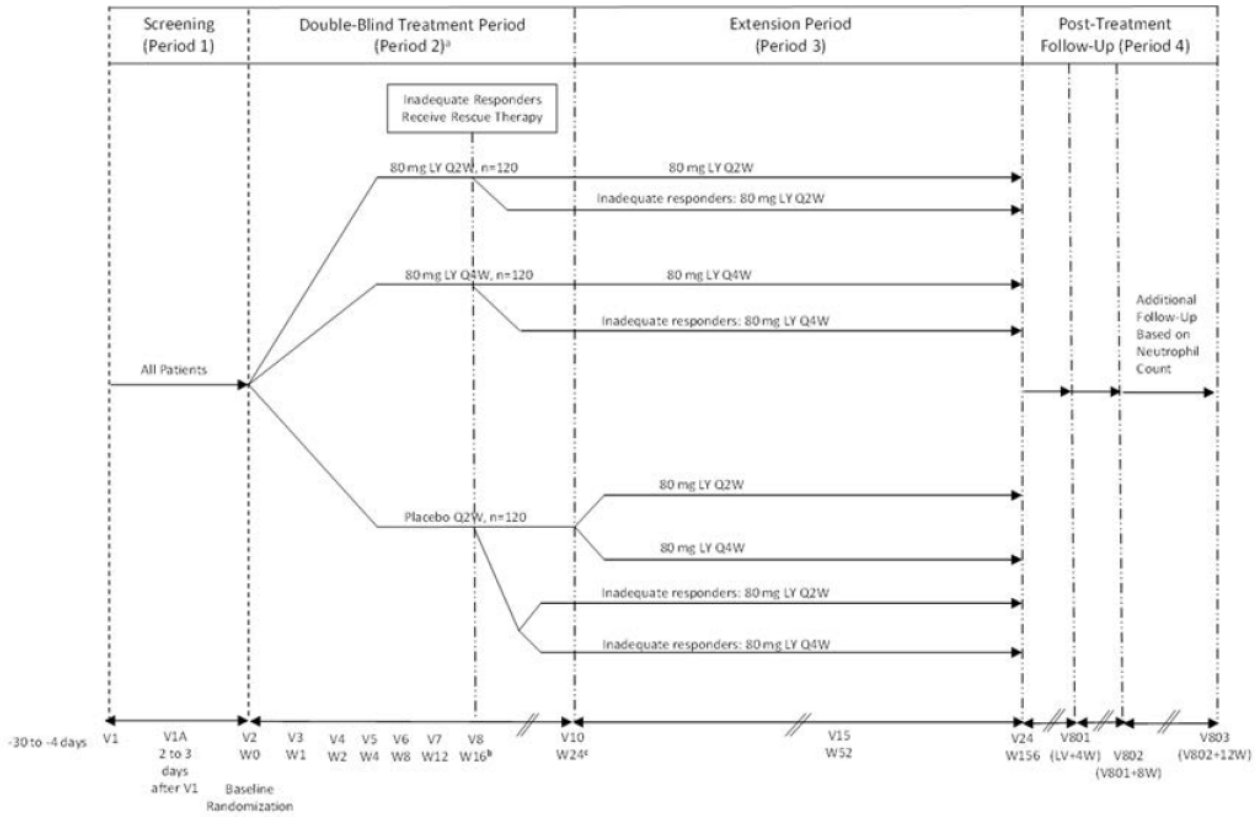
The study design is presented in **Figure 10**. Patients were randomised to either

Eligible patients were randomized at a 1:1:1 ratio to 1 of 3 treatment groups:

- ixekizumab 80 mg Q2W SC
- ixekizumab 80 mg Q4W SC, or
- placebo

Patients were stratified by country and TNFi experience (inadequate responder [IR] to 1 TNFi, IR to 2 TNFi, or intolerance to a TNFi).

Figure 13 RHBE Study Design



The study consisted of 4 periods:

- Period 1: Screening Period lasting from 4 to 30 days prior to Period 2
- Period 2: Double-Blind Treatment Period from Week 0 (baseline) to Week 24 inclusive.
- Period 3: Extension Period after Week 24 to Week 156
- Period 4: Post-Treatment Follow-Up Period occurring from last treatment period visit or Early Termination Visit to a minimum of 12 weeks following that visit.

Both ixekizumab dosing regimens required a starting dose of 160 mg at baseline. From Week 2, patients received the randomised treatment.

Patients who were incomplete responders (IRs) at Week 16 as defined by blinded TJC and SJC criteria received rescue therapy (modification of background treatment). The IRs at Week 16 who had been assigned to placebo were also re-randomized (1:1) to either ixekizumab dose regimen at that time. Patients who remained on placebo at Week 24 were re-randomized (1:1) to receive ixekizumab 80 mg Q2W or 80 mg Q4W, beginning with a starting dose of 160 mg (given as 2 injections).

After Week 16, dose change or introduction of new cDMARD was allowed. Not more than 1 adjustment of DMARDs at 1 time within 12 weeks was recommended. The maximum allowed dose was 25 mg/week for MTX, 400 mg/day for hydroxychloroquine, 20 mg/day for leflunomide, and 3 g/day for sulfasalazine. The maximum corticosteroid dose allowed was 10 mg/day of prednisone or its equivalent. Intra-articular injection of max 1 corticosteroid injection within 1 year was recommended.

Objectives

The primary objective was to compare ixekizumab 80 mg Q2W and 80 mg Q4W versus placebo in the treatment of patients with active PsA who are bDMARD-experienced, as measured by the proportion of patients achieving ACR20 response at Week 24.

The major secondary objectives were to compare ixekizumab 80 mg Q2W and 80 mg Q4W versus placebo in the treatment of patients with active PsA who were bDMARD-experienced based on the following measures:

- change from baseline to Week 24 in Health Assessment Questionnaire-Disability Index (HAQ-DI) scores
- proportion of patients achieving ACR20 response rate at Week 12
- proportion of patients achieving Psoriasis Activity and Severity Index (PASI) 75 response rate at Week 12 (restricted to patients with baseline psoriatic lesion involving ≥3% body surface area [BSA])
- proportion of patients achieving Coates criteria for Minimum Disease Activity (MDA) at Week 24 (using LEI [6 entheseal points (E6)] to assess enthesitis)
- proportion of patients achieving complete resolution in enthesitis as assessed by the LEI at Week 24 in patients with enthesitis at baseline (LEI >0)

Outcomes/endpoints

The primary efficacy endpoint was the proportion of patients with ACR20 response at Week 24.

The major secondary endpoints (multiplicity-corrected) were

- Change in HAQ-DI at Week 24
- ACR20 at Week 12
- PASI 75 at Week 12
- MDA at Week 24
- LEI resolution at Week 24

Other secondary endpoints are shown in table 8. The endpoints are defined in the methods to study RHAP.

Sample size

The total planned sample size for the study was 360 patients, 120 patients per arm. Assumptions and inputs to determine sample size included a 2-sided Fisher's exact test at the 0.025 level to maintain an overall type I error rate of 0.05 across the two ixekizumab doses. With 120 patients per arm and assuming the Week 24 ACR20 response rates of 15% for placebo and 35% for ixekizumab 80 mg Q2W, power was approximately 90%. These assumptions were based on the review of historical clinical studies in PsA (Mease et al. 2004, 2005, 2011a; Gladman et al. 2005; Kavanaugh et al. 2009). Calculations were performed using nQuery + nTerim 2.0 software.

For Study RHBE, the sample size was estimated taking into account only the primary endpoint (which is acceptable). Compared to the assumptions made in Study RHAP, the difference in ACR20 response rate between ixekizumab and placebo was assumed to be smaller (i.e. 20% compared to 33%).

Randomisation

At Week 0 (baseline, Visit 2), patients who met all criteria for enrolment at Visits 1/1A and 2 were randomly assigned in a 1:1:1 ratio to treatment arms using an interactive web-response system (IWRS). Randomisation was stratified by country and TNFi experience (inadequate responder to 1 TNFi, inadequate responder to 2 TNFi, or intolerance to a TNFi). A patient who was an inadequate responder to one TNFi and intolerant to another TNFi was classified as IR to one TNFi.

Inadequate Responders (IRs) at Week 16 receiving placebo were re-randomised (1:1) to ixekizumab 80 mg Q2W or 80 mg Q4W and received rescue therapy. The IRs at Week 16 in the ixekizumab groups continued receiving ixekizumab to both maintain the blind and allow additional response time in case of slow-responders in this group. At Week 24, patients remaining in the placebo treatment group at the completion of Period 2 were re-randomised (1:1) to ixekizumab 80 mg Q2W or Q4W.

Blinding

This was a double-blind study; patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments, including re-randomisations at Week 16 and Week 24, until all patients completed Week 24 or had discontinued from the study (moved into Period 4) and the clinical trial database through Week 24 had been locked.
There were no events of premature unblinding at the time of the Week 24 database lock.

Statistical methods

Unless otherwise specified, the efficacy analyses for the Double-Blind Treatment Period were conducted on the Intent to Treat Population (ITT), defined as all randomised patients analysed according to the treatment to which they were assigned at Week 0.

The primary analyses of ACR 20 compared each ixekizumab dose regimen (80 mg Q2W or 80 mg Q4W) with placebo using a logistic regression analysis model with treatment, geographic region, and TNFi experience (inadequate responder to 1 TNFi, inadequate responder to 2 TNFi, or intolerance to a TNFi). The odds ratio, the corresponding 95% CIs and p-value, as well as the treatment differences and the corresponding 95% CIs, were reported. Missing data were imputed using non-responder imputation (NRI). Sensitivity analyses were performed for the primary analysis using a MMRM model for categorical outcomes. The primary analyses were also repeated using the Per Protocol Set (PPS); a subset of the ITT Population defined as all randomised patients who were compliant with therapy, who did not have significant protocol violations, and whose investigator's site did not have significant GCP issues. For patients eligible for rescue therapy at Week 16 to be included in the PPS, the above requirements only applied up to Week 16.

Multiplicity controlled analyses were performed on the primary and key secondary analyses in order to control the overall Type I error rate at a 2-sided alpha level of 0.05. The total α was initially split equally between the ixekizumab 80 mg Q2W and 80 mg Q4W dose regimen and the primary hypothesis (ACR20) for these two doses were allocated a type I error of α/2 (of 0.025) implying a gatekeeping strategy within each treatment arm. A graphical approach was used. Initially, all the primary and secondary endpoints within a dose were tested in a sequential manner. If all the hypotheses for a dose regimen were rejected at α/2 (or 0.025 level) then the hypotheses related to other dose regimen could be tested at level α (or 0.05 level). There was no adjustment for multiple comparisons for other secondary analyses.

For the analysis of categorical outcome variables besides the primary (e.g. ACR50, ACR70, PASI75, PASI 90, PASI 100, sPGA [0,1]), the same logistic regression model was used as was the same non-responder imputation (NRI) approach for both missing values and for patients receiving rescue

treatment (inadequate responders). The odds ratio, the corresponding 95% CIs and p-value, as well as the treatment differences and the corresponding 95% CIs, were reported. Secondary analyses were conducted using a Fisher's exact test.

The primary analyses for all continuous outcome variables were based on a mixed-effects models for repeated measures (MMRM) analysis. Treatment comparisons of continuous efficacy variables were also made using analysis of covariance (ANCOVA).

Missing data were handled using a modified baseline-observation-carried-forward approach (mBOCF). For patients discontinuing investigational product due to an AE, the baseline observation were carried forward to Week 24. For patients discontinuing investigational product for any other reason, the last non-missing observation before discontinuation were carried forward, with the exception for patients eligible for rescue therapy at Week 16 (Inadequate Responders at Week 16). For inadequate responders, the last non-missing observation up to Week 16 was carried forward to the corresponding primary endpoint for evaluation. Randomised patients without at least one post-baseline observation were to be excluded for evaluation with the exception of patients discontinuing study treatment due to an AE.

As a sensitivity analysis an ANCOVA using LOCF were performed. This approach was identical to the mBOCF approach, with one exception: for patients discontinuing investigational product due to an AE, the last non-missing post-baseline observation before discontinuation was carried forward to the corresponding endpoint for evaluation. For patients eligible for rescue therapy at Week 16, their last non-missing observation up to Week 16 were carried forward to the corresponding primary endpoint for evaluation. Randomised patients without at least one post-baseline observation were excluded.

In addition, analyses of major continuous endpoints Week 24 were repeated using MMRM and a Placebo Multiple Imputation (pMI) method; pMI assumes that the statistical behavior of drug- and placebo- treated patients after discontinuing study medication becomes that of placebo-treated patients.

For time-to analyses, the proportion of patients achieving response was to be presented for each visit using Kaplan-Meier estimates. Treatment group comparisons were performed using both an unadjusted log-rank test and an adjusted log-rank test stratified by geographic region and TNFi experience (inadequate responder to 1 TNFi, inadequate responder to 2 TNFi, or intolerance to a TNFi). In addition, Kaplan-Meier plots were to be provided.

For the primary endpoint, ACR20 response rate at Week 24, pre-defined subgroup analyses were conducted for using the ITT Population.

Safety analyses for Period 2 were conducted on the Safety Population, defined as all randomised patients who received at least 1 dose of study treatment. For those patients classified as inadequate responders at Week 16, data after Week 16 were excluded. Patients were to be analysed according to the treatment to which they were assigned at Week 0.

Unblinded interim analyses of safety data were evaluated by an independent Data Monitoring Committee (DMC), which consisted of members external to Lilly and study team. The primary database lock occurred when all patients completed or discontinued from the Double-Blind Treatment Period (Period 2, Week 24).

Following this database lock the study team was unblinded and the primary analysis performed. Unblinding details were to be specified in the unblinding plan.

CHMP comments :

Considering similar designs and endpoints the statistical analysis plan for Study RHBE shared a number of features with the statistical analysis plan for Study RHAP. Same comments are raised below:

As for Study RHAP, the primary analysis population included all randomised subjects. In all analyses, data collected after start of rescue/week 16 were ignored. Although this is an acceptable primary approach, sensitivity/supportive analyses including data post-rescue should have been planned as discussed within the scientific advice procedure 2011 (EMA/CHMP/SAWP/339078/2011). Categorical endpoints, including the primary endpoint, were analysed using logistic regression and missing data were handled using a non-responder imputation. For the analysis of the primary endpoint (and other categorical endpoints) this implied that patients with inadequate response week 16 were treated as non-responders.

Treating patients with completely missing data as non-responders is considered to be an appropriate approach, especially considering that the majority of the missing data at week 24 was created by the study design and was those patients with an inadequate response at week 16.

Unlike in study RHAP it was not specified that LOCF would be used for patients with partially missing data for a visit.

For continuous endpoints the primary analysis approach was MMRM. Considering the missing at random assumption, the planning and performing of sensitivity/supportive analyses is endorsed.

Sensitivity analyses for major categorical endpoints included categorical MMRM and logistic regression using placebo Multiple Imputation (pMI). Sensitivity analysis for continuous endpoints included ANCOVA using a modified baseline-observation-carried-forward (mBOCF) approach and last-observation-carried-forward (LOCF) respectively as well as MMRM using pMI. The mBOCF implied that the baseline observation was carried forward only for patients discontinuing study treatment due to an AE, for other reasons, the last non-missing observation before discontinuation were carried forward. In all cases except treatment discontinuation due to an AE, a post-baseline observation was used for imputation. The difference between analyses using mBOCF and analyses using LOCF may hence be small.

For primary and key secondary analyses, multiplicity was appropriately handled through the use of a graphical approach implying a gatekeeping strategy within each treatment arm. To handle the two pairwise comparisons α was initially split equally between the ixekizumab 80 mg Q2W and 80 mg Q4W dose regimen and the primary hypothesis (ACR20) for these two doses tested at α/2 (of 0.025).

Regarding the definition of the Safety Population, patients were to be analysed according to the treatment to which they were assigned at Week 0. Generally, and more appropriate, patients should be analysed according to the actual treatment received. During the double-blind period all patients seemingly received the correct assigned treatment; treatment errors did however occur during the long-term extension.

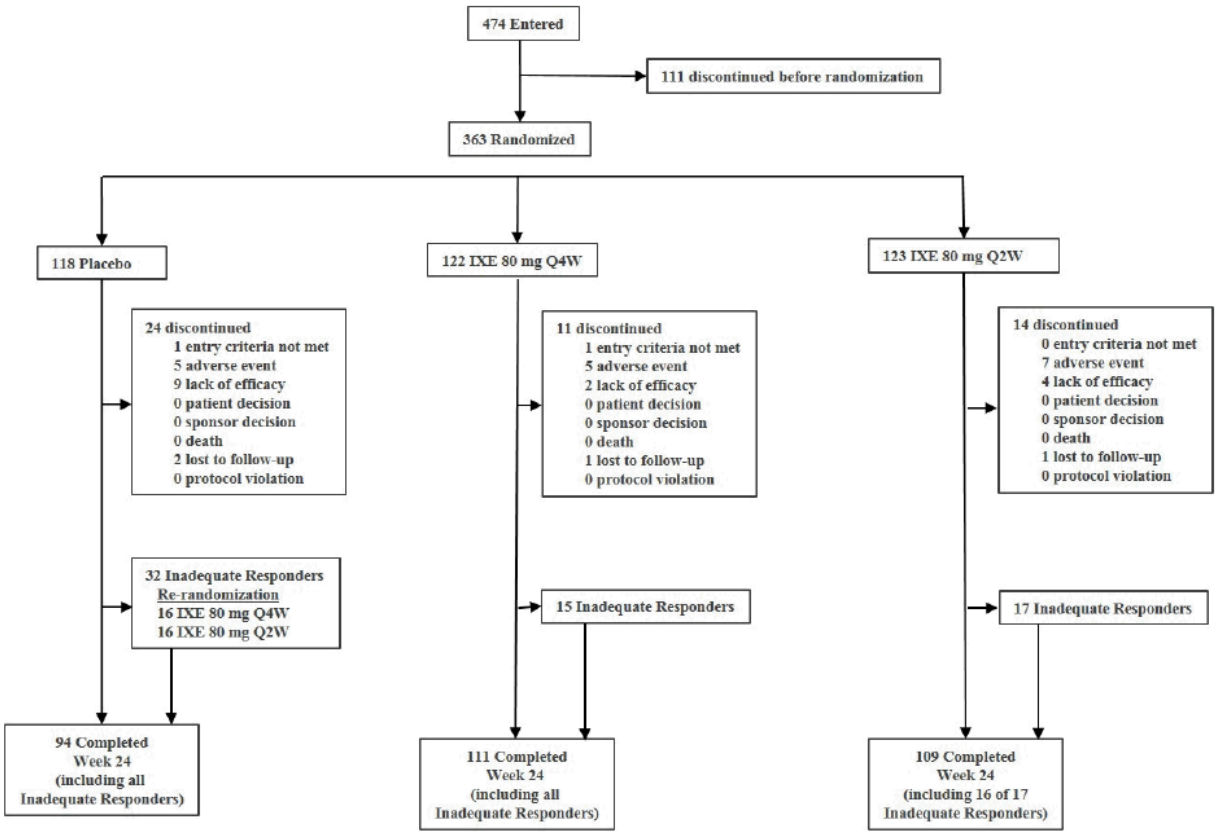
The interim database lock to perform the primary analysis was pre-defined to occur once all patients had completed or discontinued in the Double-Blind Treatment Period (Week 24). SAP Version 1 was approved prior to unblinding the unblinded team for the first data monitoring committee (DMC).

Participant flow

A total of 474 patients entered the study. Prior to randomization at Week 0, 111 patients discontinued from the study. In total, 363 patients were randomized to 1 of 3 treatment groups as the ITT

Population: 122 to ixekizumab 80 mg Q4W, 123 to ixekizumab 80 mg Q2W, 118 to placebo. A total of 86.5% of randomized patients completed the Double-Blind Treatment Period. **Figure 14** summarizes patient disposition from study drug (trial entry through the end of the Double-Blind Treatment Period) for the ITT Population. A total of 64 patients in the ITT Population were classified as IRs at Week 16.

Figure 14. Patient disposition from study treatment during the Double-Blind Treatment Period for the Intent-to-Treat Population



Abbreviations: IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

The main reason for discontinuation was lack of efficacy, which was more frequent in the placebo group. Slightly higher proportion of patients in the IXE 80 mg Q2W group than in the other groups discontinued due to adverse events (5.7 % vs 4.2 % in placebo). There was a higher proportion of inadequate responders in the placebo group (27.1%) than in the IXEQ4W (12.3 %) and IXEQ2W (13.8 %) groups (Table 17).

Table 17. Patient Completion and Disposition, Intent-to-Treat Population, Double-Blind Treatment Period Study RHBE

	RHBE n (%)			
	Placebo (N = 118)	**IXEQ4W (N = 122)**	**IXEQ2W (N = 123)**	**Total (N = 363)**
Number of Patients (%)				
Randomized at Week 0	118	122	123	363
Inadequate Responders (Week 16)	32 (27.1)	15 (12.3)	17 (13.8)	64 (17.6)
Completed Week 24	94 (79.7)	**111 (91.0)[a]**	109 (88.6)	314 (86.5)

	RHBE n (%)			
	Placebo (N = 118)	IXEQ4W (N = 122)	IXEQ2W (N = 123)	Total (N = 363)
Reason for Treatment Discontinuation (Double-Blind Treatment Period)				
Adverse Event	5 (4.2)	5 (4.1)	7 (5.7)	17 (4.7)
Lack of Efficacy	9 (7.6)	**2 (1.6)[a]**	4 (3.3)	15 (4.1)
Patient Decision	7 (5.9)	2 (1.6)	2 (1.6)	11 (3.0)
Entry Criteria not Met	1 (0.8)	1 (0.8)	0	2 (0.6)
Lost to Follow-Up	2 (1.7)	1 (0.8)	1 (0.8)	4 (1.1)
Sponsor Decision	0	0	0	0
(Other) Protocol Violation	0	0	0	0
Death	0	0	0	0
Clinical Relapse	0	0	0	0
Physician Decision	0	0	0	0
Caregiver Decision	0	0	0	0

Reasons for discontinuation from study drug for the ITT Population during the Double-Blind Treatment Period were similar across treatment groups. The most common reasons for study drug discontinuation among patients in the placebo group were lack of efficacy, withdrawal by subject, and AE. For the total ixekizumab group, the most common reasons for study drug discontinuation were AE, lack of efficacy, and withdrawal by subject.

Recruitment

Date of first patient enrolled: 03 March 2015
Date of last patient completed Week 24 Visit or early termination: 09 September 2016
Date of database lock: 30 September 2016

Conduct of the study

There were no protocol amendments.

Baseline data

The mean age of patients in the ITT Population was 51.9 years. The majority of patients were female (53.4%) and white (91.7%).

Patient demographics and baseline characteristics are summarized in **Table 18**.

Table 18. Patient demographics and Baseline Characteristics

	RHBE (N=363)			
	Placebo (N = 118)	IXEQ4W (N = 122)	IXEQ2W (N = 123)	Total (N = 363)
Demographics				
Age (Years)				
Mean (SD)	51.5 (10.39)	52.6 (13.57)	51.7 (11.85)	51.9 (12.00)
Median	52.0	56.0	51.0	53.0
Sex, n (%)				
Male	56 (47.5)	63 (51.6)	50 (40.7)	169 (46.6)
Female	62 (52.5)	59 (48.4)	73 (59.3)	194 (53.4)
Race, n (%)				
American Indian or Alaska Native	0	0	0	0

	RHBE (N=363)								
	Placebo (N = 118)	IXEQ4W (N = 122)	IXEQ2W (N = 123)	Total (N = 363)	Placebo (N = 118)	IXEQ2W (N = 103)	Total (N = 417)	IXEQ4W (N = 122)	Pla (N =
Asian	7 (5.9)	7 (5.7)	7 (5.7)	21 (5.8)					
Black or African American	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.8)					
Native Hawaiian or Other Pacific Islander	0	1 (0.8)	0	1 (0.3)					
White	108 (9.15)	111 (91.0)	113 (92.6)	332 (91.7)					
Multiple	2 (1.7)	2 (1.6)	1 (0.8)	5 (1.4)					
Geographic Region, n (%)									
Europe	50 (42.4)	49 (40.2)	50 (40.7)	149 (41.0)					
United States	60 (50.8)	65 (53.3)	63 (51.2)	188 (51.8)					
Rest of the World	8 (6.8)	8 (6.6)	10 (8.1)	26 (7.2)					
Weight (kg)									
Mean (SD)	91.0 (22.11)	89.9 (22.04)	85.2 (20.65)	88.7 (21.69)					
Median	86.9	88.1	83.7	86.0					
BMI, (kg/m^2)									
Mean (SD)	31.6 (7.58)	30.9 (7.14)	30.1 (6.77)	30.9 (7.17)					
Median	29.8	30.0	28.7	29.4					
Previous Therapy									
Yes	40 (33.9)	48 (39.3)	61 (49.6)	149 (41.0)					
No	78 (66.1)	74 (60.7)	62 (50.4)	214 (59.0)					
Background Therapy, n (%)									
cDMARD naive			NA						
cDMARD past use	66 (55.9)	62 (50.8)	50 (40.7)	178 (49.0)					
cDMARD current use	52 (44.1)	60 (49.2)	73 (59.3)	185 (51.0)					
Background Therapy, n (%)									
Inadequate responder to 1 TNFi	68 (57.6)	71 (58.2)	65 (52.8)	204 (56.2)					
Inadequate responder to 2 TNFi	41 (34.7)	41 (33.6)	46 (37.4)	128 (35.3)					
Intolerance to a TNFi	9 (7.6)	10 (8.2)	12 (9.8)	31 (8.5)					
Disease Characteristics									
CASPAR Total Score									
Mean (SD)	4.0 (0.86)	4.3 (0.83)	4.1 (0.86)	4.1 (0.85)					
Median	4.0	4.0	4.0	4.0					
Moll and Wright Classification, n (%)									
DIP joint only	3 (2.5)	2 (1.6)	6 (4.9)	11 (3.0)					
Asymmetrical Oligoarthritis	10 (8.5)	12 (9.8)	14 (11.4)	36 (9.9)					
Polyarthritis	103 (87.3)	103 (84.4)	98 (79.7)	304 (83.7)					
Spondylitis	1 (0.8)	4 (3.3)	3 (2.4)	8 (2.2)					
Arthritis Mutilans	1 (0.8)	1 (0.8)	2 (1.6)	4 (1.1)					
Time Since PsA Onset (years)									
Mean (SD)	11.1 (8.45)	13.8 (10.63)	11.5 (7.46)	12.2 (9.00)					
Median	9.2	11.4	9.6	10.1					
Time Since PsA Diagnosis (years)									
Mean (SD)	9.2 (7.30)	11.0 (9.63)	9.9 (7.39)	10.0 (8.19)					
Median	7.9	8.8	8.8	8.2					
Time Since Ps Onset (years)									
Mean (SD)	17.0 (12.15)	18.8 (13.11)	18.4 (13.39)	18.1 (12.89)					
Median	13.6	15.9	14.4	14.8					
Time Since Ps Diagnosis (years)									

	RHBE (N=363)						
	Placebo (N = 118)	IXEQ4W (N = 122)	IXEQ2W (N = 123)	Total IXEQ2W (N = 417)	Placebo (N = 118)	Total IXEQ4W (N = 122)	Pla (N =
Mean (SD)	15.3 (12.64)	15.7 (12.29)	16.5 (13.00)	15.8 (12.63)			
Median	11.0	12.0	12.8	12.0			
Enthesitis[a]							
Yes	85 (72.0)	89 (73.0)	99 (80.5)	273 (75.2)			
No	33 (28.0)	33 (27.0)	24 (19.5)	90 (24.8)			
LEI score[b]							
Mean (SD)	2.9 (1.67)	2.9 (1.40)	3.0 (1.66)	2.9 (1.58)			
Median	2.0	3.0	3.0	3.0			
Dactylitis[c]							
Yes	20 (16.9)	38 (31.1)	28 (22.8)	86 (23.7)			
No	98 (83.1)	84 (68.9)	95 (77.2)	277 (76.3)			
LDI-B score[d]							
Mean (SD)	37.3 (25.19)	31.5 (33.80)	53.9 (37.62)	40.1 (34.34)			
Median	29.1	17.7	39.4	25.4			
Baseline TJC (68 joints)							
Mean (SD)	23.0 (16.24)	22.0 (14.08)	25.0 (17.28)	23.4 (15.94)			
Median	17.5	18.0	20.0	19.0			
Baseline SJC (66 joints)							
Mean (SD)	10.3 (7.35)	13.1 (11.16)	13.5 (11.50)	12.3 (10.28)			
Median	8.0	10.0	9.0	9.0			
Mean (SD)	58.9 (20.70)	60.3 (20.86)	64.6 (16.77)	61.2 (19.68)			
Median	61.0	66.0	68.0	64.5			
Mean (SD)	64.1 (21.48)	66.4 (20.49)	66.0 (20.52)	65.5 (20.80)			
Median	66.0	67.0	68.0	67.0			
Patient's assessment of joint pain (mm)							
Mean (SD)	63.9 (20.11)	63.9 (21.40)	62.7 (20.87)	63.5 (20.76)			
Median	63.0	63.5	65.0	64.0			
HAQ-DI Total Score							
Mean (SD)	1.2 (0.67)	1.2 (0.62)	1.2 (0.63)	1.2 (0.64)			
Median	1.1	1.3	1.3	1.3			
CRP (mg/L), n (%)							
>6	57 (49.1)	60 (50.4)	53 (43.1)	170 (47.5)			
≤6	59 (50.9)	59 (49.6)	70 (56.9)	188 (52.5)			
CRP (mg/L)							
Mean (SD)	12.1 (19.62)	17.0 (27.48)	13.5 (26.12)	14.2 (24.72)			
Median	5.9	6.1	4.6	5.6			
Baseline Severity							
DAS28-CRP							
Mean (SD)	5.0 (1.09)	5.1 (1.06)	5.1 (1.13)	5.1 (1.09)			
Median	4.9	5.2	5.2	5.1			
PASI total score[e]							
Mean (SD)	7.1 (7.08)	9.3 (9.12)	8.8 (10.29)	8.4 (8.94)			
Median	4.8	6.3	5.5	5.4			
PASI total score, n (%)[e]							
≥12	12 (17.9)	16 (23.5)	13 (19.1)	41 (20.2)			

	RHBE (N=363)								
	Placebo (N = 118)	IXE Q4W (N = 122)	IXE Q2W (N = 123)	IXE Total (N = 363)	Placebo (N = 118)	IXE Q2W (N = 123)	IXE Total (N = 363)	Placebo (N = 118)	IXE Q4W (N = 122)
<12	55 (82.1)	52 (76.5)	55 (80.9)	162 (79.8)					
sPGA score, n (%)[f]									
≥3	55 (50.9)	60 (50.8)	62 (54.9)	177 (52.2)					
<3	53 (49.1)	58 (49.2)	51 (45.9)	162 (47.8)					
BSA ≥3%, n (%)[f]									
Yes	67 (62.6)	68 (61.8)	68 (63.0)	203 (62.5)					
No	40 (37.4)	42 (38.2)	40 (37.0)	122 (37.5)					
Itch NRS score[e]									
Mean (SD)	5.7 (2.82)	5.5 (2.49)	5.6 (2.95)	5.6 (2.75)					
Median	6.0	6.0	6.5	6.0					
NAPSI total score[g]									
Mean (SD)	18.7 (18.75)	20.5 (19.99)	21.0 (21.96)	20.1 (20.19)					
Median	11.0	14.5	12.0	12.0					
SF-36 PCS score									
Mean (SD)	33.9 (8.96)	34.8 (8.78)	34.3 (9.10)	34.3 (8.93)					
Median	34.2	34.4	33.3	33.8					
SF-36 MCS score									
Mean (SD)	48.0 (13.08)	49.6 (11.35)	49.1 (11.51)	48.9 (11.98)					
Median	51.5	51.4	51.0	51.4					
Van der Heijde mTSS									
Mean (SD)			NA						
Median			NA						

a Investigator-reported enthesitis

b In patients who have baseline enthesitis (LEI >0)

c Investigator-reported dactylitis

d In patients who have baseline dactylitis (LDI-B >0)

e In patients with baseline BSA ≥3%

f In patients who have baseline investigator-reported plaque psoriasis

g In patients with baseline fingernail involvement

Overall baseline characteristics were balanced between the groups, with some exceptions. The disease duration was significantly longer in the ixekizumab 80 mg Q4W group (11.4 years) compared with the placebo group (9.2 years). The baseline SJC was different between groups, with each ixekizumab group having a higher count (mean Q4W, 13.1; Q2W, 13.5) compared with the placebo group (10.3). The incidence of dactylitis was different between groups, with the ixekizumab 80 mg Q4W group having a greater incidence (31.1%) compared with the placebo group (16.9%). The use of MTX was different between groups, with greater proportions of patients in the ixekizumab 80 mg Q2W group using MTX at baseline (49.6%) compared with the placebo group (33.9%).

Similar to the study population in RHAP, the majority had a polyarticular course disease (83.7 %), with a minor proportion of patients with assymetrical oligoarthritis (9.9 %) and spondylitis (2.2 %).

Concomitant therapy

Table 19 Summary of Concomitant Therapy Safety Population Double-Blind Treatment Period in study RHBE

ATC 4 Term Preferred Term	PBO (N=118)		IXE80Q4W (N=122)		IXE80Q2W (N=123)		Total IXE (N=245)		Total (N=363)		p-values				
												Pairwise*b		Odds Ratios*c	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	Overall *a	PBO vs IXE80Q4W	PBO vs IXE80Q2W	IXE80Q4W /PBO	IXE80Q2W /PBO
Patients with >=1 concomitant therapy	117	(99.2)	120	(98.4)	122	(99.2)	242	(98.8)	359	(98.9)	0.848	>0.999	>0.999	0.51	1.04
Other Specific Antirheumatic Agents	41	(34.7)	48	(39.3)	61	(49.6)	109	(44.5)	150	(41.3)	0.057	0.505	0.026	1.22	1.85
Methotrexate	41	(34.7)	48	(39.3)	61	(49.6)	109	(44.5)	150	(41.3)	0.057	0.505	0.026	1.22	1.85
Other Antiinflammatory And Antirheumatic Agents, Non-Steroids	5	(4.2)	12	(9.8)	9	(7.3)	21	(8.6)	26	(7.2)	0.257	0.130	0.411	2.47	1.78
Sulfasalazine	5	(4.2)	5	(4.1)	5	(4.1)	10	(4.1)	15	(4.1)	>0.999	>0.999	>0.999	0.97	0.96
Selective Immunosuppressants	6	(5.1)	5	(4.1)	5	(4.1)	10	(4.1)	16	(4.4)	0.901	0.766	0.765	0.80	0.79
Leflunomide	6	(5.1)	5	(4.1)	5	(4.1)	10	(4.1)	16	(4.4)	0.901	0.766	0.765	0.80	0.79

Abbreviations: PBO = placebo; IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q2W = ixekizumab 80 mg Q2W; IXE = ixekizumab; N = number of patients in the safety population; n = number of patients in the specified category

As in study RHAP, the majority of the patients on cDMARD therapy was on MTX. Only a minority was treated with other cDMARDs, for example sulfasalazine or leflunomide. This was a major objection in the first RSI. The MAH has now presented further information, which is not regarded sufficient to justify the broad indication requested by the MAH. (see discussion later in the report)

Numbers analysed

In total, 363 patients were randomized to 1 of 3 treatment groups as the ITT Population: 122 to ixekizumab 80 mg Q4W, 123 to ixekizumab 80 mg Q2W, 118 to Placebo. Unless otherwise specified, the efficacy and health outcome endpoints were conducted on the ITT Population. The primary endpoint analysis of ACR20 response rate at Week 24 was repeated using the PPS. Selected efficacy and health outcome analyses were also conducted on the IR Population.

Outcomes and estimation

The primary efficacy endpoint, the percentage of patients achieving ACR20 response at Week 24 in the ITT population, is shown in **Table 20** and Figure 15.

Table 20. Key Outcomes from RHBE

	PBO	IXE80Q4W		IXE80Q2W	
	Result	Result	Difference vs PBO[a]	**Result**	**Difference vs PBO[a]**
ACR response rate, n(%)					
ACR20, Week 12	26 (22.0%)	61 (50.0%)	28.0% (16.4, 39.6) p<.001	59 (48.0%)	25.9% (14.4, 37.5) **p<.001**
ACR20, Week 24[b]	23 (19.5%)	65 (53.3%)	33.8% (22.4, 45.2) p<.001	59 (48.0%)	28.5% (17.1, 39.8) **p<.001**
ACR50, Week 12	4 (3.4%)	38 (31.1%)	27.8% (18.9, 36.6) p<.001	41 (33.3%)	29.9% (21.0, 38.9) **p<.001**
ACR50, Week 24	6 (5.1%)	43 (35.2%)	30.2% (20.8, 39.5) p<.001	41 (33.3%)	28.3% (19.0, 37.5) **p<.001**
ACR70, Week 12	2 (1.7%)	18 (14.8%)	13.1% (6.4, 19.8) p<.001	13 (10.6%)	8.9% (3.0, 14.8) **p=.006**
ACR70, Week 24	0	27 (22.1%)	22.1% (14.8, 29.5) p<.001	15 (12.2%)	12.2% (6.4, 18.0) **p<.001**
HAQ-DI					
Change from baseline, Week 12, LSM (95% CI)	-0.1 (0.06)	-0.4 (0.06)	-0.3 (-0.5, -0.2) p<.001	-0.4 (0.06)	-0.3 (-0.4,-0.1) **p<.001**
Change from baseline, Week 24, LSM (95% CI)	-0.2 (0.08)	-0.6 (0.07)	-0.4 (-0.5, -0.3) p<.001	-0.4 (0.07)	-0.3 (-0.4,-0.1) **p<.001**
≥0.35 response[c], Week 12, n(%)	17 (15.9%)	53 (51.0%)	35.1% (23.2, 46.9) p<.001	48 (44.4%)	28.6% (16.9, 40.2) **p<.001**
≥0.35 response[c], Week 24, n(%)	18 (16.8%)	45 (43.3%)	26.4% (14.6, 38.3) p<.001	43 (39.8%)	23.0% (11.4, 34.6) **p<.001**
MDA response rate, n (%)					
Week 12	6 (5.1%)	31 (25.4%)	20.3% (11.6, 29.0) p<.001	21 (17.1%)	12.0% (4.2, 19.7) **p=.004**
Week 24	4 (3.4%)	34 (27.9%)	24.5% (15.9, 33.1) p<.001	29 (23.6%)	20.2% (12.0, 28.4) **p<.001**
DAS28-CRP, Change from baseline, LSM (95% CI)					
Week 12	-0.6 (0.17)	-1.8 (0.17)	-1.1 (-1.4, -0.8) p<.001	-1.5 (0.16)	-0.9 (-1.2,-0.6) **p<.001**
Week 24	-0.8 (0.20)	-2.1 (0.19)	-1.3 (-1.6, -0.9) p<.001	-1.8 (0.18)	-1.0 (-1.3,-0.6) **p<.001**
LEI[d]					
Change from baseline, Week 12, LSM (95% CI)	-0.6 (0.34)	-0.8 (0.32)	-0.1 (-0.8, 0.5) p=.670	-1.3 (0.31)	-0.7 (-1.3, -0.1) **p=.029**
Change from baseline, Week 24, LSM (95% CI)	-1.0 (0.35)	-1.1 (0.32)	-0.1 (-0.8, 0.5) p=.728	-1.4 (0.30)	-0.4 (-1.0, 0.2) p=.198
LEI (0), Week 12, n (%)	20 (29.0%)	19 (27.9%)	-1.0% (-16.2, 14.1) p>.999	29 (34.5%)	5.5% (-9.2, 20.3) p=.491
LEI (0), Week 24, n (%)	15 (21.7%)	24 (35.3%)	13.6% (-1.4, 28.5) p=.091	26 (31.0%)	9.2% (-4.7, 23.1) p=.271
LDI-B[e]					
Change from baseline, Week 12, LSM (95% CI)	-18.3 (9.47)	-33.8 (8.87)	-15.5 (-36.4, 5.3) p=.141	-40.4 (8.99)	-22.1 (-44.0, -0.2) **p=.048**
Change from baseline, Week 24, LSM (95% CI)	-36.2 (8.43)	-34.7 (6.67)	1.5 (-15.0, 18.0) p=.854	-32.1 (6.66)	4.0 (-14.0, 22.1) p=.652
LDI-B (0), Week 12, n (%)	5 (35.7%)	19 (67.9%)	32.1% (1.7, 62.6) p=.096	12 (60.0%)	24.3% (-8.7, 57.3) p=.296
LDI-B (0), Week 24, n (%)	3 (21.4%)	21 (75.0%)	53.6% (26.8, 80.4) p=.002	10 (50.0%)	28.6% (-2.1, 59.3) p=.153

	PBO	IXE80Q4W		IXE80Q2W	
	Result	Result	Difference vs PBO[a]	**Result**	**Difference vs PBO[a]**
SF-36, Change from baseline, LSM (95% CI)					
SF-36 PCS, Week 12	2.7 (1.07)	7.1 (1.06)	4.3 (2.4, 6.3) p<.001	7.2 (1.03)	4.4 (2.5,6.4) **p<.001**
SF-36 PCS, Week 24	3.3 (1.36)	8.9 (1.29)	5.6 (3.2, 8.0) p<.001	8.2 (1.23)	4.9 (2.5,7.3) **p<.001**
SF-36 MCS, Week 12	-1.2 (1.16)	3.1 (1.15)	4.3 (2.2, 6.4) p<.001	3.2 (1.11)	4.3 (2.2,6.5) **p<.001**
SF-36 MCS, Week 24	0.9 (1.32)	3.6 (1.24)	2.7 (0.4, 5.0) p=.023	4.0 (1.18)	3.1 (0.8,5.4) **p=.009**
PASI response rate, n (%)[f]					
PASI 75, Week 12	7 (10.4%)	39 (57.4%)	46.9% (33.1, 60.8) p<.001	42 (61.8%)	51.3% (37.6, 65.0) **p<.001**
PASI 75, Week 24	10 (14.9%)	38 (55.9%)	41.0% (26.4, 55.5) p<.001	41 (60.3%)	45.4% (30.9, 59.8) **p<.001**
PASI 90, Week 12	4 (6.0%)	26 (38.2%)	32.3 (19.4, 45.1) p<.001	29 (42.6%)	36.7 (23.6, 49.7) **p<.001**
PASI 90, Week 24	8 (11.9%)	30 (44.1%)	32.2 (18.1, 46.3) p<.001	34 (50.0%)	38.1 (23.9, 52.3) **p<.001**
PASI 100, Week 12	4 (6.0%)	13 (19.1)	13.1 (2.2, 24.1) p=.036	16 (23.5)	17.6 (6.0, 29.1) **p=.007**
PASI 100, Week 24	3 (4.5)	24 (35.3)	30.8 (18.4, 43.2) p<.001	19 (27.9)	23.5 (11.7, 35.2) **p<.001**

Notes: Major secondary objectives are shaded, primary objective is shaded with dotted outline.

a Difference (IXE - PBO), (95% CI)

b Primary objective

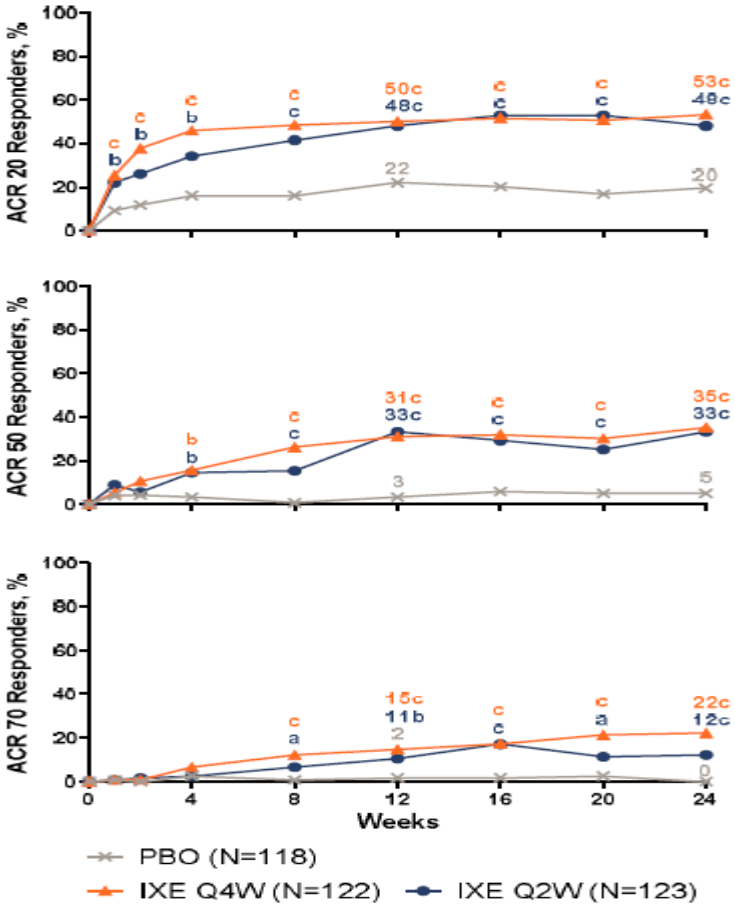
c Intent-to-Treat Population with Baseline HAQ-DI ≥0.35

d Intent-to-Treat Population with baseline LEI >0

e Intent-to-Treat Population with LDI-B >0 at baseline

f Intent-to-Treat Population with baseline psoriatic lesions involving ≥3% BSA

Figure 15. ACR20/50/70 response rates at each postbaseline visit (NRI), Intent-to-Treat Population, Double-Blind Treatment Period



CHMP's comment:

The primary endpoint of the study was met. A larger proportion of patients in both ixekizumab groups reached ACR 20 response at Week 24 (48.0 % in the Ixekizumab 80 mg Q2W group and 53.3% in the Ixekizumab 80 mg Q4W group, compared to 19.5% in the placebo group.

The proportion of patients classified as Inadequate Responders in each of the ixekizumab groups were smaller (Q4W, 15 patients [12.3%]; Q2W, 17 patients [13.8%]) compared with the placebo group (32 patients [27.1%]). This is considered to support the efficacy of ixekizumab. In the primary analysis data collected post-rescue were ignored and patients with inadequate response week 16 were treated as non-responders. This is acceptable. However, although recognised as being conservative, the company was requested to repeat the analysis of the primary endpoint including all data collected up to week 24 irrespective of whether a patient received rescue. In the submitted analysis where observed data after Week 16 for Week 16 inadequate responders was included, the difference in ACR20 response rate at Week 24 between IXE80Q4W and IXE80Q2W respectively and placebo was smaller tha in the primary analysis, due to a higher placebo response rate. The difference between treatment arms were however still statistically significant irrespective of comparison.

Secondary efficacy results

For the key secondary (multiplicity-adjusted) endpoints, the response to ixekizumab in both doses was different from placebo for the following endpoints: HAQ-DI at Week 24, ACR20 at Week 12, PASI75 at Week 12 and MDA at Week 24. There were no difference in number of patients achieving LEI score = 0 at Week 24. Results are shown in Table 21.

Table 21. Summary of Major Secondary Analyses of RHBE with Multiple Testing Procedure

	IXE80Q4W			IXE80Q2W		
	Difference[a]	p-value	Significant?[b]	Difference[a]	p-value	Significant?[b]
RHBE						
HAQ-DI at Week 24	-0.4 (-0.5, -0.3)	<0.001	Yes	-0.3 (-0.4, -0.1)	<0.001	Yes
ACR20 at Week 12	28.0% (16.4, 39.6)	<.001	Yes	25.9% (14.4, 37.5)	<.001	Yes
PASI 75 at Week 12[d]	46.9% (33.1, 60.8)	<.001	Yes	51.3% (37.6, 65.0)	<.001	Yes
MDA at Week 24	24.5% (15.9, 33.1)	<0.001	Yes	20.2% (12.0, 28.4)	<0.001	Yes
LEI=0 at Week 24[e]	13.6% (-1.4, 28.5)	.091	No	9.2% (-4.7, 23.1)	.271	No

a Difference (IXE - PBO), (95% CI)

b Alpha set to .025

c Primary objective of Studies RHAP and RHBE

d Restricted to patients with baseline psoriatic lesions involving ≥3% BSA

e Restricted to patients with LEI >0 at baseline

CHMP's comment:

There was a difference in response for both ixekizumab groups vs placebo for the following key secondary endpoints: HAQ-DI at Week 24, ACR20 at Week 12, PASI75 at Week 12 and MDA at Week 24. There was no difference in treatment effect on enthesitis, measured as proportion of patients with LEI=0 at Week 24.

Immunogenicity effects on efficacy

In Primary PsA Placebo-Controlled Integrated Analysis Set (Studies RHAP and RHBE), of the patients receiving ixekizumab at the recommended dosing regimen (80 mg Q4W), 14 patients developed Treatment-Emergent Anti-Drug Antibodies (TE-ADA). The majority were classified as TE-ADA of low titer (10 out of 14 patients) and no patient was classified as TE-ADA high titer. Two of the 14 patients had confirmed neutralizing antibodies.

Of the 14 patients classified as TE-ADA positive, 12 patients achieved ACR20 at week 24 (Table 22). Of the 2 patients that were classified as neutralizing antibody (Nab) positive, both achieved ACR20. Seven of the 8 patients classified as NAb inconclusive achieved ACR20. Of the 26 patients considered to be inadequate responders to ixekizumab Q4W at Week 16, only 1 patient was TE-ADA positive at least once (NAb negative, low titer).

Table 22. ACR20 Response Rates at Week 24 (NRI), Effect of Nab, Double-Blind Treatment Period, ITT Population, Primary PsA Placebo-Controlled Integrated Analysis Set

	PBO N=218	IXE80Q4W N=225	IXE80Q2W N=222	All Ixekizumab N=447
ACR20 response rate at Week24				

		PBO N=218	IXE80Q4W N=225	IXE80Q2W N=222	All Ixekizumab N=447
TE-ADA Positive (All titers)	n/Ns (%)	0/1 (0)	12/14 (85.7)	6/9 (66.7)	18/23 (78.3)
	% Diff (95% CI)		85.7 (67.4, 100.0)	66.7 (35.9, 97.5)	78.3 (61.4, 95.1)
NAb Positive	n/Ns (%)	0/0 (0)	2/2 (100.0)	1/2 (50.0)	3/4 (75.0)
	% Diff (95% CI)		NA	NA	NA
NAb Negative	n/Ns (%)	0/0 (0)	3/4 (75.0)	0/0 (0)	3/4 (75.0)
	% Diff (95% CI)		NA	NA	NA
NAb Inconclusive	n/Ns (%)	0/1 (0)	7/8 (87.5)	5/7 (71.4)	12/15 (80.0)
	% Diff (95% CI)		**87.5 (64.6, 100.0)**[a]	71.4 (38.0, 100.0)	80.0 (59.8, 100.0)

a p<.05 versus PBO (p-value versus placebo not calculated for Total IXE, All TE-ADA Positive)

CHMP's comment:

In summary, an assessment of ACR20 responses at Week 24 among ADA positive patients did not demonstrate any significant impact of ADA on efficacy, irrespective of titer or neutralizing antibody activity.

Efficacy in subpopulations

The efficacy of ixekizumab was analysed in the following subgroups: demographics (sex, age, weight, BMI, race, ethnicity, geographic region), disease characteristics (CRP, time since PsA onset, time since PsA diagnosis, baseline enthesitis, baseline dactylitis), previous therapy (cDMARD use at baseline, methotrexate use at baseline) and other characteristics (smoking, baseline psoriasis, baseline moderate-to-severe psoriasis). The ACR20 response was higher for ixekizumab 80Q4W compared to placebo for all subgroups except for patients with weight <25th percentile. ACR20 response rates for ixekizumab 80Q2W was higher compared to placebo in all groups except patients with weight ≥ 100 kg and patients with disease duration <5 years.

In PsA patients with a high level of skin involvement (BSA≥10%) and those defined as having concomitant moderate-to-severe plaque psoriasis, the PASI90 response rate was higher for ixekizumab 80 mg Q2W than for ixekizumab 80 mg Q4W (**Table 23**).

Table 23. PASI 75/90/100 Response Rates at Week 12 (NRI), Intent-to-Treat Population: Patients with Psoriasis with or without PsA, and Patients with both PsA and Coexistent Psoriasis, Psoriasis and PsA Development Programs

	PASI 75 Response Rate (%)			PASI 90 Response Rate (%)			PASI 100 Response Rate (%		
	IXE 80Q4W	IXE80 Q2W	Difference, %	IXE 80Q4W	IXE80 Q2W	Difference, %	IXE 80Q4W	IXE80 Q2W	Differen %
Phase III **psoriasis** program[d,e]	951/1165 (81.6)	1037/1169 (88.7)	**7.1**[c]	738/1165 (63.3)	817/1169 (69.9)	**6.5**[c]	387/1165 (33.2)	440/1169 (37.6)	**4.4**[a]
Psoriasis patients with coexistent **PsA**[e,f]	215/265 (81.1)	254/283 (89.8)	**8.6**[b]	161/265 (60.8)	196/283 (69.3)	**8.5**[a]	92/265 (34.7)	105/283 (37.1)	2.4
RHAP[g,h]	55/73 (75.3)	41/59 (69.5)	-5.8	38/73 (52.1)	34/59 (57.6)	5.5	23/73 (31.5)	24/59 (40.7)	9.2
RHBE[g,h]	39/68 (57.4)	42/68 (61.8)	4.4	26/68 (38.2)	29/68 (42.6)	4.4	13/68 (19.1)	16/68 (23.5)	4.4
Phase III **PsA** program (integrated RHAP and RHBE)[g]	94/141 (66.7)	83/127 (65.4)	-1.3	64/141 (45.4)	63/127 (49.6)	4.2	36/141 (25.5)	40/127 (31.5)	6.0
PsA patients with coexistent **psoriasis (BSA ≥3% to <10%])**	41/57 (71.9)	29/55 (52.7)	-19.2	30/57 (52.6)	22/55 (40.0)	-12.6	19/57 (33.3)	17/55 (30.9)	-2.4
PsA patients with coexistent **psoriasis (BSA ≥10%)**	53/84 (63.1)	54/72 (75.0)	11.9	34/84 (40.5)	41/72 (56.9)	**16.5**[a]	17/84 (20.2)	23/72 (31.9)	11.7
PsA patients with coexistent **moderate-to-severe psoriasis**[e]	23/32 (71.9)	18/24 (75.0)	3.1	15/32 (46.9)	15/24 (62.5)	15.6	8/32 (25.0)	6/24 (25.0)	0.0

a p<.05; b p<.01; c p<.001 d Gordon et al. 2016; Griffiths et al. 2015 e Patients with total PASI score ≥12 and sPGA score ≥3 and BSA ≥10% at baseline. f Self-reported PsA g Patients with baseline BSA ≥3% h Statistical comparisons between ixekizumab regimens not performed

Summary on main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24. Summary of Efficacy for Pivotal Trial I1F-MC-RHAP

Title: A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 24-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Biologic Disease-Modifying Antirheumatic Drug-Naive Patients with Active Psoriatic Arthritis			
Study identifier	I1F-MC-RHAP		
Design	Phase III, multicentre, randomized, double-blind, active- and placebo-controlled, parallel-group study		
	Duration of Main phase:		24 weeks (Double-Blind Treatment Period)
	Duration of Extension phase:		28 weeks (Extension Period); 104 weeks (Long-Term Extension Period)
Hypothesis	Superiority		
Treatment groups	Ixekizumab 80 mg Q2W		Ixekizumab 80 mg Q2W. Duration 24 weeks (Double-Blind Treatment Period), 132 weeks (Extension and Long-Term Extension Periods). Number randomized 103.
	Ixekizumab 80 mg Q4W		Ixekizumab 80 mg Q4W. Duration 24 weeks (Double-Blind Treatment Period), 132 weeks (Extension and Long-Term Extension Periods). Number randomized 107.
	Placebo		Placebo. Duration 24 weeks (Double-Blind Treatment Period). Number randomized 106.
	Adalimumab (active reference group; comparison to Placebo only)		Adalimumab 40 mg Q2W. Duration 24 weeks (Double-Blind Treatment Period). Number randomized 101.
Endpoints and definitions	Primary endpoint	ACR20 at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA as measured by the proportion of patients achieving ACR20 at Week 24.
	Key secondary endpoint	HAQ-DI score at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA as measured by the change from baseline in HAQ-DI score at Week 24.
	Key secondary endpoint	mTSS score at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA as measured by the change from baseline in mTSS score on hand and foot x-rays at Week 24.
	Key secondary endpoint	ACR20 at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA as measured by the proportion of patients achieving ACR20 at Week 12.
	Key secondary endpoint	PASI 75 at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA and baseline psoriatic lesion(s) involving ≥3% BSA as measured by the proportion of patients achieving PASI 75 at Week 12.
	Key secondary endpoint	LEI score at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA and baseline enthesitis as measured by the change from baseline in LEI score at Week 12.
	Key secondary endpoint	Itch NRS score at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active PsA and baseline psoriatic lesion(s) involving ≥3% BSA as measured by the change from baseline in Itch NRS score at Week 12.
Database lock	24-week database lock (Double-Blind Treatment Period): 26 Feb 2015 (Last patient visit prior to database lock: 03 Dec 2014). Data from the 24-week database lock is presented within this table. 52-week database lock (Extension Period): 04 Sep 2015 (Last patient visit prior to database lock: 15 Jun 2015).		
Results and Analysis			
Analysis Description	**Primary Analysis: ACR20 at Week 24**		

Analysis population, time point description, and statistical model	ITT Population 24 weeks Logistic Regression Model (NRI)				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of subjects	103	107	106	101
	ACR20	64/103 (62.1%)	62/107 (57.9%)	32/106 (30.2%)	58/101 (57.4%)
Effect estimate per comparison	Primary endpoint: ACR20 at Week 24	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo		31.9	
		95% CI		19.1, 44.8	
		p-value		p<.001	
	Primary endpoint: ACR20 at Week 24	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo		27.8	
		95% CI		15.0, 40.6	
		p-value		p<.001	
	Primary endpoint: ACR20 at Week 24	Comparison groups		Adalimumab vs. Placebo	
		% Difference vs. Placebo		27.2	
		95% CI		14.2, 40.3	
		p-value		p<.001	
Analysis Description	**Key Secondary Analyses**				
Analysis population, time point description, and statistical model	ITT Population ITT Population with Baseline Psoriatic Lesion(s) Involving ≥3% BSA: PASI 75, Itch NRS Score ITT Population with Baseline Enthesitis: LEI Score 12 Weeks: ACR20, PASI 75, Itch NRS Score, LEI score 24 Weeks: HAQ-DI, mTSS Logistic Regression Model (NRI): ACR20, PASI 75 ANCOVA (mBOCF): HAQ-DI, LEI score, Itch NRS Score ANCOVA (linear extrapolation): mTSS				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of subjects	103	107	106	101
	HAQ-DI Score: LSM (SE)	-0.48 (0.051)	-0.41 (0.050)	-0.14 (0.050)	-0.37 (0.051)
	mTSS Score: LSM (SE)	0.09 (0.091)	0.18 (0.090)	0.51 (0.092)	0.13 (0.093)
	ACR20	62/103 (60.2%)	61/107 (57.0%)	33/106 (31.1%)	52/101 (51.5%)
	Number of subjects with ≥3% BSA psoriasis skin involvement at baseline	59	73	67	68

	PASI 75	41/59 (69.5%)	55/73 (75.3%)	5/67 (7.5%)	23/68 (33.8%)
	Itch NRS Score: LSM (SE)	-2.8 (0.30)	-2.6 (0.28)	0.2 (0.28)	-1.4 (0.29)
	Number of subjects with Baseline Enthesitis	59	70	57	56
	LEI Score: LSM (SE)	-1.5 (0.24)	-0.9 (0.22)	-0.9 (0.24)	-0.9 (0.24)
Effect estimate per comparison	HAQ-DI score at Week 24	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		p-value		p<.001	
	HAQ-DI score at Week 24	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		p-value		p<.001	
	HAQ-DI score at Week 24	Comparison groups		Adalimumab vs. Placebo	
		p-value		p<.001	
	mTSS score at Week 24	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		p-value		p<.001	
	mTSS score at Week 24	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		p-value		p=.006	
	mTSS score at Week 24	Comparison groups		Adalimumab vs. Placebo	
		p-value		p=.002	
	ACR20 at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		p-value		p<.001	
	ACR20 at Week 12	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		p-value		p<.001	
	ACR20 at Week 12	Comparison groups		Adalimumab vs. Placebo	
		p-value		p=.003	
	PASI 75 at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		p-value		p<.001	
	PASI 75 at Week 12	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		p-value		p<.001	
	PASI 75 at Week 12	Comparison groups		Adalimumab vs. Placebo	
		p-value		p<.001	
	LEI score at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		p-value		p=.045	
	LEI score at Week 12	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	

		p-value	p=.806
	LEI score at Week 12	Comparison groups	Adalimumab vs. Placebo
		p-value	p=.914
	Itch NRS score at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		p-value	p<.001 (NS due to hierchial testing)
	Itch NRS score at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		p-value	p<.001 (NS due to multiple testing procedure)
	Itch NRS score at Week 12	Comparison groups	Adalimumab vs. Placebo
		p-value	p<.001 (NS due to multiple testing procedure)

Table 25. Summary of Efficacy for Pivotal Trial I1F-MC-RHBE

Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled 24-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Biologic Disease-Modifying Antirheumatic Drug-Experienced Patients with Active Psoriatic Arthritis					
Study identifier	I1F-MC-RHBE				
Design	Phase III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study				
	Duration of Main phase:		24 weeks (Double-Blind Treatment Period)		
	Duration of Extension phase:		132 weeks (Extension Period)		
Hypothesis	Superiority				
Treatment groups	Ixekizumab 80 mg Q2W		Ixekizumab 80 mg Q2W. Duration 24 weeks (Double-Blind Treatment Period), 132 weeks (Extension Period). Number randomized 123.		
	Ixekizumab 80 mg Q4W		Ixekizumab 80 mg Q4W. Duration 24 weeks (Double-Blind Treatment Period), 132 weeks (Extension Period). Number randomized 122.		
	Placebo		Placebo. Duration 24 weeks (Double-Blind Treatment Period). Number randomized 118.		
Endpoints and definitions	Primary endpoint	ACR20 at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-experienced patients with active PsA as measured by the proportion of patients achieving ACR20 at Week 24.		
	Key secondary endpoint	HAQ-DI score at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-experienced patients with active PsA as measured by the change from baseline in HAQ-DI score at Week 24.		
	Key secondary endpoint	ACR20 at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-experienced patients with active PsA as measured by the proportion of patients achieving ACR20 at Week 12.		
	Key secondary endpoint	PASI 75 at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-experienced patients with active PsA and baseline psoriatic lesion(s) involving ≥3% BSA as measured by the proportion of patients achieving PASI 75 at Week 12.		
	Key secondary endpoint	MDA at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-experienced patients with active PsA as measured by the proportion of patients achieving MDA at Week 24.		
	Key secondary endpoint	LEI Resolution at Week 24	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-experienced patients with active PsA and baseline LEI score >0 as measured by the proportion of patients achieving complete resolution in enthesitis (LEI score=0) at Week 24.		
Database lock	30 Sep 2016 (Last patient visit prior to database lock: 09 Sep 2016)				
Results and Analysis					
Analysis Description	**Primary Analysis: ACR20 at Week 24**				
Analysis population, time point description, and statistical model	ITT Population 24 weeks Logistic Regression Model (NRI)				
Descriptive statistics and estimate variability	Treatment group		Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects		123	122	118
	ACR20		59/123 (48.0%)	65/122 (53.3%)	23/118 (19.5%)

Effect estimate per comparison	Primary endpoint: ACR20 at Week 24	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		% Difference vs. Placebo	28.5
		95% CI	17.1, 39.8
		p-value	p<.001
	Primary endpoint: ACR20 at Week 24	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		% Difference vs. Placebo	33.8
		95% CI	22.4, 45.2
		p-value	p<.001

Results and Analysis				
Analysis Description	**Key Secondary Analyses**			
Analysis population, time point description, and statistical model	ITT Population: HAQ-DI, ACR20, MDA ITT Population with Baseline Psoriatic Lesion(s) Involving ≥3% BSA: PASI 75 ITT Population with Baseline LEI score >0: LEI Resolution 12 Weeks: ACR20, PASI 75 24 weeks: HAQ-DI, MDA, LEI Resolution ANCOVA (mBOCF): HAQ-DI Logistic Regression Model (NRI): ACR20, PASI 75, MDA, LEI Resolution			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	123	122	118
	HAQ-DI Score: LSM (SE)	-0.4 (0.07)	-0.5 (0.07)	-0.1 (0.07)
	ACR20	59/123 (48.0%)	61/122 (50.0%)	26/118 (22.0%)
	MDA	29/123 (23.6%)	34/122 (27.9%)	4/118 (3.4%)
	Number of subjects with Baseline Psoriatic Lesion(s) Involving ≥3% BSA	68	68	67
	PASI 75	42/68 (61.8%)	39/68 (57.4%)	7/67 (10.4%)
	Number of subjects with Baseline LEI score >0	84	68	69
	LEI score =0	26/84 (31.0%)	24/68 (35.3%)	15/69 (21.7%)

Effect estimate per comparison	HAQ-DI score at Week 24	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		p-value	p<.001
	HAQ-DI score at Week 24	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		p-value	p<.001
	ACR20 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		p-value	p<.001

	ACR20 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		p-value	p<.001
	PASI 75 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		p-value	p<.001
	PASI 75 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		p-value	p<.001
	MDA at Week 24	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		p-value	p<.001
	MDA at Week 24	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		p-value	p<.001
	LEI score =0 at Week 24	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		p-value	p=.271
	LEI score =0 at Week 24	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		p-value	p=.091

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The development program to support the variation for Taltz in psoriatic arthritis includes two pivotal phase III studies (RHAP and RHBE). Efficacy data up to Week 52 (RHAP) and Week 24 (RHBE) have been provided.

Recommendations of the EMA clinical guidance for psoriatic arthritis (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriatic arthritis, CHMP/EWP/438/04) have been taken into account in the clinical development programme. Advice was sought from CHMP (EMA/CHMP/SAWP/339078/2011), and in line with this an active comparator (adalimumab) was added. According to the Applicant, all studies were conducted in compliance with Good Clinical Practice (GCP).

The dosing regimen in phase III studies were based dose-ranging data from phase II studies in rheumatoid arthritis (RA, study RHAK) and psoriasis (study RHAJ), as well as the final dosing regimen selection for the pivotal phase III studies in moderate-to-severe plaque psoriasis. The doses selected for the phase III program were ixekizumab 160 mg as a loading dose, followed by 80 mg Q2W or Q4W.

The study population in phase III studies consisted of adults with active PsA. They fulfilled the CASPAR diagnostic criteria for PsA and the disease activity was based on at least 3 tender and swollen joints in 66/68 joint index. The population is comparable to other phase III programs on biologics developed for PsA, for example Cosentyx. In study RHAP, aiming to evaluate radiographic progression, patients also needed to have ≥1 disease-related definite joint erosion on hand or foot radiographs OR CRP >6 mg/L at screening. In study RHAP, patients could be either cDMARD-naïve or cDMARD-experienced. All

patients were bDMARD-naïve. In study RHAP, all patients were bDMARD-experienced. Primary endpoint in both studies was ACR20 at Week 24.

Study RHAP was a phase III, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient study in patients with active PsA who were bDMARD-naive. Patients were randomised to treatment with ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab (Humira) 40 mg Q2W or placebo. The efficacy variables chosen are relevant and cover the diverse disease manifestations of PsA.

Study RHBE was a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study in patients with active PsA who were cDMARD- and bDMARD-experienced and either inadequate responders (have discontinued at least 1 TNFi due to either an inadequate response [based on a minimum of 12 weeks on therapy]), or intolerant to, a TNFi (8.5% of the study population). Patients were randomised to treatment with ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W or placebo. In this study, no active comparator was included.

In Study RHAP, the sample size was seemingly determined to provide sufficient power to show a difference (versus placebo) with regard to the major secondary mTSS endpoint. For the primary analyses the power was >99% implying a high power also in the subpopulation of cDMARD-experienced patients since expected to comprise approximately 75% of the total sample size. For this subset a number of analyses, besides analyses of the primary endpoint, were pre-planned. For Study RHBE, the sample size estimation was based on the primary endpoint. Compared to the assumptions made in Study RHAP, the difference in ACR20 response rate between ixekizumab and placebo was assumed to be smaller; 20% compared to 33%. In both studies the Week 24 ACR20 response rate for placebo was assumed to be 15%.

Considering similar designs and endpoints the statistical analysis plan for Study RHAP and Study RHBE shared a number of features and were overall acceptable. Analyses were based on all randomised subjects and analysis models included the stratifications variables used at randomisation. Multiplicity concerns were appropriately handled through the use of a split of α between the two ixekizumab dose regimens and gatekeeping using a graphical approach. Categorical endpoints, including the primary endpoint, were analysed using logistic regression with missing data handled using a non-responder imputation. In all analyses, data collected after start of rescue/week 16 were ignored. For the analysis of the primary endpoint (and other categorical endpoints) this implied that patients with inadequate response week 16 were treated as non-responders. Although this is an acceptable primary approach, sensitivity/supportive analyses including data post-rescue should have been planned (as also discussed within the scientific advice procedure 2011; EMA/CHMP/SAWP/339078/2011) and they were requested during the assessment. In both the studies, the primary analysis was performed after an interim database lock pre-defined to occur once all patients had completed or discontinued in the Double-Blind Treatment Period (Week 24). Following this database lock the study team was unblinded with unblinding details specified in the unblinding plan. For Study RHAP, a number of post hoc analyses were performed after database lock and unblinding including a sensitivity analysis on ACR20 response rates at Week 24 based on the PPS and excluding all patients from one site, which was closed for persistent GCP noncompliance. Considered to be for check of robustness or for clarifying/exploratory purposes, no concern is raised.

Efficacy data and additional analyses

In Study RHAP, 417 subjects were randomised to each of the 4 treatment groups (ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab 40 mg Q2W or placebo). All ixekizumab-treated patients received a starting dose of 160 mg.

The primary efficacy endpoint was achieved as ixekizumab at both 80 mg Q2W and Q4W were superior to placebo for ACR20 response at Week 24 ($p<0.001$). The ACR20 response rates at Week 24 were 62.1% for ixekizumab 80 mg Q2W, 57.9% for ixekizumab 80 mg Q4W, 57.4% for adalimumab and 30.2% for placebo. Superior ACR20 response rates compared to placebo were seen already at Week 1, and response rates were maintained over time. The difference vs placebo was 31.9% for ixekizumab 80 mg Q2W, 27.8% for ixekizumab 80 mg Q4W and 27.2% for adalimumab.

The proportion of patients classified as Inadequate Responders at week 16 in each of the ixekizumab groups were smaller than in the placebo group; 10.3% (11/107) and 9.7% (10/103) for the Q4W and Q2W arm respectively compared to 25.5% (27/106) in the placebo group. This difference between active treatment and placebo is considered to support the efficacy of ixekizumab. In the primary analysis data collected post-rescue were ignored and patients with inadequate response week 16 were treated as non-responders. This is acceptable. However, although recognised as being conservative, the MAH was requested to repeat the analysis of the primary endpoint taking all data collected up to week 24 into account irrespective of whether a patient received rescue or not. In this analysis, where observed data after Week 16 for Week 16 inadequate responders was included, the difference in ACR20 response rate at Week 24 between IXE80Q4W and IXE80Q2W respectively and placebo was smaller than in the primary analysis, due to a higher placebo response rate. The difference between treatment arms was however still statistically significant irrespective of comparison.

Both dosing regimens of ixekizumab were superior to placebo for the secondary endpoints mTSS at Week 24, HAQ-DI at Week 24, ACR20 at Week 12 and PASI 75 at Week 12. No statistically significant response was shown for the secondary endpoints LEI score at Week 12 or Itch NRS at Week 12, for either ixekizumab dose compared to placebo.

Regarding the inhibition of radiographic progression, it is difficult to draw safe conclusions since the follow-up time is very short. From a clinical perspective, data on mTSS at Week 52 are more relevant and some concern is raised on the results from this analysis. Patients in the ixekizumab 80 mg Q4W had a larger mTSS change from baseline compared to patients initially randomised to placebo or adalimumab (both switched to ixekizumab at Week 16 or 24). The applicant justifies this with the fact that the progression per se was low, and mainly driven by one patient. This may be true and will be verified when data from the long-term extension(108 Weeks) are submitted. These studies are included in the RMP as category 3 studies.

Study RHAP included efficacy analyses in the subset of patients who were cDMARD-experienced. A majority of these were on concomitant therapy with MTX and only a minority on other DMARDs. Both ixekizumab doses were superior to placebo for the primary endpoint ACR20 at Week 24 and for the major secondary endpoints HAQ-DI, mTSS, ACR20 (at Week 12), PASI 75, and Itch NRS. The efficacy in the subgroups treated with DMARDs other than MTX has not been sufficiently justified and the indication has been revised to include combination therapy with MTX only.

In Study RHBE, 363 subjects were randomised to each of the 3 treatment groups (ixekizumab 80 mg Q2W, ixekizumab Q4W or placebo). Baseline disease characteristics were generally balanced between the groups.

The primary efficacy endpoint was achieved as ixekizumab at both dosing regimens were superior to placebo for ACR20 response at Week 24 ($p<0.001$). The ACR20 response rates at Week 24 were 48.0% for ixekizumab 80 mg Q2W, 53.3% for ixekizumab 80 mg Q4W and 19.5% for placebo. Superior ACR20 response rates compared to placebo were seen already at Week 2 for ixekizumab 80 mg Q4W and continued to improve until a plateau was reached around Week 8. The difference vs placebo was 28.5% for ixekizumab 80 mg Q2W and 33.8% for ixekizumab 80 mg Q4W. It is noted that the lower dose has higher response rates.

A majority of the patients were on concomitant therapy with MTX and only a minority on other cDMARDs. The efficacy in the subgroups treated with cDMARDs other than MTX has not been sufficiently justified **.** The restricted revised indication described hereafter is acceptable and reflects the scientific data submitted.

Here the proportion of Inadequate Responders at week 16 were 12.3% (15/122) and 13.8% (17/123) for the Q4W and Q2W arm respectively compared with 27.1% (32/118) in the placebo group, i.e. of similar magnitude although slightly higher in Study RHBE than in Study RHAP. As concluded above, this difference between active treatment and placebo, evident in both studies, is considered to support the efficacy of ixekizumab. The MAH was however, analogous as for Study RHAP, requested to repeat the analysis of the primary endpoint taking all data collected up to week 24 into account irrespective of whether a patient received rescue or not. In the submitted analysis, in which observed data after Week 16 for Week 16 inadequate responders was included, the difference in ACR20 response rate at Week 24 between IXE80Q4W and IXE80Q2W respectively and placebo was, as could be expected, smaller than in the primary analysis, due to a higher placebo response rate. The difference between treatment arms were however still statistically significant irrespective of comparison.

Both dosing regimens of ixekizumab were superior to placebo for the secondary endpoints HAQ-DI at Week 24, ACR20 at Week 12, PASI 75 at Week 12 and MDA at Week 24. No difference was shown in proportion of patients achieving remission of enthesitis defined by LEI score=0 at Week 24, compared to placebo.

The extension period of RHBE is ongoing, and the Week 52 data are anticipated to become available in August 2017. The data will be submitted post approval. This is agreed by CHMP.

The efficacy of ixekizumab was analysed in the following subgroups: demographics (sex, age, weight, BMI, race, ethnicity, geographic region), disease characteristics (CRP, time since PsA onset, time since PsA diagnosis, baseline enthesitis, baseline dactylitis), previous therapy (cDMARD use at baseline, methotrexate use at baseline) and other characteristics (smoking, baseline psoriasis, baseline moderate-to-severe psoriasis). For ACR20, ixekizumab 80Q4W was superior to placebo for all subgroups except for patients with weight <25th percentile. Ixekizumab 80Q2W was superior to placebo in all groups except patients with weight ≥ 100 kg and patients with disease duration <5 years.

In addition to the studies described above, a third phase III study (RHBF) is ongoing. It was designed to address CHMP scientific advice recommendation of employing a randomised-withdrawal design to further evaluate maintenance of efficacy. RHBF is a Phase III, multicentre study with a 36-week, initial, open-label treatment period, examining the effect of ixekizumab 80 mg every 2 weeks (Q2W) in patients with active PsA who are inadequate responders (IRs) to cDMARDs and are bDMARD-naive, followed by a randomised, doubleblind withdrawal period from Week 36 to Week 104, examining the effect of ixekizumab 80 mg Q2W compared to placebo. The primary objective of the study is to compare ixekizumab 80 mg Q2W with placebo in the maintenance of treatment response, as measured by the time to relapse during the randomised, double-blind withdrawal period.

2.4.1. Conclusions on the clinical efficacy

Both phase III studies met their primary endpoint. ACR20 response rates with both ixekizumab doses were statistically significantly higher compared to placebo at Week 24. In the bDMARD-naive population, the proportion of patients achieving the primary endpoint ACR20 response at Week 24 was similar to the response for adalimumab.

The wording of the indication as initially proposed by the MAH, "*Taltz, alone or in combination with a conventional disease-modifying antirheumatic drug (cDMARD), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have responded inadequately to or who are intolerant to one or more DMARD therapies",* could not be sufficiently justified. The majority of the patients in the studies were treated with MTX, and only a minority with other cDMARDs such as sulfasalazine. Further studies are needed to justify the proposed wording. Taking this into consideration the wording of the indication has been revised as recommended by CHMP as follows : "*Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have responded inadequately to or who are intolerant to one or more DMARD therapies".*

There were no significant differences in treatment response between the two posologies for the pre-specified endpoints. Data from the psoriasis phase III program for patients with moderate-to-severe plaque psoriasis indicated that following a 160 mg starting dose, a dosing regimen of ixekizumab 80 mg Q2W provided greater efficacy at Week 12 for the skin endpoints of PASI 75/90/100 and sPGA (0,1)/(0), when compared to a dosing regimen of ixekizumab 80 mg Q4W. The dose approved for skin psoriasis is 160 mg at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg Q4W.

As such PsA patients with coexistent moderate-to-severe plaque psoriasis should receive the dose approved for skin psoriasis.

2.5. Clinical safety

Introduction

Taltz (ixekizumab) solution for injection 80 mg is currently indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The recommended dose is 160 mg by SC injection (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. In the pivotal studies for the plaque psoriasis indication, the most common AEs following 12 weeks treatment with ixekizumab were infections (nasopharyngitis, upper respiratory tract infection), injection site reactions and headache. The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of treatment. Opportunistic infections were also observed, mainly candida infections. The long term safety of ixekizumab, evaluated following 48 weeks of treatment, was mainly similar to the 12 week induction period (though the exposure-adjusted incidence rate of TEAEs was somewhat lower in the Maintenance Dosing Period than in the Induction). There is a possible association between systemic IL-17A blockade and reduction in peripheral neutrophil counts. Approximately 9% of psoriasis patients receiving Taltz developed neutropenia. Thrombocytopenia has also been observed. In most cases, this did not require discontinuation of treatment.

Based on the biological target of ixekizumab important safety concerns such as infections, serious hypersensitivity and inflammatory bowel disease have been identified. Treatment during clinically important active infections (e.g. active TB) has been contraindicated and a warning of late (10-14 days following injection) hypersensitivity reactions with urticaria, dyspnea and high antibody titers is stated in section 4.4 of the SmPC. Furthermore, *identified* (infections, neutropenia, hypersensitivity) and *potential* risks (IBD, MACE, malignancies) are being followed as safety concerns in the RMP.

The applied for posology for the PsA indication is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. Thus, based on the applied for dosing regimen for the PsA

indication, the level of exposure to ixekizumab will not exceed that for the approved plaque psoriasis indication.

Methods – analysis of data submitted

There are 2 pivotal studies for the PsA indication, studies I1F-MC-RHAP (RHAP) (active and placebo controlled) and RHBE (placebo controlled). In addition, supportive safety data in PsA is provided by 1 ongoing double-blind, randomized withdrawal study, preceded by an Open-Label Period, in patients with active PsA who have had inadequate response to conventional disease-modifying antirheumatic drugs (cDMARD-IR) and are bDMARD-naive (I1F-MC-RHBF [RHBF]). The following integrated datasets were submitted to support the safety for the current application:

- The Primary PsA Placebo-Controlled Integrated Analysis Set (N=678) "Primary PsA Analysis Set" comprised data from patients from the pivotal studies RHAP and RHBE. The primary analysis was conducted using data from the Double-Blind Treatment Period (Weeks 0 to 24) but excluding observed data after Week 16 through Week 24 for patients classified as Week 16 Inadequate Responders (IRs) in order to avoid confounding the data.

This set includes 454 ixekizumab and 224 placebo patients. Of note, study RHAP also included an additional active reference arm of treatment with adalimumab (n= 101). IRs were rescued with standard of care therapies and, if receiving adalimumab or placebo, were re-randomized to ixekizumab. Supplementary analyses were performed that included all patients for (1) Weeks 0 to 16 (i.e. prior to rescue therapy), and (2) Weeks 0 to 24 including the observed data after Week 16 through Week 24 from the Week 16 Inadequate Responders (IRs).

- The All PsA Ixekizumab Exposures Integrated Analysis Set (N=1118) "All PsA Analysis Set" was a larger analysis set comprising data from ixekizumab-treated patients from all treatment periods of studies RHAP and RHBE and from the Open-Label Treatment Period of Study RHBF. The primary analysis of this set used all data after Week 0, that is, through the patient last visit before database lock. (A supplementary analysis was conducted using data from Weeks 0 to 52.)
- The All Psoriasis Ixekizumab Exposures Integrated Analysis Set (N=5689) "All Psoriasis Analysis Set" with data from ixekizumab-treated patients in all treatment periods of 11 completed or ongoing studies in psoriasis, as of the September 2016 data cutoff date.

The safety population was defined as all randomized patients who received at least 1 dose of their assigned study treatment. A treatment-emergent adverse event (TEAE) was defined as an event that first occurred or worsened in severity after baseline and on or before the date of the last visit within the treatment period. The presentation of clinical safety in this AR will mainly focus on the first 2 datasets in PsA patients. Data from the psoriasis population will be also presented, however, given the overlap between the patient populations.

Overall, the approach for the presentation of the safety data is considered acceptable by the CHMP.

The data cutoff date for the safety data was 15 Sep 2016 for all studies, with the following exceptions: 30 Sep 2016 for Study I1F-MC-RHBE (RHBE) (PsA), 23 Sep 2016 for Study I1F-EW-RHBZ (RHBZ) (psoriasis), and 22 Sep 2016 for Study I1F-JE-RHAT (RHAT) (psoriasis).

2.5.1. Patient exposure

Patient exposure in each of the primary safety data sets for ixekizumab PsA studies is summarized below. In the ixekizumab clinical development program, 1118 patients with active PsA have received at least 1 dose of ixekizumab, representing 1050.6 patients-years of exposure.

Table 26: Extent and Duration of Study Drug Exposure - Psoriatic Arthritis Studies

		Primary PsA Placebo-Controlled Integrated Analysis Set Studies RHAP, RHBE (Weeks 0 to 24)				All PsA Ixekizumab Exposures Integrated Analysis Set Studies RHAP, RHBE, RHBF		
Days of Exposure		Placebo N=224	80 mg Q4W N=229	80 mg Q2W N=225	Total IXE N=454	80 mg Q4W N=365	80 mg Q2W N=752	Pooled IXE N=1118[a]
>0	n	224	229	225	454	365	752	1118
≥90	n	201	219	214	433	330	597	927
≥120	n	136	191	183	374	320	471	791
≥168	n	118	167	160	327	—	—	—
≥183	n	NA	NA	NA	NA	296	314	610
≥365	n	NA	NA	NA	NA	183	182	365
Total Patient-Years		85.7	98.3	95.5	193.8	465.7	584.9	1050.6

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable; PsA= psoriatic arthritis.

Notes: Patients included in the Primary PsA Placebo-Controlled Integrated Analysis Set are included in the All PsA Ixekizumab Exposures Integrated Analysis Set; the results for the 2 analysis sets cannot be summed.

Dash symbol ("—") means the n and % were not calculated.

Total patient-years is calculated as sum of duration of exposure in days (for all patients in treatment group)/365.25.

[a] One patient in Study RHAP received ixekizumab due to a drug dispensing error; in the exposure calculations for the All PsA Ixekizumab Exposures Integrated Analysis Set, this patient is included in the Pooled IXE group but is excluded from the individual dosing regimen groups.

Sources: Table AP1.2.7.4.2; Table AP1.2.7.4.3

In addition, 5689 patients with moderate-to-severe plaque psoriasis have received at least 1 dose of ixekizumab cumulatively, representing 12061.5 patient-years of exposure cumulatively, or 7331.8 additional patient-years of exposure (155% increase) since the time of the MAA for the plaque psoriasis indication (see table below). Overall, across therapeutic indications (including RA for which development was stopped), 7339 patients have been exposed to ixekizumab (13645.6 patient-years).

Table 27: Extent and Duration of Study Drug Exposure - Current and Ongoing Psoriasis Studies

		Pooled IXE N=5689
Days of Exposure		
>0	n	5689
≥90	n	5461
≥120	n	5374
≥183	n	5186
≥365	n	3787
Total Patient-Years		12061.5

Abbreviations: IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category.

Note: Total patient-years is calculated as sum of duration of exposure in days (for all patients in treatment group)/365.25.

Source: Table AP1.2.7.4.4

- Co-morbidities and previous/concomitant medications

In the Primary PsA Analysis Set, of patients in the total ixekizumab group and the placebo group, 45.6% and 47.3%, respectively, had at least 1 pre-existing condition at baseline. The most frequent in the total ixekizumab group were psoriasis (43.0%), nail psoriasis (31.5%), tendonitis (28.4%), dactylitis (20.7%), and hypertension (16.1%). At baseline, 0.2% to 25.8% of patients in the total ixekizumab group were reported with a medical history of hypertension, diabetes mellitus (type 2), coronary artery disease, stroke, or dyslipidemia; no patients had a history of diabetes mellitus (type 1). In the placebo group, 0.9% to 25.0% of patients had a history of hypertension, coronary artery disease, or dyslipidemia; no patients had a history of diabetes mellitus (type 1 or type 2) or stroke.

At baseline, 54.2% of patients in the total ixekizumab and 52.7% in the placebo group had used biologic therapy for PsA (were biologic-experienced), whereas 15.6% of patients in the total ixekizumab and 17.0% in the placebo group were naive to systemic PsA therapies (e.g., cDMARDs, bDMARDs, and other systemic therapies, such as NSAIDs, analgesics, corticosteroids).

In the total ixekizumab and placebo groups, 62.8% and 62.5% of patients, respectively, received at least 1 concomitant medication; at baseline, 48.1% of patients in the total ixekizumab and 44.2% of patients in the placebo group were current users of methotrexate (ITT Population) and 58.0% of ixekizumab and 54.0% of placebo patients had current use of cDMARDs (including methotrexate, methotrexate sodium, sulfasalazine, leflunomide, ciclosporin, hydroxychloroquine, and hydroxychloroquine sulfate).

Regarding baseline characteristics in the All PsA Analysis Set, these were generally comparable to the Primary PsA Analysis Set. However, a greater proportion of ixekizumab-treated patients in the Primary PsA Analysis Set (54.2%) had previous biologic therapy experience compared to the All PsA Analysis Set (30.2%). This is due to the inclusion of data from study RHBF in the All PsA Analysis Set, which is an ongoing study in patients with active PsA with inadequate response to conventional disease-modifying antirheumatic drugs and who are bDMARD-naive.

- Patient Disposition and Reasons for Discontinuation

In the Primary PsA Analysis Set, 71.1% of all patients completed the Double-Blind Treatment Period; 16.5% of patients completed the Double-Blind Treatment Period but were classified as IRs. Approximately 12% of patients discontinued treatment early for any reason. Overall, 78.9% of ixekizumab (IXE) patients and 55.4% of placebo patients completed the Double-Blind Treatment Period and 4.2% of IXE patients and 3.6% of placebo patients, respectively, discontinued due to an AE. Compared with either ixekizumab treatment group, a greater percentage of patients in the placebo group discontinued treatment, primarily due to lack of efficacy and subject decision. In the IXE 80 mg Q2W group, 5.3% of patients discontinued due to an AE as compared to 3.1% of patients in the Q4W group.

In the All PsA and the All Psoriasis Analysis Sets, 64 (5.7%) patients and 379 (6.7%) patients, respectively, discontinued from the studies because of an AE.

Common adverse events

Primary PsA Analysis Set

A summary of treatment-emergent AEs (TEAEs) in the Primary PsA Analysis Set is provided below.

Table 28: Overview of TEAEs - Double-Blind Treatment Period (Weeks 0 to 24)
Primary PsA Placebo-Controlled Integrated Analysis Set

Event Type *Severity*	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Deaths	0	0	0	0
Patients with ≥1 SAE	6 (2.7%)	9 (3.9%)	11 (4.9%)	20 (4.4%)
Patients with ≥1 TEAE	127 (56.7%)	153 (66.8%) [a]	156 (69.3%) [a]	309 (68.1%) [a]
Mild	60 (26.8%)	91 (39.7%)	81 (36.0%)	172 (37.9%)
Moderate	63 (28.1%)	54 (23.6%)	61 (27.1%)	115 (25.3%)
Severe	4 (1.8%)	8 (3.5%)	14 (6.2%) [a]	22 (4.8%)
Discontinuation from study drug due to AE	8 (3.6%)	7 (3.1%)	12 (5.3%)	19 (4.2%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; AE = adverse event; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 event in the specified category; PsA = psoriatic arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Notes: Patients may be counted in more than one category. Patients with multiple occurrences of the same event are categorized by the highest severity. Deaths are included among SAEs and among discontinuations due to AEs.

[a] Statistically significant compared with placebo.

Source: Table AP1.2.7.4.20

Patients in the ixekizumab group reported TEAEs more frequently compared to placebo (68.1% vs. 56.7%). Somewhat more patients in the ixekizumab 80 mg Q2W group had one or more severe TEAEs (6.2%) compared to the 80 mg Q4W group (3.5%).

A summary of all TEAEs by SOC and by PT is presented in the tables below.

Table 29: TEAEs by SOC - Double-Blind Treatment Period (Weeks 0 to 24)
Primary PsA Placebo-Controlled Integrated Analysis Set

MedDRA SOC	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Infections and infestations	62 (27.7%)	77 (33.6%)	72 (32.0%)	149 (32.8%)
General disorders and administration site conditions	21 (9.4%)	48 (21.0%) [a]	63 (28.0%) [a]	111 (24.4%) [a]
Gastrointestinal disorders	25 (11.2%)	21 (9.2%)	33 (14.7%)	54 (11.9%)
Musculoskeletal and connective tissue disorders	31 (13.8%)	32 (14.0%)	22 (9.8%)	54 (11.9%)
Skin and subcutaneous tissue disorders	12 (5.4%)	22 (9.6%)	23 (10.2%)	45 (9.9%) [a]
Investigations	12 (5.4%)	15 (6.6%)	18 (8.0%)	33 (7.3%)
Respiratory, thoracic, and mediastinal disorders	16 (7.1%)	16 (7.0%)	16 (7.1%)	32 (7.0%)
Nervous system disorders	13 (5.8%)	19 (8.3%)	12 (5.3%)	31 (6.8%)
Injury, poisoning, and procedural complications	14 (6.3%)	13 (5.7%)	12 (5.3%)	25 (5.5%)
Metabolism and nutrition disorders	8 (3.6%)	10 (4.4%)	8 (3.6%)	18 (4.0%)
Psychiatric disorders	11 (4.9%)	8 (3.5%)	9 (4.0%)	17 (3.7%)
Vascular disorders	8 (3.6%)	3 (1.3%)	8 (3.6%)	11 (2.4%)
Reproductive system and breast disorders	3 (1.3%)	4 (1.7%)	7 (3.1%)	11 (2.4%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	4 (1.8%)	6 (2.6%)	4 (1.8%)	10 (2.2%)
Blood and lymphatic system disorders	6 (2.7%)	2 (0.9%)	7 (3.1%)	9 (2.0%)
Ear and labyrinth disorders	1 (0.4%)	4 (1.7%)	5 (2.2%)	9 (2.0%)
Immune system disorders	2 (0.9%)	5 (2.2%)	4 (1.8%)	9 (2.0%)
Eye disorders	1 (0.4%)	3 (1.3%)	5 (2.2%)	8 (1.8%)
Renal and urinary disorders	4 (1.8%)	3 (1.3%)	4 (1.8%)	7 (1.5%)
Cardiac disorders	1 (0.4%)	4 (1.7%)	2 (0.9%)	6 (1.3%)
Hepatobiliary disorders	2 (0.9%)	3 (1.3%)	2 (0.9%)	5 (1.1%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; PsA = psoriatic arthritis; SOC = system organ class.

[a] Statistically significant compared with placebo ($p<.05$).

Source: Table AP1.2.7.4.25

Table 30: TEAEs by PT (≥1% of Pts in Total IXE group) - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

MedDRA Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 TEAE	127 (56.7%)	153 (66.8%) [a]	156 (69.3%) [a]	309 (68.1%) [a]
Injection site reaction	1 (0.4%)	22 (9.6%) [a]	32 (14.2%) [a]	54 (11.9%) [a]
Upper respiratory tract infection	16 (7.1%)	16 (7.0%)	15 (6.7%)	31 (6.8%)
Injection site erythema	0	9 (3.9%) [a]	17 (7.6%) [a]	26 (5.7%) [a]
Nasopharyngitis	9 (4.0%)	15 (6.6%)	7 (3.1%)	22 (4.8%)
Diarrhoea	6 (2.7%)	7 (3.1%)	10 (4.4%)	17 (3.7%)
Headache	4 (1.8%)	10 (4.4%)	6 (2.7%)	16 (3.5%)
Sinusitis	5 (2.2%)	9 (3.9%)	6 (2.7%)	15 (3.3%)
Urinary tract infection	5 (2.2%)	8 (3.5%)	4 (1.8%)	12 (2.6%)
Bronchitis	7 (3.1%)	4 (1.7%)	7 (3.1%)	11 (2.4%)
Psoriatic arthropathy	9 (4.0%)	5 (2.2%)	5 (2.2%)	10 (2.2%)
Cough	4 (1.8%)	5 (2.2%)	5 (2.2%)	10 (2.2%)
Back pain	2 (0.9%)	7 (3.1%)	3 (1.3%)	10 (2.2%)
Hypertension	5 (2.2%)	2 (0.9%)	7 (3.1%)	9 (2.0%)
Oropharyngeal pain	1 (0.4%)	7 (3.1%) [a]	2 (0.9%)	9 (2.0%)
Muscle spasms	3 (1.3%)	3 (1.3%)	5 (2.2%)	8 (1.8%)
Alanine aminotransferase increased	1 (0.4%)	3 (1.3%)	5 (2.2%)	8 (1.8%)
Injection site hypersensitivity	0	1 (0.4%)	6 (2.7%) [a]	7 (1.5%)
Pharyngitis	2 (0.9%)	2 (0.9%)	5 (2.2%)	7 (1.5%)
Aspartate aminotransferase increased	2 (0.9%)	3 (1.3%)	4 (1.8%)	7 (1.5%)
Depression	3 (1.3%)	4 (1.7%)	3 (1.3%)	7 (1.5%)
Nausea	3 (1.3%)	1 (0.4%)	5 (2.2%)	6 (1.3%)
Alopecia	2 (0.9%)	2 (0.9%)	4 (1.8%)	6 (1.3%)
Seasonal allergy	1 (0.4%)	2 (0.9%)	4 (1.8%)	6 (1.3%)
Injection site pruritus	0	2 (0.9%)	4 (1.8%) [a]	6 (1.3%)
Oral herpes	1 (0.4%)	3 (1.3%)	3 (1.3%)	6 (1.3%)
Conjunctivitis	0	3 (1.3%)	3 (1.3%)	6 (1.3%)
Fatigue	3 (1.3%)	4 (1.7%)	2 (0.9%)	6 (1.3%)
Vulvovaginal mycotic infection [b]	1 (0.8%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Toothache	2 (0.9%)	1 (0.4%)	4 (1.8%)	5 (1.1%)
Oral candidiasis	0	1 (0.4%)	4 (1.8%) [a]	5 (1.1%)
Rhinitis	0	1 (0.4%)	4 (1.8%) [a]	5 (1.1%)
Anxiety	3 (1.3%)	2 (0.9%)	3 (1.3%)	5 (1.1%)
Hepatic enzyme increased	1 (0.4%)	2 (0.9%)	3 (1.3%)	5 (1.1%)
Abdominal pain upper	4 (1.8%)	3 (1.3%)	2 (0.9%)	5 (1.1%)
Abdominal pain	3 (1.3%)	3 (1.3%)	2 (0.9%)	5 (1.1%)
Blood creatine phosphokinase increased	1 (0.4%)	3 (1.3%)	2 (0.9%)	5 (1.1%)
Arthralgia	2 (0.9%)	5 (2.2%)	0 [c]	5 (1.1%)
Tonsillitis	0	5 (2.2%) [a]	0 [c]	5 (1.1%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.

[a] Statistically significant compared with placebo (p<.05).

[b] Denominator adjusted because gender-specific event for females: N=120 (placebo), N=121 (80 mg Q4W), and N=128 (80 mg Q2W).

[c] Statistically significant comparison for ixekizumab 80 mg Q2W versus 80 mg Q4W (p<.05).

Source: Table AP1.2.7.4.22

There were significantly higher incidences of patients with Injection site reaction and Injection site erythema in the total ixekizumab group as well as for the separate dose groups, as compared with placebo. There were numerically higher percentages of patients with these TEAEs in the ixekizumab 80 mg Q2W as compared with the Q4W group. Also, compared with placebo, there were significantly higher incidences of patients with Injection site hypersensitivity and Injection site pruritus for the ixekizumab 80 mg Q2W group, but not for the Q4W group. Compared with placebo, the incidence of oral candidiasis, rhinitis and tonsillitis was higher in patients treated with ixekizumab.

The profile of most common AEs is consistent with those observed in the plaque psoriasis MAA.

In the active controlled study RHAP, the pattern of most frequent TEAEs in adalimumab-treated patients included Nasopharyngitis and Upper respiratory tract infection, similarly to ixekizumab, whereas the frequency of injection site reactions was lower. To illustrate the comparative AE profile, a summary of most frequent TEAEs displayed by study is provided in the table below.

Table 31: TEAEs (≥3% of Pts in Total IXE group or either study) - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

	Study I1F-MC-RHAP					Study I1F-MC-RHBE			
MedDRA Preferred Term	Placebo N=106 n (%)	ADA N=101 n (%)	80 mg Q4W N=107 n (%)	80 mg Q2W N=102 n (%)	Total IXE N=209 n (%)	Placebo N=118 n (%)	80 mg Q4W N=122 n (%)	80 mg Q2W N=123 n (%)	Total IXE N=245 n (%)
Injection site reaction	0	2 (2.0%)	13 (12.1%) [a]	16 (15.7%) [a]	29 (13.9%)	1 (0.8%)	8 (6.6%) [a]	15 (12.2%) [a]	23 (9.4%)
Nasopharyngitis	5 (4.7%)	7 (6.9%)	7 (6.5%)	3 (2.9%)	10 (4.8%)	4 (3.4%)	8 (6.6%)	4 (3.3%)	12 (4.9%)
Upper respiratory tract infection	7 (6.6%)	5 (5.0%)	5 (4.7%)	3 (2.9%)	8 (3.8%)	9 (7.6%)	11 (9.0%)	12 (9.8%)	23 (9.4%)
Diarrhoea	3 (2.8%)	3 (3.0%)	2 (1.9%)	5 (4.9%)	7 (3.3%)	3 (2.5%)	5 (4.1%)	5 (4.1%)	10 (4.1%)
Injection site erythema	0	2 (2.0%)	7 (6.5%) [a]	13 (12.7%) [a]	20 (9.6%)	0	2 (1.6%)	4 (3.3%)	6 (2.4%)
Headache	1 (0.9%)	3 (3.0%)	4 (3.7%)	4 (3.9%)	8 (3.8%)	3 (2.5%)	5 (4.1%)	2 (1.6%)	7 (2.9%)
Alanine aminotransferase increased	0	3 (3.0%)	3 (2.8%)	4 (3.9%)	7 (3.3%)	0	0	2 (1.6%)	2 (0.8%)
Muscle spasms	1 (0.9%)	1 (1.0%)	3 (2.8%)	4 (3.9%)	7 (3.3%)	2 (1.7%)	0	1 (0.8%)	1 (0.4%)
Sinusitus	3 (2.8%)	2 (2.0%)	1 (0.9%)	1 (1.0%)	2 (1.0%)	2 (1.7%)	7 (5.7%)	5 (4.1%)	12 (4.9%)
Urinary tract infection	2 (1.9%)	4 (4.0%)	2 (1.9%)	0	2 (1.0%)	3 (2.5%)	6 (4.9%)	4 (3.3%)	10 (4.1%)
Cough	1 (0.9%)	2 (2.0%)	1 (0.9%)	1 (1.0%)	2 (1.0%)	3 (2.5%)	4 (3.3%)	4 (3.3%)	8 (3.3%)
Oropharyngeal pain	1 (0.9%)	0	0	1 (1.0%)	1 (0.5%)	0	7 (5.7%) [a]	1 (0.8%)	8 (3.3%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; ADA = adalimumab 40 mg every 2 weeks; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 event in the specified category.

[a] p-value <.05 compared with placebo. In the individual studies, the Total IXE group was not compared with placebo.

Sources: Table RHAP 14.223 of RHAP 24-week CSR(a); Table RHBE.14.191 of RHBE 24-week CSR

All PsA Analysis Set

A summary of TEAEs in the All PsA Analysis Set is provided below. Most TEAEs were mild or moderate in severity. There were 2 deaths, one in Study RHAP (Cerebrovascular accident) and one in Study RHBF (Pneumonia).

Table 32: Overview of TEAEs – All Treatment Periods All PsA Ixekizumab Exposures Integrated Analysis Set

Event Type *Severity*	Pooled IXE N=1118 n (%)
Death	2 (0.2%)
Patients with ≥1 SAE	73 (6.5%)
Patients with ≥1 TEAE	734 (65.7%)
Mild	357 (31.9%)
Moderate	314 (28.1%)
Severe	63 (5.6%)
Discontinuation from study drug due to AE	64 (5.7%)

Abbreviations: AE = adverse event; IXE= ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 event in the specified category; PsA = psoriatic arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Notes: Patients may be counted in more than one category. Patients with multiple occurrences of the same event are categorized by the highest severity. Deaths are included among SAEs and among discontinuations due to AEs.

Source: Table AP1.2.7.4.47

TEAEs in the All PsA Ixekizumab Exposures Integrated Analysis Set were most often reported in the General disorders and administration site conditions SOC (most frequent PTs: injection site reaction,

injection site erythema) and in the Infections and infestations SOC (most frequent PTs: upper respiratory tract infection, nasopharyngitis).

Table 33: TEAEs (≥1% of Pts) – All Treatment Periods
All PsA Ixekizumab Exposures Integrated Analysis Set

MedDRA Preferred Term	Pooled IXE N=1118 n (%)
Patients with ≥1 TEAE	734 (65.7%)
Injection site reaction	132 (11.8%)
Upper respiratory tract infection	89 (8.0%)
Nasopharyngitis	76 (6.8%)
Injection site erythema	50 (4.5%)
Urinary tract infection	38 (3.4%)
Sinusitis	36 (3.2%)
Bronchitis	34 (3.0%)
Diarrhoea	34 (3.0%)
Hypertension	33 (3.0%)
Back pain	29 (2.6%)
Headache	29 (2.6%)
Pharyngitis	27 (2.4%)
Tonsillitis	24 (2.1%)
Psoriatic arthropathy	23 (2.1%)
Oropharyngeal pain	21 (1.9%)
Conjunctivitis	19 (1.7%)
Influenza	19 (1.7%)
Cough	17 (1.5%)
Oral herpes	17 (1.5%)
Alanine aminotransferase increased	14 (1.3%)
Nausea	14 (1.3%)
Neutropenia	14 (1.3%)
Rhinitis	14 (1.3%)
Vulvovaginal mycotic infection [a]	7 (1.2%)
Abdominal pain	13 (1.2%)
Fatigue	13 (1.2%)
Injection site pain	13 (1.2%)
Psoriasis	13 (1.2%)
Seasonal allergy	13 (1.2%)
Alopecia	12 (1.1%)
Aspartate aminotransferase increased	12 (1.1%)
Cystitis	12 (1.1%)
Oral candidiasis	12 (1.1%)
Osteoarthritis	12 (1.1%)
Pruritis	12 (1.1%)
Rash	12 (1.1%)
Viral upper respiratory tract infection	12 (1.1%)

Abbreviations: IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.

Notes: Patients with multiple occurrences of these categories are counted once for each category. Patients may be counted in more than one category.

[a] Denominator adjusted because gender-specific event for females: N=601, patient-years (PY)=551.5 (Pooled IXE).

Source: Table AP1.2.7.4.50

A summary of exposure-adjusted IRs of TEAEs within 12-week time periods through 84 weeks of treatment is provided in the table below. Overall rates of TEAEs did not increase over time.

Table 34: Overview of TEAEs – Frequency and Incidence Rate by 12-Week Intervals All PsA Ixekizumab Exposures Integrated Analysis Set

Interval	Nx	Frequency n (%) [CI]	Total PY	Incidence Rate n (IR) [CI]
Weeks 0 to 12	1118	533 (47.7%) [44.7, 50.6]	244.8	533 (217.7) [200.0, 237.0]
Weeks 12 to 24	980	328 (33.5%) [30.5, 36.4]	180.6	328 (181.6) [163.0, 202.3]
Weeks 24 to 36	641	226 (35.3%) [31.6, 39.0]	126.5	226 (178.7) [156.9, 203.6]
Weeks 36 to 48	477	133 (27.9%) [23.9, 31.9]	96.1	133 (138.4) [116.8, 164.1]
Weeks 48 to 60	380	111 (29.2%) [24.6, 33.8]	80.1	111 (138.6) [115.1, 166.9]
Weeks 60 to 72	324	79 (24.4%) [19.7, 29.1]	69.0	79 (114.5) [91.9, 142.8]
Weeks 72 to 84	291	67 (23.0%) [18.2, 27.9]	62.9	67 (106.6) [83.9, 135.4]

Abbreviations: CI = confidence interval; IR = incidence rate; Nx = number of patients entered each time interval; n = number of patients with ≥1 event; PsA = psoriatic arthritis; PY = patient-years.

Notes: Incidence rate is for patients reporting ≥1 event in the category per 100 PY.

Sources: Table AP1.2.7.4.61; Table AP1.2.7.4.49

A summary of exposure-adjusted IRs of TEAEs by SOC has also been provided. Similarly, these data did not indicate an increase in the exposure-adjusted IR over time, e.g. for the Infections and infestations SOC. It should be considered that the majority of the data is still limited to the first 24-36 weeks of treatment. However, the Applicant also provided the frequencies and exposure-adjusted IRs within 12-week time periods through 156 weeks of treatment for the All Psoriasis Analysis Set, which also illustrated that the reported rate of TEAEs, by SOC did not increase over time, during longer exposures to ixekizumab. In this data set, at Weeks 144-156, 2275 patients of the total of 5689 psoriasis patients were still included.

All Psoriasis Analysis Set

Overall, the most frequently reported TEAEs were consistent with the established safety profile of ixekizumab, taking into consideration the longer period of patient follow-up represented in this updated analysis set. Very common TEAEs (≥10%) in this analysis set were Nasopharyngitis and Upper respiratory tract infection.

Also, individual terms most frequently reported in this updated psoriasis analysis set are comparable to those most frequently reported in the All PsA Analysis Set. To illustrate this, the table below summarizes clusters (of AEs of interest) and PTs within clusters reported for at least 1% of patients in this data set. See also the section AEs of Special Interest (AESI).

Table 35: TEAE Clusters and PTs (≥1% of Pts) All Treatment Periods
All Psoriasis Ixekizumab Exposures Integrated Analysis Set

Cluster Preferred Term	Pooled IXE N=5689 n (%)
Upper Respiratory Tract Infection	2001 (35.2%)
Nasopharyngitis	1302 (22.9%)
Upper respiratory tract infection	769 (13.5%)
Viral upper respiratory tract infection	87 (1.5%)
Injection Site Reactions HLT	840 (14.8%)
Injection site reaction	540 (9.5%)
Injection site erythema	178 (3.1%)
Injection site pain	94 (1.7%)
Injection site swelling	59 (1.0%)
Lower Urinary Tract Infections	341 (6.0%)
Urinary tract infection	272 (4.8%)
Cystitis	90 (1.6%)
Sinusitis	314 (5.5%)
Sinusitis	309 (5.4%)
Gastroenteritis	307 (5.4%)
Gastroenteritis	173 (3.0%)
Gastroenteritis viral	82 (1.4%)
Pharyngeal Infection	304 (5.3%)
Pharyngitis	240 (4.2%)
Pharyngitis streptococcal	57 (1.0%)
Candida Infection	249 (4.4%)
Vulvovaginal candidiasis[a]	43 (2.3%)
Vulvovaginal mycotic infection[a]	36 (1.9%)
Oral candidiasis	103 (1.8%)
Tinea	191 (3.4%)
Tinea pedis	115 (2.0%)
Cellulitis	153 (2.7%)
Cellulitis	109 (1.9%)
Skin Infection/Cellulitis	153 (2.7%)
Cellulitis	109 (1.9%)
Tonsilitis	152 (2.7%)
Tonsillitis	127 (2.2%)
Rash	140 (2.5%)
Rash	64 (1.1%)
Skin and External Abscesses	112 (2.0%)
Oral Candidiasis	111 (2.0%)
Oral candidiasis	103 (1.8%)
Lower Respiratory Tract Infection	105 (1.8%)
Pneumonia	71 (1.2%)
Staphylococcal-Related Infections	93 (1.6%)

Abbreviations: HLT = high level term; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; TEAE = treatment-emergent adverse event.

[a] Denominator adjusted because gender-specific event for females: N=1848; patient-years=3809.4 (Pooled IXE).

Source: Table AP1.2.7.4.74

Serious adverse event / deaths / other significant events

In total, there were 25 deaths in the studies of PsA and psoriasis, of which 2 occurred in studies of patients with PsA and 23 in studies of patients with psoriasis (of which 8 were previously reported in the plaque psoriasis MAA).

According to the narrative, the patient's medical history included hypertension from 2012 and transient ischaemic attack (TIA) in 04-2013. Concomitant medication included amlodipine besilate, methyldopa, perindopril arginine, rilmenidine, indapamide and doxazosin for hypertension, metformin and gliclazide for diabetes mellitus, rosuvastatin for dyslipidemia and caffeine, paracetamol and leflunomide for psoriasis arthritis. The patient had been hospitalized for approximately 2 weeks prior to the death due to a stroke that resulted in left-sided hemiplegia. The death was considered not related to blinded therapy by the investigator. This can be agreed by CHMP based on the patient's medical history, which included a previous TIA.

The second cases refers to patient who received ixekizumab 80 mg Q2W died due to pneumonia, onset after 19 days of treatment. The narrative states that the patient had started the initial open-label treatment period of study RHBF, (which included a 160 mg ixekizumab start dose followed by 80 mg Q2W). Five days after receiving the second dose, the patient experienced high fever with sweating, chills, dyspnea, fatigue, weakness, anorexia and productive cough. Apparently the patient was not hospitalized for this event but diagnosed with community-acquired pneumonia and treated at home by a physician with cefotaxime, salmeterol, budesonide, and oxygen support. No additional diagnostic testing was performed. The patient failed to show improvement and died 2days later at home as a result of this event. An autopsy was not performed. The cause of death was considered to be pneumonia.

The patient's medical history was not remarkable for prior conditions in terms of pulmonary or cardiovascular disease. No history of alcohol abuse. Treatments received for treatment of psoriatic arthritis prior to start study drug were: cyclosporine, loratadine and diclofenac. Concomitant medications included: amitriptyline for depression. The narrative indicates that the patient was in poor 'general health' which may have facilitated development of pneumonia and fatal outcome. However, a causal relationship to ixekizumab cannot be excluded. The investigator considered the event as related to study drug.

A cumulative listing of all deaths is provided in the table below.

Table 36: Cumulative Listing of Deaths in Patients Treated with Ixekizumab Across Clinical Studies of Ixekizumab in Psoriatic Arthritis and Psoriasis

Study	Study Diagnosis	Center	Patient ID	Age (yrs)	Sex	Dose at Time of Death	Days of Exposure to Ixekizumab[a]	Cause of Death (Actual Term)	Other Medications
RHAP	PsA	[redacted]	[redacted]	59	M	IXE 80 mg Q4W	537	Undetermined stroke	amlodipine besilate, atorvastatin, ciprofloxacin, coveram, doxazosin mesilate, gliclazide, indapamide, leflunomide, metformin HcL, methyldopa, para-selzer, paynocil, rilmenidine
RHBF	PsA			52	M	IXE 80 mg Q2W	21	Pneumonie	—
RHAZ	Ps			52	M	IXE 80 mg Q4W	1159	Cardiogenic shock	amlodipine, naproxen, vicodin
RHAZ	Ps			70	F	—	949	Diffuse large B-cell lymphoma	colecalciferol, cyclobenzaprine, furosemide, glibenclamide, glipizide, hydrochlorothiazide, levothyroxine, liraglutide, loperamide HcL, losartan, procet, ranitidine, tramadol
RHAZ	Ps			73	M	—	1085	Metastatic lung cancer	rosuvastatin calcium
RHAZ	Ps			58	F	IXE 80 mg Q4W	1015	Death (unknown)	—
RHAZ	Ps			57	F	IXE 80 mg Q4W	1015	Death	ibuprofen, piritramide
RHAZ	Ps			52	M	IXE 80 mg Q4W/ IXE 80 mg Q4W	134	Unknown	valsartan, hydrochlorothiazide, ticlopidine
RHAZ	Ps			70	F	IXE 80 mg Q2W/ IXE 80 mg Q4W	246	Myocardial infarction	ASA, clopidogrel, atorvastatin, insulin, zofenopril, carvedilol
RHAZ	Ps			65	M	—	863	Respiratory failure	amitriptyline HcL, domperidone, fenofibrate, pantoprazole, rivaroxaban
RHBA	Ps			63	F	IXE 80 mg Q4W	900	Coronary artery disease	amlodipine besilate, furosemide
RHBA	Ps			58	M	IXE 80 mg Q4W	1126	Death (unknown)	metoprolol, hydroxyzine
RHBA	Ps	[redacted]	[redacted]	62	M	IXE 80 mg Q4W	842	Heart failure	allopurinol, clopidogrel bisulfate, hydrochlorothiazide, insulin aspart, insulin glargine, losartan, metformin, metoprolol, pantoprazole, simvastatin, terazosin
RHBA	Ps			72	M	IXE 80 mg Q4W	898	Acute on chronic hypoxemic respiratory failure	doxycycline, fluocinonide, oxazepam, oxycocet, paroxetine, rabeprazole, ramipril
RHBA	Ps			39	M	IXE 80 mg Q4W/ IXE 80 mg Q12W	454	Sudden cardiac arrest	levothyroxine, clotrimazole
RHBC	Ps			66	F	IXE 80 mg Q2W/ IXE 80 mg Q4W	219	Hemorrhagic cerebral infarction	lansoprazole, iron, warfarin, vitamins, ascorbic acid
RHBC	Ps			36	M	IXE 80 mg Q4W	577	Cardiopulmonary arrest	aspirin, hydrochlorothiazide, lisinopril, metoprolol, simvastatin
RHBC	Ps			57	F	IXE 80 mg Q4W	1072	Death (unknown)	citalopram, fluticasone, hydrochlorothiazide, hydrocortisone valerate, metoprolol tartrate, perindopril, rosuvastatin calcium, salbutamol, salmeterol, sertraline
RHBC	Ps			47	M	IXE 80 mg Q4W	462	Accidental death	No relevant concomitant medications reported during the study.
RHBC	Ps			88	M	IXE 80 mg Q4W	620	End-stage senile dementia	diltiazem, fluticasone, furosemide, hydroxyzine HcL, metoprolol, pradaxa
RHBC	Ps			52	M	IXE 80 mg Q4W	432	Possible heart attack	paracetamol
RHBL	Ps			55	M	IXE 80 mg Q2W/ IXE 80 mg Q4W	128	Cardio-respiratory arrest	ASA, captopril, ciprofloxacin, clopidogrel, glipizide, omeprazole, ranitidine, and simvastatin
RHBP	Ps			61	M	IXE 80 mg Q4W	171	NSTEMI	none
RHBP	Ps			54	M	IXE 80 mg Q2W	65	Heart failure	ASA, allopurinol, ferrous glycine sulfate, pancreatin, pantoprazole sodium sesquihydrate, ramipril

Study	Study Diagnosis	Center	Patient ID	Age (yrs)	Sex	Dose at Time of Death	Days of Exposure to Ixekizumab[a]	Cause of Death (Actual Term)	Other Medications
RHBP	Ps	[redacted]	[redacted]	37	M	IXE 80 mg Q2W	68	Trauma	none

Abbreviations: ASA = acetylsalicylic acid; F = female; HcL = hydrochloride; ID = identification number; IXE = ixekizumab; M = male; NSTEMI = non-ST-elevation myocardial infarction; Ps = psoriasis; PsA = psoriatic arthritis; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; yrs = years.

[a] Duration of exposure in days at the start time of the event relative to ixekizumab treatment start date.

[b] Reported during assessment of the plaque psoriasis MAA.

Note: Deaths of patients in all studies of rheumatoid arthritis were described in Section 2.7.4.2.1.4 of the Summary of Clinical for in the plaque psoriasis Marketing Authorization Application.

Sources: l_death_apsa.rtf; l_death_aps.rtf

Most of these new deaths (updated from the plaque psoriasis MAA) pertain to cardiovascular events as the cause of death or presumed (but unconfirmed) cardiovascular events based on medical history. All of these patients had relevant medical and/or medication history for cardiovascular disease, such as hypertension, obesity, diabetes, angina, etc. Three new deaths were related to malignancy, one patient due to diffuse large B-cell lymphoma and one patient due to metastatic lung cancer. In addition, another patient was reported in the narrative to have died from lung cancer (as reported by relatives but unconfirmed). In most cases, the deaths were not considered related to ixekizumab by the investigator. It can be agreed that no new safety concerns were evoked by the reported cases.

A summary of all SAEs (including death) for the Primary PsA Analysis Set is provided in the table below.

Twenty patients in the total ixekizumab group (4.4%) and 6 patients in the placebo group (2.7%) were reported to have ≥1 SAE. No individual PT was reported for more than 1 patient. Among the SOCs, the Infections and infestations SOC had the greatest incidence of SAEs. This was the only SOC for which there was a statistical difference between an ixekizumab group (the ixekizumab 80 mg Q2W group) compared with the placebo group (5 patients in the Q2W group versus 0 in the placebo group; p=.026).

Table 37: SAEs by PT within SOC – Double-Blind Treatment Period (Weeks 0 to 24)
Primary PsA Placebo-Controlled Integrated Analysis Set

SOC Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 SAE	6 (2.7%)	9 (3.9%)	11 (4.9%)	20 (4.4%)
Infections and infestations	0	1 (0.4%)	5 (2.2%) [a]	6 (1.3%)
Abscess jaw	0	0	1 (0.4%)	1 (0.2%)
Anal abscess	0	0	1 (0.4%)	1 (0.2%)
Herpes zoster	0	0	1 (0.4%)	1 (0.2%)
Oesophageal candidiasis	0	0	1 (0.4%)	1 (0.2%)
Perirectal abscess	0	0	1 (0.4%)	1 (0.2%)
Gastroenteritis	0	1 (0.4%)	0	1 (0.2%)
Reproductive system and breast disorders	2 (0.9%)	1 (0.4%)	2 (0.9%)	3 (0.7%)
Uterine prolapse [b]	0	0	1 (0.8%)	1 (0.4%)
Uterine polyp [b]	0	1 (0.8%)	0	1 (0.4%)
Acquired phimosis	0	0	1 (0.4%)	1 (0.2%)
Adnexa uteri cyst [b]	1 (0.8%)	0	0	0
Bartholin's cyst [b]	1 (0.8%)	0	0	0

Gastrointestinal disorders	1 (0.4%)	1 (0.4%)	2 (0.9%)	3 (0.7%)
Anal fistula	0	0	1 (0.4%)	1 (0.2%)
Impaired gastric emptying	0	0	1 (0.4%)	1 (0.2%)
Pancreatitis	0	1 (0.4%)	0	1 (0.2%)
Abdominal pain	1 (0.4%)	0	0	0
Nervous system disorders	0	2 (0.9%)	1 (0.4%)	3 (0.7%)
Cervical myelopathy	0	0	1 (0.4%)	1 (0.2%)
Cervicobrachial syndrome	0	1 (0.4%)	0	1 (0.2%)
Post-traumatic headache	0	1 (0.4%)	0	1 (0.2%)
Injury, poisoning, and procedural complications	2 (0.9%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Fall	0	0	1 (0.4%)	1 (0.2%)
Foot fracture	0	0	1 (0.4%)	1 (0.2%)
Fibula fracture	0	1 (0.4%)	0	1 (0.2%)
Femoral neck fracture	1 (0.4%)	0	0	0
Tendon rupture	1 (0.4%)	0	0	0
Musculoskeletal and connective tissue disorders	0	2 (0.9%)	0	2 (0.4%)
Lumbar spinal stenosis	0	1 (0.4%)	0	1 (0.2%)
Myofascial pain syndrome	0	1 (0.4%)	0	1 (0.2%)
Blood and lymphatic system disorders	0	0	1 (0.4%)	1 (0.2%)
Iron deficiency anaemia	0	0	1 (0.4%)	1 (0.2%)
Metabolism and nutrition disorders	0	0	1 (0.4%)	1 (0.2%)
Diabetes mellitus	0	0	1 (0.4%)	1 (0.2%)
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.4%)	1 (0.2%)
Abortion spontaneous [b]	0	0	1 (0.8%)	1 (0.4%)
Ear and labyrinth disorders	0	1 (0.4%)	0	1 (0.2%)
Vertigo	0	1 (0.4%)	0	1 (0.2%)
Hepatobiliary disorders	0	1 (0.4%)	0	1 (0.2%)
Cholelithiasis	0	1 (0.4%)	0	1 (0.2%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	1 (0.4%)	0	1 (0.2%)
Prostate cancer [c]	0	1 (0.9%)	0	1 (0.5%)
Investigations	1 (0.4%)	0	0	0
Hepatic enzyme increased	1 (0.4%)	0	0	0
Vascular disorders	1 (0.4%)	0	0	0
Peripheral arterial occlusive disease	1 (0.4%)	0	0	0

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 SAE in the specified category; PsA = psoriatic arthritis; SAE = serious adverse event; SOC = system organ class.

[a] Statistically significant compared with placebo ($p<.05$).

[b] Denominator adjusted because gender-specific event for females: N=120 (placebo), N=121 (ixekizumab 80 mg Q4W), N=128 (ixekizumab 80 mg Q2W).

[c] Denominator adjusted because gender-specific event for males: N=104 (placebo), N=108 (ixekizumab 80 mg Q4W), N=97 (ixekizumab 80 mg Q2W). Source: Table AP1.2.7.4.31

Overall, 4.4% of patients in the total IXE group reported one or more SAEs and 2.2% had SAEs in the SOC Infections and infestations. To compare, this is similar to the 5.0% overall SAE rate and 2.0% in Infections and infestations reported for the adalimumab treatment group in one of the underlying pivotal studies (RHAP). There were no SAEs reported in the Cardiac Disorders SOC in the primary analysis set of the PsA studies (see also AEs of Special Interest for a summary and discussion of MACE events).

There were 9 (4.3%) patients with SAEs in the total IXE group in study RHAP and 11 (4.5%) in study RHBE. Events that were typically considered possibly related to study drug by the investigator were events of infection or autoimmune in nature. Infections and IBD are reflected in sections 4.4 and 4.8 of the SmPC.

All PsA Analysis Set

Overall, 73 of the 1118 ixekizumab-treated PsA patients (6.5%) in this analysis set reported ≥1 SAE. Consistent with the Primary PsA Analysis Set, the Infections and infestations SOC had the greatest incidence of SAEs among the SOCs (1.3%). Few individual preferred terms for an SAE were reported for 2 or more patients: Pneumonia, Lower respiratory tract infection, Carotid artery stenosis, Cerebrovascular accident, Fall, Acute myocardial infarction, Coronary artery disease, Cholecystitis acute, Cholelithiasis, and Osteoarthritis.

The table below provides a summary of exposure-adjusted IR of (treatment emergent) SAEs by 12-week intervals to Week 84 for this data set.

Table 38: Overview of SAEs – Frequency and Incidence Rate by 12-Week Intervals All PsA Ixekizumab Exposures Integrated Analysis Set

Interval	Nx	Frequency n (%) [CI]	Total PY	Incidence Rate n (IR) [CI]
Weeks 0 to 12	1118	19 (1.7%) [0.9, 2.5]	244.8	19 (7.8) [5.0, 12.2]
Weeks 12 to 24	980	20 (2.0%) [1.2, 2.9]	180.6	20 (11.1) [7.1, 17.2]
Weeks 24 to 36	641	4 (0.6%) [0.0, 1.2]	126.5	4 (3.2) [1.2, 8.4]
Weeks 36 to 48	477	5 (1.0%) [0.1, 2.0]	96.1	5 (5.2) [2.2, 12.5]
Weeks 48 to 60	380	6 (1.6%) [0.3, 2.8]	80.1	6 (7.5) [3.4, 16.7]
Weeks 60 to 72	324	7 (2.2%) [0.6, 3.7]	69.0	7 (10.1) [4.8, 21.3]
Weeks 72 to 84	291	11 (3.8%) [1.6, 6.0]	62.9	11 (17.5) [9.7, 31.6]

Abbreviations: CI = confidence interval; IR = incidence rate per 100 patient-years; IXE = ixekizumab; N = number of patients in the analysis population; Nx = number of patients entered each time interval; n = number of patients with ≥1 event in the specified category; PsA = psoriatic arthritis; PY = patient-years (total time patients were in each interval).

Note: The data collection for the clinical trial database does not contain a specification on when events become serious; thus, the numbers may represent more events considered serious than were actually serious during the treatment period.

Sources: Table AP2.2.7.4.2; Table AP2.2.7.4.1

The frequency and incidence rate was numerically somewhat higher in the final 12-week period than in any other period. However, at the time of database lock, there were only approximately one fourth of the patients included in this final time period compared with the initial 12-week period. Also, a similar trend was not observed in the larger 'All Psoriasis Analysis Set' for the psoriasis studies.

All Psoriasis Analysis Set

A total of 670 ixekizumab-treated psoriasis patients (11.8%) in this analysis set had ≥1 SAE. Consistent with the other analysis sets, in this larger analysis set, the Infections and infestations SOC had the greatest incidence of SAEs among the SOCs. Among individual preferred terms, the most frequently reported SAEs were Cellulitis (0.5%), Fall (0.3%), Myocardial infarction (0.3%), and Osteoarthritis (0.3%). An analysis of onset of SAEs by 12-week intervals to Week 156 does not suggest an increase in the frequency or rate of SAEs with increasing durations of exposure to ixekizumab.

Adverse events of special interest

Adverse events pre-specified as being of special interest (AESIs) are listed in the table below. These AESIs were selected based on standard drug registration topics (eg, hepatic toxicity/liver function), safety findings from the ixekizumab clinical development programme, potential risks associated with biologic immunomodulators, and comorbidities and risk factors prevalent in PsA and psoriasis populations (e.g., MACE, IBD), as well as regulatory topics of special interest for this class of compounds (e.g., depression). Although AEs were collected by spontaneous report, for AESIs (e.g., infection, ISRs, and general allergic/ hypersensitivity reactions), investigators were to collect additional information about these events. Cardiovascular-related MedDRA preferred terms were identified to facilitate independent adjudication.

Table 39: Treatment-Emergent AESI Primary PsA Analysis Set Double-Blind Treatment Period (Weeks 0 to 24)

Analysis Set	Primary PsA Analysis Set			
Treatment Group	PBO N=224	80 mg Q4W N=229	80 mg Q2W N=225	Total IXE N=454
AESI, n (%)				
Infections	62 (27.7)	77 (33.6)	72 (32.0)	149 (32.8)
Candida Infection [c]	1 (0.4)	4 (1.7)	8 (3.6) [a]	12 (2.6)
Oral candidiasis (PT)	0	1 (0.4)	4 (1.8) [a]	5 (1.1)
TE-Neutropenia [d]	6 (2.7)	24 (10.6) [a]	19 (8.7) [a]	43 (9.7) [a]
Grade 3 or Grade 4 [d]	0	0	0	0
Allergic Reactions/Hypersensitivities	4 (1.8)	10 (4.4)	14 (6.2) [a]	24 (5.3) [a]
Potential anaphylaxis [e]	0	0	0	0
Non-anaphylaxis	4 (1.8)	10 (4.4)	14 (6.2) [a]	24 (5.3) [a]
Injection Site Reactions (HLT)	10 (4.5)	40 (17.5) [a]	57 (25.3) [a,b]	97 (21.4) [a]
Discontinuations	1 (0.4)	1 (0.4)	4 (1.8)	5 (1.1)
Cerebro-Cardiovascular Events (confirmed)	2 (0.9)	0	0	0
MACE (confirmed)	0	0	0	0
Malignancies	0	2 (0.9)	0	2 (0.4)
Hepatic Events (narrow terms)	9 (4.0)	7 (3.1)	11 (4.9)	18 (4.0)
Depression	3 (1.3)	4 (1.7)	4 (1.8)	8 (1.8)
Suicide	0	0	0	0
Inflammatory bowel disease (PT)	0	0	0	0
Crohn's disease	0	0	0	0
Ulcerative colitis	0	0	0	0
IBD (non-specific PTs) [f]	0	0	1 (0.4)	1 (0.2)
Interstitial Lung Disease	0	0	0	0

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; AESI = adverse event of special interest; HLT = high level term; IBD = inflammatory bowel disease; IXE = ixekizumab; MACE = major adverse cerebro-cardiovascular events; PBO = placebo; Primary PsA Analysis Set = Primary PsA Placebo-Controlled Integrated Analysis Set; PsA = psoriatic arthritis; PT = preferred term; TE = treatment-emergent.

a $p<.05$ versus PBO.

b $p<.05$ versus ixekizumab 80 mg Q4W.

c TE-*Candida* infections defined by HLTs for *Candida* and additional clinical terms likely to represent *Candida* infections.

d TE-neutropenia based upon laboratory assessment.

e Results were similar whether Criterion 1 or Criterion 2 were used. Criterion 1: Treatment-emergent adverse events (TEAEs) based on selected MedDRA preferred terms from the anaphylactic reaction standardised Medical Dictionary for Regulatory Activities query (SMQ). Criterion 2: TEAEs from 2 or more 4 categories of AEs, as described by Sampson et al. (2006).

f The non-specific PTs were Anal abscess and Anal fistula.

Infections

In the **Primary PsA Analysis Set**, infection-related TEAEs occurred in a numerically higher proportion of patients treated with ixekizumab than with placebo and similar between the dose groups.

Table 40: Overview of Infection-Related TEAEs Primary PsA Analysis Set Double-Blind Treatment Period (Weeks 0 to 24)

Treatment Group	PBO N=224	80 mg Q4W N=229	80 mg Q2W N=225	Total IXE N=454
Category, n (%)				
Patients with ≥1 TEAE	62 (27.7)	77 (33.6)	72 (32.0)	149 (32.8)
Mild	37 (16.5)	59 (25.8)	49 (21.8)	108 (23.8)
Moderate	25 (11.2)	17 (7.4)	20 (8.9)	37 (8.1)
Severe	0	1 (0.4)	3 (1.3)	4 (0.9)
Patients with ≥1 SAE	0	1 (0.4)	5 (2.2) [a]	6 (1.3)
Discontinuation due to AE	1 (0.4)	2 (0.9)	1 (0.4)	3 (0.7)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; AE = adverse event; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; Primary PsA Analysis Set = Primary PsA Placebo-Controlled Integrated Analysis Set; PsA = psoriatic arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a $p<.05$ versus PBO.

Note: Patients may be counted in more than one category. Patients with multiple occurrences of the same event are categorised by the highest severity.

Within the Infections and infestations SOC, the most common events by PT were Upper respiratory tract infection (6.8% total IXE, 7.1% placebo), Nasopharyngitis (4.8% vs. 4.0%), and Sinusitis (3.3% vs. 2.2%). Most of the infection-related TEAEs were mild or moderate in severity and did not lead to early discontinuation. There were 3 infection events in the ixekizumab 80 mg Q2W group that were reportedly severe (Rhinitis, Abscess jaw, and Oesophageal candidiasis), compared with 1 severe infection in the Q4W group (Otitis media).

Overall infection rates observed in psoriatic arthritis clinical studies were similar to those observed in the placebo-controlled period of the pivotal plaque psoriasis studies. In these studies, nasopharyngitis (9.2%) and upper respiratory tract infection (4.1%) were similarly the most commonly reported type of treatment-emergent infection.

Within the active-controlled study RHAP, the frequency of infection-related TEAEs in adalimumab-treated patients (25.7%) was comparable to the ixekizumab group (25.8%) and the placebo group (25.5%), respectively.

Table 41: Infection-Related TEAEs (≥2 Pts) - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE [a] N=454 n (%)
Patients with ≥1 TEAE – Infections	62 (27.7%)	77 (33.6%)	72 (32.0%)	149 (32.8%)
Upper respiratory tract infection	16 (7.1%)	16 (7.0%)	15 (6.7%)	31 (6.8%)
Nasopharyngitis	9 (4.0%)	15 (6.6%)	7 (3.1%)	22 (4.8%)
Sinusitis	5 (2.2%)	9 (3.9%)	6 (2.7%)	15 (3.3%)
Urinary tract infection	5 (2.2%)	8 (3.5%)	4 (1.8%)	12 (2.6%)
Bronchitis	7 (3.1%)	4 (1.7%)	7 (3.1%)	11 (2.4%)
Pharyngitis	2 (0.9%)	2 (0.9%)	5 (2.2%)	7 (1.5%)
Oral herpes	1 (0.4%)	3 (1.3%)	3 (1.3%)	6 (1.3%)
Conjunctivitis	0	3 (1.3%)	3 (1.3%)	6 (1.3%)
Vulvovaginal mycotic infection [b]	1 (0.8%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Oral candidiasis	0	1 (0.4%)	4 (1.8%) [c]	5 (1.1%)
Rhinitis	0	1 (0.4%)	4 (1.8%) [c]	5 (1.1%)
Tonsillitis	0	5 (2.2%) [c]	0	5 (1.1%)
Otitis media	4 (1.8%)	1 (0.4%)	3 (1.3%)	4 (0.9%)
Folliculitis	1 (0.4%)	1 (0.4%)	3 (1.3%)	4 (0.9%)
Gastroenteritis	2 (0.9%)	2 (0.9%)	2 (0.9%)	4 (0.9%)
Influenza	1 (0.4%)	3 (1.3%)	1 (0.4%)	4 (0.9%)
Vulvovaginal candidiasis [b]	0	0	2 (1.6%)	2 (0.8%)
Viral pharyngitis	1 (0.4%)	1 (0.4%)	2 (0.9%)	3 (0.7%)
Viral upper respiratory tract infection	1 (0.4%)	2 (0.9%)	1 (0.4%)	3 (0.7%)
Tooth infection	0	2 (0.9%)	1 (0.4%)	3 (0.7%)
Respiratory tract infection viral	0	0	2 (0.9%)	2 (0.4%)
Tooth abscess	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Gastroenteritis viral	0	1 (0.4%)	1 (0.4%)	2 (0.4%)
Pharyngitis streptococcal	0	1 (0.4%)	1 (0.4%)	2 (0.4%)
Viral infection	0	1 (0.4%)	1 (0.4%)	2 (0.4%)
Cystitis	1 (0.4%)	2 (0.9%)	0	2 (0.4%)
Respiratory tract infection	1 (0.4%)	2 (0.9%)	0	2 (0.4%)
Otitis externa	0	2 (0.9%)	0	2 (0.4%)
Skin *Candida*	0	2 (0.9%)	0	2 (0.4%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.

[a] Cutoff criteria for table chosen in order to allow presentation of clinically important *Candida* infection events.

[b] Denominator adjusted because gender-specific event for females: N=120 (placebo), N=121 (ixekizumab 80 mg Q4W), N=128 (ixekizumab 80 mg Q2W).

[c] Statistically significant compared with placebo (p<.05).

Source: Table AP2.2.7.4.5

The total ixekizumab group had a higher percentage of patients with an infection-related SAE (1.3%, n=6) than the placebo group (0). Individual preferred terms for infection-related SAEs were as follows.

- Gastroenteritis (1 patient in the ixekizumab 80 mg Q4W group)
- Abscess jaw (1 patient in the ixekizumab 80 mg Q2W group)
- Anal abscess (1 patient in the ixekizumab 80 mg Q2W group)
- Herpes zoster (1 patient in the ixekizumab 80 mg Q2W group)
- Oesophageal candidiasis (1 patient in the ixekizumab 80 mg Q2W group)
- Perirectal abscess (1 patient in the ixekizumab 80 mg Q2W group)

Most infection-related SAEs were reported in the 80 mg Q2W dose group. The events of abscess jaw, anal abscess, and herpes zoster were considered related to study drug by the investigator. From the

narrative, it appears that also for the SAE of oesophageal candidiasis, a causal relationship to ixekizumab cannot be excluded although the patient had an extensive medical and concomitant medication history, including diabetes and the use of steroids. In the active-controlled study RHAP, 2 serious infections occurred in adalimumab-treated patients (Cellulitis and Pneumonia mycoplasma).

In the **All PsA Analysis Set**, 37.2% of patients (n=416) had ≥1 infection-related TEAE. A total of 1.3% of patients (n=15) had ≥1 infection-related SAE. Serious events that occurred in 2 or more patients were Pneumonia (n=3) and Lower respiratory tract infection (n=2). A total of 1.3% of patients (n=14) discontinued due to an infection-related AE.

For the **All Psoriasis Analysis Set** which includes 5689 patients with 12,061.5 total patient-years of ixekizumab exposure, infection-related TEAEs (exposure-adjusted incidence rate) is summarized below. There was no indication of an increase in the risk of infections with increasing durations of exposure to ixekizumab.

Table 42: Infection-Related TEAEs - Frequency and Incidence Rate by 12-Week Intervals All Psoriasis Ixekizumab Exposures Integrated Analysis Set

Interval	Nx	Frequency n (%) [CI]	Total PY	Incidence Rate n (IR) [CI]
Weeks 0 to 12	5689	1293 (22.7%) [21.6, 23.8]	1272.0	1293 (101.6) [96.3, 107.3]
Weeks 12 to 24	5520	1131 (20.5%) [19.4, 21.6]	1232.7	1131 (91.8) [86.6, 97.3]
Weeks 24 to 36	5244	960 (18.3%) [17.3, 19.4]	1176.0	960 (81.6) [76.6, 87.0]
Weeks 36 to 48	5041	891 (17.7%) [16.6, 18.7]	1075.2	891 (82.9) [77.6, 88.5]
Weeks 48 to 60	4216	635 (15.1%) [14.0, 16.1]	829.2	635 (76.6) [70.8, 82.8]
Weeks 60 to 72	3421	455 (13.3%) [12.2, 14.4]	774.5	455 (58.7) [53.6, 64.4]
Weeks 72 to 84	3367	409 (12.1%) [11.0, 13.3]	759.1	409 (53.9) [48.9, 59.4]
Weeks 84 to 96	3296	398 (12.1%) [11.0, 13.2]	744.2	398 (53.5) [48.5, 59.0]
Weeks 96 to 108	3243	388 (12.0%) [10.8, 13.1]	729.7	388 (53.2) [48.1, 58.7]
Weeks 108 to 120	3182	397 (12.5%) [11.3, 13.6]	707.0	397 (56.2) [50.9, 62.0]
Weeks 120 to 132	3021	324 (10.7%) [9.6, 11.8]	646.9	324 (50.1) [44.9, 55.8]
Weeks 132 to 144	2707	263 (9.7%) [8.6, 10.8]	537.2	263 (49.0) [43.4, 55.3]
Weeks 144 to 156	2275	223 (9.8%) [8.6, 11.0]	437.9	223 (50.9) [44.7, 58.1]

Abbreviations: CI = confidence interval; IR = incidence rate per 100 patient-years; IXE = ixekizumab; Nx = number of patients entered each time interval; n = number of patients with ≥1 event in the specified category; PY = patient-years (total time patients were in each interval); TEAE = treatment-emergent adverse event.

Sources: Table AP2.2.7.4.4; Table AP2.2.7.4.3

- Opportunistic infections

Table 43: Opportunistic and Potential Opportunistic Infections Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Broad/Narrow Category Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 TE opportunistic or potential opportunistic infections	1 (0.4%)	5 (2.2%)	10 (4.4%) [a]	15 (3.3%) [a]
Opportunistic infections – broad	1 (0.4%)	4 (1.7%)	4 (1.8%)	8 (1.8%)
Opportunistic infections – narrow	0	1 (0.4%)	6 (2.7%) [a]	7 (1.5%)
Candidiasis (invasive disease or oral) – narrow	0	1 (0.4%)	5 (2.2%) [a]	6 (1.3%)
Oral candidiasis	0	1 (0.4%)	4 (1.8%) [a]	5 (1.1%)
Oesophageal candidiasis	0	0	1 (0.4%)	1 (0.2%)
Herpes simplex (invasive disease only) – broad	1 (0.4%)	4 (1.7%)	4 (1.8%)	8 (1.8%)
Oral herpes	1 (0.4%)	3 (1.3%)	3 (1.3%)	6 (1.3%)
Genital herpes simplex	0	0	1 (0.4%)	1 (0.2%)
Herpes simplex	0	1 (0.4%)	0	1 (0.2%)
Herpes zoster (any form) – narrow	0	0	1 (0.4%)	1 (0.2%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; PsA = psoriatic arthritis; TE = treatment-emergent.

Note: Opportunistic infections are defined as the narrow terms and potential opportunistic infections are defined as the broad terms as defined by Lilly-specified lists (Section 2.7.4.5.10.1.3).

[a] Statistically significant ($p<.05$) compared with placebo.

Source: Table AP2.2.7.4.12

For treatment-emergent Candida infections, there was a greater proportion of patients in the ixekizumab 80 mg Q2W and 80 mg Q4W group with ≥1 such infection compared with placebo. Candida infections in the placebo group were limited to vulvovaginal infections. All but 1 *Candida* infections were mild to moderate in severity; in the Q2W group, 1 case of Oesophageal candidiasis was an SAE and rated as severe. No patients in the Primary PsA Analysis Set discontinued due to a *Candida* infection.

Consistent with the plaque psoriasis Phase III studies, the incidence of candida infections identified by the PT 'oral candidiasis' was significantly greater with ixekizumab 80 mg Q2W compared to placebo and there was a trend for more such cases for the 80 mg Q2W versus 80 mg Q4W group. There were no cases of invasive herpes simplex, viral hepatitis, confirmed active or reactivated TB, endemic mycoses, invasive *Aspergillus*, or other deep fungal infections in the Primary PsA Analysis Set. The patient with Herpes simplex listed in the 80 mg Q4W group had an HSV-II outbreak which was confirmed to be a cutaneous outbreak.

In the **All PsA Analysis Set**, the proportion of patients with TE opportunistic infections was 3.9%. Tuberculin test positive was reported in 0.3% (n=3) of ixekizumab-treated PsA patients. No patient was reported to have active TB. Herpes zoster was reported in 0.7% (n=8) of ixekizumab-treated PsA patients; no disseminated Herpes zoster was reported.

Of note, an event of Hepatitis B was reported in 0.1% (n=1) of ixekizumab-treated PsA patients. One patient had a routine serum HBV DNA polymerase chain reaction (PCR) test reported as qualitatively positive, without quantitation, at Week 36. HBV DNA was not detected in 4 subsequent samples, the first of which was drawn 3 weeks after the sample reported to be HBV DNA positive. The patient discontinued study treatment due to this event as required by study protocol

TE serious infections considered as opportunistic included 1 case of Oesophageal candidiasis and 1 case of Herpes zoster (ophthalmic branch of trigeminal nerve) (both also included in the Primary PsA Analysis Set). Both events occurred in patients receiving ixekizumab 80 mg Q2W.

The types of opportunistic infections reported in patients with plaque psoriasis (**All Psoriasis Analysis Set**) were consistent with those described in the plaque psoriasis MAA.

There were no reports indicating invasive Herpes simplex. Herpes zoster or Varicella zoster were reported in 1.4% (n=80) of patients in this analysis set. Testing for TB was required yearly in the clinical development program. As a result, cases of potential TB considered as a broad term occurred in 0.8% of patients (n=43) in this analysis set. There have been no reported cases of active or reactivated TB. There has been 1 patient each who were reported with Primary Cytomegalovirus Infection, Bartonellosis, and Toxoplasma Infection, respectively. These patients were previously described in the plaque psoriasis MAA.

Overall, the profile of infections in the Primary PsA Analysis Set for the current application is considered consistent with the prior experience of ixekizumab. The current data of hepatitis virus re-activation appears to be too limited to warrant specific inclusion in the product information.

Potential opportunistic infections (as considered by using broad terms) required medical review and according to the MAH no cases of invasive Herpes Simplex were reported. Although there was no statistically significant difference to placebo, there were numerical differences between the ixekizumab treatment groups and placebo with respect to patients with mucocutaneous Herpes simplex infections (1.8% vs 0.4%), more so than in the previous plaque psoriasis studies. In addition, oral herpes is included as ADR in the SmPC for secukinumab. Accordingly, Herpes Simplex (mucocutaneous) has now been included in section 4.8 of the SmPC.

Infections are already included as identified risk in the current RMP with the objective to monitor the incidence rate and nature of rare and clinically relevant infections through submission of additional safety data from ongoing studies, a post-marketing safety registry (the Corrona Registry), accompanied by routine pharmacovigilance.

Cytopenia

A greater reduction in total neutrophils was noted in the total ixekizumab group compared to placebo (-0.77 and 0.02 x109/L change from baseline, respectively) in the **Primary PsA Analysis Set**, with no evidence of a dose response. Similarly, there were statistically significant and clinically meaningful reductions in each of the ixekizumab groups compared with placebo with respect to the LSMean changes in leukocytes and platelets from the last observation during baseline to the last observation postbaseline (see table below). From baseline to last observation, mean neutrophil counts decreased more with ixekizumab 80 mg Q4W (- 0.903x109/L) and Q2W (- 0.634x109/L) than with placebo (0.018x109/L). Mean platelet counts decreased more with ixekizumab 80 mg Q4W (-32.5x109/L) and Q2W (-27.3x109/L) than with placebo (-3.2x109/L).

Table 44: Leukocytes, Neutrophils, Lymphocytes, and Platelets; Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Parameter Statistics	Placebo N=224	80 mg Q4W N=229	80 mg Q2W N=225	Total IXE N=454
Leukocytes (10^9/L)	n=222	n=229	n=224	n=453
Mean baseline (SD)	7.124 (1.9578)	7.500 (2.3423)	7.381 (2.1299)	7.441 (2.2381)
LSMean change (SE)	0.063 (0.1088)	–0.922 (0.1070) [a]	–0.633 (0.1082) [a]	–0.779 (0.0763) [a]
Neutrophils (10^9/L)	n=222	n=229	n=224	n=453
Mean baseline (SD)	4.790 (1.7430)	5.057 (2.1114)	4.938 (1.8614)	4.998 (1.9904)
LSMean change (SE)	0.018 (0.0980)	–0.903 (0.0965) [a]	–0.634 (0.0976) [a]	–0.770 (0.0688) [a]
Lymphocytes (10^9/L)	n=222	n=229	n=224	n=453
Mean baseline (SD)	1.691 (0.5517)	1.756 (0.5491)	1.797 (0.5837)	1.776 (0.5662)
LSMean change (SE)	0.040 (0.0290)	0.038 (0.0285)	0.028 (0.0289)	0.033 (0.0203)
Platelets (10^9/L)	n=221	n=228	n=224	n=452
Mean baseline (SD)	280.9 (75.74)	289.6 (86.50)	286.5 (77.79)	288.1 (82.22)
LSMean change (SE)	–3.2 (3.30)	–32.5 (3.25) [a]	–27.3 (3.28) [a]	–30.0 (2.31) [a]

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; LS = least squares; N = number of patients in the analysis population ; n = number of patients with a baseline and postbaseline value in that treatment group; SD = standard deviation; SE = standard error.

[a] p<.05 compared with placebo.

Source: Table AP1.2.7.4.104

- Neutrophils

The percentage of patients with TE-low neutrophil counts and the percentage of patients shifting from baseline to a lower grade postbaseline were higher in ixekizumab groups versus placebo. At least one TE Grade 1 or worse neutrophil count (<2x109/L) was observed in approximately 8% to 10% of ixekizumab patients from all 3 datasets. At least one TE Grade 2 or worse neutrophil count (<1.5x109/L) was observed in approximately 3% of ixekizumab patients from all 3 datasets.

It is stated in the Clinical Safety Summary that an exposure-response relationship was not observed for grade 2 neutropenia. In order to assist understanding the drug exposure-response relationships to the cytopenias, the company was requested to submit figures of (i) trough concentration quartile versus percent neutropenia [grades 1 to 4 combined], (ii) trough concentration quartile versus percent lymphopenia [grades 1 to 4 combined] and (iii) trough concentration quartile versus percent thrombocytopenia [grades 1 to 4 combined]. As there was no Grade 3 or Grade 4 event of neutropenia or Grade 2-4 thrombopenia in the defined periods (through Week 52 for Study RHAP and Week 24 for Study RHBE) the company provided an analysis of of Grade 1 and Grade 2 neutropenia. In Study RHAP, higher frequencies of Grades 1 or 2 neutropenia appeared to be associated with higher ixekizumab trough levels. However, this phenomenon was not observed in Study RHBE. No apparent correlation between higher trough ixekizumab exposures and higher percentages of patients with Grade 1 thrombocytopenia was observed. Overall, no firm conclusions could be drawn considering the small numbers of subjects in each group.

Treatment-emergent Grades 3 and 4 neutropenia were not observed during the Double-Blind Treatment Period, but occurred in respectively 3 (0.3%) and 0 patients of the **All PsA Analysis Set**, and in 16 (0.3%) and 3 (0.1%) patients of the **All Psoriasis Analysis Set**.

There were 3 cases of Grade 4 neutropenia (0.1%) all in the **All Psoriasis Analysis Set**; 2 cases were categorised as transient and 1 case persisted at least 7 months after ixekizumab treatment discontinuation, without concomitant infection.

- Platelets

In the **Primary Analysis Set**, no meaningful difference was observed between ixekizumab groups and the placebo group for the percentage of patients with TE-low platelet counts at any time postbaseline, nor for the percentage of patients shifting from baseline to a lower grade postbaseline.

No Grade 2 or worse platelet count was observed during the Double-Blind Treatment Period. Treatment-emergent Grade 2, 3, and 4 platelet counts were observed, respectively, in 1 (0.1%), 0, and 0 patients in the **All PsA Analysis Set**, and in 12 (0.2%), 1 (<0.05%), and 2 (<0.05%) patients in the **All Psoriasis Analysis Set**. Both cases of TE Grade 4 platelet count were single occurrences despite study drug being continued thereafter, and none was associated with any event of bleeding.

Five TEAEs that could be considered as bleeding (preferred terms: Contusion [n=2], Ecchymosis, Muscle contusion, and Purpura) were reported as temporally associated with Grade 1 thrombocytopenia but none with Grades 2, 3, or 4. No case of thrombocytopenia was reported as serious.

Neutropenia and thrombocytopenia are already included in section 4.8 of the currently approved SmPC. Additionally neutropenia is included in the RMP as an important identified risk. Overall, the current findings seem to be consistent with previous data.

However, in order to assist further understanding, the company was requested to provide shift figures of (i) baseline neutrophil count versus lowest neutrophil count, (ii) baseline lymphocyte count versus lowest lymphocyte count and (iii) baseline platelet count versus lowest platelet count. This showed that exposure to ixekizumab is associated with a reduction in neutrophil and platelet counts. This is appropriately reflected in the current section 4.8 of the SmPC.

Allergic reactions/Hypersensitivity reactions

An overview of allergic reaction/hypersensitivity events in the Primary PsA Analysis Set is provided in the table below. Potential anaphylaxis events were defined by specific MedDRA preferred terms (Criterion 1) or by other Sampson criteria (Criterion 2). Specifically, Criterion 1 for anaphylaxis was defined by the presence of a TEAE based on the following MedDRA preferred terms from the Anaphylactic Reaction SMQ:

- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactoid reaction
- Anaphylactoid shock
- Kounis Syndrome
- Type 1 hypersensitivity.

Criterion 2 for anaphylaxis required having TEAEs from 2 or more of 4 categories of AEs as described by Sampson et al. (2006). Occurrence of these events had to be nearly coincidental, based on recording of events on CRFs. All qualifying events had to be within ≤1 day of study drug injection. The 4 categories considered in Criterion 2 were:

- Category A: Involvement of the skin-mucosal tissue
- Category B: Respiratory compromise
- Category C: Reduced blood pressure or associated symptoms
- Category D: Persistent gastrointestinal symptoms.

There were no confirmed cases of ixekizumab-related anaphylaxis events across the clinical development program. Of note, the nonanaphylactic AEs that are summarized in the table below do not include injection site reactions.

Table 45: Overview of Allergic Reaction / Hypersensitivity Events - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Type of Event Category	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 TEAE	4 (1.8%)	10 (4.4%)	14 (6.2%) [a]	24 (5.3%) [a]
Potential anaphylaxis	0	0	0	0
Nonanaphylaxis	4 (1.8%)	10 (4.4%)	14 (6.2%) [a]	24 (5.3%) [a]
Patients with ≥1 SAE	0	0	0	0
Potential anaphylaxis	0	0	0	0
Nonanaphylaxis	0	0	0	0
Discontinuations due to AE	0	2 (0.9%)	0	2 (0.4%)
Potential anaphylaxis	0	0	0	0
Nonanaphylaxis	0	2 (0.9%)	0	2 (0.4%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 event in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Statistically significant compared with placebo.

Sources: Table AP2.2.7.4.90; Table AP2.2.7.4.95; Table AP2.2.7.4.97

Non-anaphylaxis allergic reaction/hypersensitivity TEAEs were more frequent in the ixekizumab treatment groups (Q4W: n= 10 [4.4%]; Q2W: n=14 [6.2%]) compared to placebo (n=4; 1.8%). Eczema, Rash, and Urticaria, which were each reported by 3 ixekizumab-treated patients and no placebo patients, were the most frequently reported preferred terms. All of these TEAEs were mild or moderate in severity and none was reported as an SAE. Two patients in the Q4W group discontinued: 1 due to Rash pruritic and 1 due to Hypersensitivity.

Table 46: TEAEs of Non-anaphylaxis Events - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 TEAE – Nonanaphylaxis events	4 (1.8%)	10 (4.4%)	14 (6.2%) [a]	24 (5.3%) [a]
Eczema	0	0	3 (1.3%)	3 (0.7%)
Rash	0	0	3 (1.3%)	3 (0.7%)
Urticaria	0	1 (0.4%)	2 (0.9%)	3 (0.7%)
Rhinitis allergic	0	0	2 (0.9%)	2 (0.4%)
Rash pruritic	0	1 (0.4%)	1 (0.4%)	2 (0.4%)
Angioedema	0	2 (0.9%)	0	2 (0.4%)
Dermatitis contact	1 (0.4%)	0	1 (0.4%)	1 (0.2%)
Conjunctivitis allergic	0	0	1 (0.4%)	1 (0.2%)
Eye swelling	0	0	1 (0.4%)	1 (0.2%)
Rash pustular	0	0	1 (0.4%)	1 (0.2%)
Hypersensitivity	1 (0.4%)	1 (0.4%)	0	1 (0.2%)
Rash maculo-papular	1 (0.4%)	1 (0.4%)	0	1 (0.2%)
Drug eruption	0	1 (0.4%)	0	1 (0.2%)
Drug hypersensitivity	0	1 (0.4%)	0	1 (0.2%)
Erythema nodosum	0	1 (0.4%)	0	1 (0.2%)
Rash erythematous	0	1 (0.4%)	0	1 (0.2%)
Dermatitis allergic	1 (0.4%)	0	0	0

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 TEAE in the specified category; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.

[a] Statistically significant compared with placebo.

Source: Table AP2.2.7.4.90

In study RHAP, non-anaphylaxis allergic reaction/hypersensitivity TEAEs were reported in 3.3% of

ixekizumab patients as compared to 5.0% and 2.8% for adalimumab and placebo, respectively.

In the **All PsA Analysis Set**, a total of 5.4% of patients (n=60) had ≥1 non-anaphylaxis event. None of the events were reported as severe. There were no patients with a TEAE that met the criteria for an anaphylaxis event.

One patient had a nonanaphylaxis SAE (angioedema) of moderate severity, 28 days after starting ixekizumab, was hospitalized and treated with chlorpheniramine and prednisolone with resolution of event 8 days after onset. No other relevant medical history was reported. The investigator considered the AE of angioedema as related to the study drug and patient was discontinued from the study. A total of 0.4% of patients (n=5) discontinued due to 5 different nonanaphylaxis events. Events leading to discontinuation included Angioedema, Drug eruption, Hypersensitivity, Rash, and Rash pruritic.

Key findings from the **All Psoriasis Analysis Set** include:

- Approximately 12.9% of patients reported ≥1 AE classified as an allergic reaction/hypersensitivity event. Among the most frequently reported of these were events of uncertain relationship to ixekizumab (for example, dermatitis contact, eczema).
- Serious hypersensitivity-type AEs and discontinuation of ixekizumab due to allergic reaction/hypersensitivity events were uncommon with 0.4% of patients reporting such events, respectively.
- There was no indication of an increased risk for allergic reaction/hypersensitivity events with increasing durations of exposure to ixekizumab.
- Three patients experienced a potential anaphylaxis SAE based on the specific MedDRA preferred term of Anaphylactic reaction. Two of the events occurred approximately 14 days after the first and only administration of ixekizumab, while the third event occurred after a colonoscopy exam in the patient. There were no confirmed cases of anaphylaxis associated with administration of ixekizumab in the psoriasis clinical development program.

Anaphylactic reactions are already covered by the current SmPC. After data lock for the first PSUR period (22 March 2016 to 22 September 2016), a signal for serious immediate hypersensitivity reactions consistent with anaphylaxis was identified from postmarketing spontaneous adverse event reports of ixekizumab leading to a review of data for serious immediate hypersensitivity reactions. Based on the findings from postmarketing spontaneous reports and mechanistic plausibility, a cautionary statement on hypersensitivity reactions was included in section 4.4 of the SmPC and the MedDRA PT of anaphylaxis was added as a rare event in section 4.8.

Consistent with urticaria (already included in section 4.8), the following additional PTs have been added to section 4.8: eczema, rash, angioedema.

Of note, an association between the reporting of anaphylaxis or non-anaphylaxis allergic reaction/hypersensitivity TEAEs and the development of TE-ADA was not established. For example, in the All Psoriasis Analysis Set in Immunogenicity Evaluable patients (N=4118), among TE-ADA negative patients (n=3222), 14.4% of patients reported ≥1 nonanaphylaxis TEAEs, as compared to 15.5% of patients who were TE-ADA positive (n=896).

Injection Site reactions

Injection site reaction TEAEs were reported more frequently in each of the ixekizumab treatment groups compared with placebo.

Table 47: Overview of Injection Site-Related AEs - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Type of Event	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 TEAE	10 (4.5%)	40 (17.5%) [a]	57 (25.3%) [a,b]	97 (21.4%) [a]
Patients with ≥1 SAE	0	0	0	0
Discontinuation from study drug due to AE	1 (0.4%)	1 (0.4%)	4 (1.8%)	5 (1.1%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; AE = adverse event; IXE = ixekizumab; N = number of patients; n = number of patients with ≥1 event in the specified category; PsA = psoriatic arthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Statistically significant ($p<.05$) compared with placebo.

[b] Statistically significant ($p<.05$) compared with ixekizumab 80 mg Q4W.

Sources: Table AP2.2.7.4.131; Table AP2.2.7.4.140; Table AP2.2.7.4.142

Individual PTs for ISR TEAEs, terms reported significantly more frequently in one of the ixekizumab groups compared with placebo were Injection site reaction, Injection site erythema, Injection site hypersensitivity, and Injection site pruritus.

In each of the ixekizumab groups, the maximum severity of ISR TEAEs was mild or moderate for 95% to 98% of patients who reported such events. The proportion of patients with ≥1 ISR TEAE was significantly higher in the ixekizumab 80 mg Q2W versus the Q4W group (25.3% versus 17.5%, respectively; p=.037). The proportions of patients who discontinued due to an ISR AE were 5 patients in the total ixekizumab group [1.1%] and 1 patient [0.4%] in the placebo group, respectively.

The rate of severe ISRs was numerically higher with ixekizumab 80 mg Q2W versus Q4W, (1.3% versus 0.4%, respectively). Likewise, the proportions of patients who discontinued due to an ISR AE was numerically higher in the ixekizumab 80 mg Q2W group versus the Q4W group (1.8% [n=4] versus 0.4% [n=1].

In the **All PsA Analysis set** (N=1118), 211 patients (18.9%) experienced ≥1 ISR TEAE. Injection site reaction PTs reported for ≥1% of patients were Injection site reaction (11.8%, n=132), Injection site erythema (4.5%, n=50), Injection site pain (1.2%, n=13), and Injection site hypersensitivity (1.0%, n=11). For most patients, the maximum severity of the event was categorized as mild or moderate (206 of 211 patients). Five patients (0.4%) had ≥1 event categorized as severe. The median duration of ISRs in ixekizumab-treated PsA patients was 0.43 weeks (3 days).

The exposure-adjusted incidence rate for ISR-related TEAEs by 12-week time intervals through 84 weeks for the All PsA Analysis Set decreased substantially over time, from 76.8 (Weeks 0 to 12) to 8.0 ISRs/100 patient-years (Weeks 72 to 84).

Similarly, for the **All Psoriasis Analysis Set**, the exposure-adjusted incidence rate for TEAEs of ISRs by 12-week time intervals decreased from 50.2 (Weeks 0 to 12) to 5.5 ISRs/100 patient-years (Weeks 144 to 156).

As discussed by the MAH, the frequency of ISRs was significantly higher in the ixekizumab 80 mg Q2W group (n=57; 25.3%) than in the Q4W group (n=40; 17.5%). However, the rates of ISRs per 100 active injections were comparable between the Q2W and Q4W treatment groups (8.1 per 100 active injections for Q2W and 7.7 per 100 active injections for Q4W), suggesting that the higher rate in the Q2W treatment group is due to the greater number of injections compared to the Q4W group.

Overall, the data for ISRs were relatively consistent across the 3 integrated analysis sets and similar to the findings from the initial plaque psoriasis MAA submission. Injection site reactions are already

included in section 4.8 of the SmPC as very common ADRs. The frequency of events is not increasing over time and only a limited number of patients on ixekizumab discontinued due to injection site reactions.

Overall, as could be expected, ISRs were reported more frequently for patients treated with ixekizumab as compared to adalimumab. In RHAP, in adalimumab patients (5.9%), this was similar to placebo (4.7%).

There were numerically somewhat more events of ISR in patients who developed TE-ADA. However, the patient numbers were small and a relationship to antibody positivity not clearly established (see section - Immunogenicity).

Cerebro-Cardiovascular Events

Cerebro-CV events, including major adverse cerebro-cardiovascular events (MACE), were adjudicated by an external, independent Clinical Events Committee (CEC). MACE were defined as follows:

- Vascular death (including CV and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system)
- Nonfatal myocardial infarction
- Nonfatal stroke (subcategories: ischemic, hemorrhagic, unknown stroke type).

There were no confirmed, adjudicated MACE among any patients in the Primary PsA Analysis Set. Across the ixekizumab clinical development programme for PsA and psoriasis, 57 patients had a confirmed, adjudicated MACE, 13 of which resulted in death of the patient (1 patient from the All PsA Analysis Set; preferred term: Cerebrovascular accident).

This event pertained to a patient with a history of dyslipidaemia, diabetes mellitus, hypertension, and a previous transient ischemic attack who was randomised to adalimumab, then received ixekizumab 80 mg Q4W, died due to ‘undetermined stroke’ (preferred term: Cerebrovascular accident) after 537 days of treatment.

In addition to this death, there were 4 additional patients with confirmed MACE in the All PsA Analysis Set: nonfatal myocardial infarction in 1 patient (0.1%) and nonfatal stroke in 3 patients (0.3%).

All 5 patients had a medical history of hypertension and additional risk factors for CV disease (e.g. dyslipidemia, diabetes mellitus).

The incidence of confirmed MACE in ixekizumab-treated patients with PsA or psoriasis did not change substantially over time with increased exposure. The exposure-adjusted incidence rate of MACE in the PsA clinical development programme (0.5/100 patient-years) was consistent with the rates reported in the initial plaque psoriasis MAA submission (0.3 to 0.7/100 patients-years) and was not higher than the rates reported in a United Kingdom population-based longitudinal cohort (Ogdie et al. 2015).

In patients with psoriasis, the exposure-adjusted IR of MACE did not change substantially with longer exposures to ixekizumab.

Table 48: CEC-Confirmed MACE - Frequency and Incidence Rate by 12-Week Intervals All Psoriasis Ixekizumab Exposures Integrated Analysis Set

Interval	Nx	Frequency n (%) [CI]	Total PY	Incidence Rate n (IR) [CI]
Weeks 0 to 12	5689	10 (0.2%) [0.1, 0.3]	1272.0	10 (0.8) [0.4, 1.5]
Weeks 12 to 24	5520	4 (0.1%) [0.0, 0.1]	1232.7	4 (0.3) [0.1, 0.9]
Weeks 24 to 36	5244	7 (0.1%) [0.0, 0.2]	1176.0	7 (0.6) [0.3, 1.2]
Weeks 36 to 48	5041	5 (0.1%) [0.0, 0.2]	1075.2	5 (0.5) [0.2, 1.1]
Weeks 48 to 60	4216	2 (<.05%) [0.0, 0.1]	829.2	2 (0.2) [0.1, 1.0]
Weeks 60 to 72	3421	4 (0.1%) [0.0, 0.2]	774.5	4 (0.5) [0.2, 1.4]
Weeks 72 to 84	3367	7 (0.2%) [0.1, 0.4]	759.1	7 (0.9) [0.4, 1.9]
Weeks 84 to 96	3296	4 (0.1%) [0.0, 0.2]	744.2	4 (0.5) [0.2, 1.4]
Weeks 96 to 108	3243	3 (0.1%) [0.0, 0.2]	729.7	3 (0.4) [0.1, 1.3]
Weeks 108 to 120	3182	1 (<.05%) [0.0, 0.1]	707.0	1 (0.1) [0.0, 1.0]
Weeks 120 to 132	3021	1 (<.05%) [0.0, 0.1]	646.9	1 (0.2) [0.0, 1.1]
Weeks 132 to 144	2707	1 (<.05%) [0.0, 0.1]	537.2	1 (0.2) [0.0, 1.3]
Weeks 144 to 156	2275	0 [0.0, 0.1]	437.9	0 [0.0, 1.8]

Abbreviations: CEC = Clinical Events Committee; CI = confidence interval; IR = incidence rate per 100 patient-years; MACE = major adverse cerebrocardiovascular events; Nx = number of patients entered each time interval; n = number of patients with ≥1 event in the specified category; PY = patient-years (total time in years that patients were in each interval).

Sources: Table AP2.2.7.4.4; Table AP2.2.7.4.3

The adjusted IRs for MACE in the updated All Psoriasis Population appear to be reflective of the population. To compare, in a population-based cohort study from 1994 to 2010 (Ogdie et al, Ann Rheum Dis. 2015; 74:326-32), unadjusted incidence rates of MACE was reported to be slightly over 0.5 (per 100 patient-years) both for PsA and psoriasis populations.

MACE has previously been identified in the RMP as an important potential risk, and similar to other low-frequency events is being monitored as part of the additional pharmacovigilance activity in the RMP, namely a prospective observational registry (Corrona Registry).

Malignancies

In an analysis that grouped PTs into categories of NMSC and malignancies excluding NMSC, the incidences for each category and subcategory of malignancy (NMSC, [basal cell carcinoma, squamous cell carcinoma]) were not significantly different between the ixekizumab treatment groups compared with placebo. Both patients who reported a malignancy were in the ixekizumab 80 mg Q4W treatment group.

Table 49: Non-Melanoma Skin Cancer and Other Malignancies - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

TEAEs Category Subcategory	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 TEAE – Malignancies	0	2 (0.9%)	0	2 (0.4%)
Non-Melanoma Skin Cancer (NMSC)	0	1 (0.4%)	0	1 (0.2%)
Basal Cell Carcinoma	0	1 (0.4%)	0	1 (0.2%)
Squamous Cell Carcinoma	0	0	0	0
Malignancies Excluding NMSC [a]	0	1 (0.4%)	0	1 (0.2%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with ≥1 event in the specified category; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.

[a] One event of prostate cancer in a 63-year-old male.

Source: Table AP2.2.7.4.215

In the **All PsA Analysis Se**t, a total of 0.5% of patients (n=6) had ≥1 malignancy event. Three of these events were NMSC (Basel Cell Carcinoma), whereas a total of 0.3% of patients (n=3) had ≥1 serious malignancy excluding NMSC: (prostate cancer [n=1], breast cancer [n=1], and invasive ductal breast carcinoma [n=1]. There was no increase in the rate of malignancy events with increasing durations of ixekizumab exposure.

In the **All Psoriasis Analysis Set**, a total of 1.7% of patients (n=94) had ≥1 TEAE malignancy event.

The table below presents the number and exposure-adjusted IR of malignancies by 12-week intervals to Week 156.

Table 50: Malignancies - Frequency and Incidence Rate by 12-Week Intervals All Psoriasis Ixekizumab Exposures Integrated Analysis Set

Interval	Nx	Frequency n (%) [CI]	Total PY	Incidence Rate n (IR) [CI]
Weeks 0 to 12	5689	18 (0.3%) [0.2, 0.5]	1272.0	18 (1.4) [0.9, 2.2]
Weeks 12 to 24	5520	14 (0.3%) [0.1, 0.4]	1232.7	14 (1.1) [0.7, 1.9]
Weeks 24 to 36	5244	4 (0.1%) [0.0, 0.2]	1176.0	4 (0.3) [0.1, 0.9]
Weeks 36 to 48	5041	6 (0.1%) [0.0, 0.2]	1075.2	6 (0.6) [0.3, 1.2]
Weeks 48 to 60	4216	9 (0.2%) [0.1, 0.4]	829.2	9 (1.1) [0.6, 2.1]
Weeks 60 to 72	3421	7 (0.2%) [0.1, 0.4]	774.5	7 (0.9) [0.4, 1.9]
Weeks 72 to 84	3367	5 (0.1%) [0.0, 0.3]	759.1	5 (0.7) [0.3, 1.6]
Weeks 84 to 96	3296	5 (0.2%) [0.0, 0.3]	744.2	5 (0.7) [0.3, 1.6]
Weeks 96 to 108	3243	2 (0.1%) [0.0, 0.1]	729.7	2 (0.3) [0.1, 1.1]
Weeks 108 to 120	3182	9 (0.3%) [0.1, 0.5]	707.0	9 (1.3) [0.7, 2.4]
Weeks 120 to 132	3021	4 (0.1%) [0.0, 0.3]	646.9	4 (0.6) [0.2, 1.6]
Weeks 132 to 144	2707	6 (0.2%) [0.0, 0.4]	537.2	6 (1.1) [0.5, 2.5]
Weeks 144 to 156	2275	6 (0.3%) [0.1, 0.5]	437.9	6 (1.4) [0.6, 3.0]

Abbreviations: CI = confidence interval; IR = incidence rate per 100 patient-years; Nx = number of patients entered each time interval; n = number of patients with ≥1 event in the specified category; PY = patient-years (total time patients were in each interval).

Sources: Table AP2.2.7.4.4; Table AP2.2.7.4.3

Most commonly, these events were coded as basal cell carcinomas (n=33; 0.6%), prostate cancer (n=10; 0.3%), squamous cell carcinoma of skin (n=7; 0.1%), invasive ductal breast carcinoma (n=5; 0.1%), and squamous cell carcinoma (n=4, 0.1%).

A total of 0.9% of patients (n=50) had≥1 malignancy SAEs. Serious malignancy PTs reported for ≥2 patients were Basal cell carcinoma (n=4), Prostate cancer (n=9), and Invasive ductal breast carcinoma (n=5). A total of 0.9% of patients (n=50) discontinued due to malignancy.

Based on the number and exposure-adjusted IR of malignancies by 12-week intervals to Week 156, there was no increase in the rate of malignancy events with increasing durations of ixekizumab exposure.

Overall, the rate of malignancy reported in clinical trials of ixekizumab for patients with either PsA or psoriasis appears to be consistent with the background rate in these populations.

Hepatic Events

Primary PsA Analysis Set

For hepatic laboratory test results, some treatment-emergent statistically significant differences between treatment groups were detected. Bilirubin mean values increased in both ixekizumab treatment groups and in the total ixekizumab group by approximately 6.7%, whereas the mean change in the placebo group decreased by approximately 4.1%. The median change from baseline in all treatment groups was 0.0.

ALT mean values increased by approximately 12.3% in the ixekizumab 80 mg Q4W group and decreased by 6.1% in the placebo group. Median changes from baseline were equal to 1.0 in each ixekizumab group. AST mean values increased by approximately 7.3% in the ixekizumab 80 mg Q4W group and by 3.4% in the total ixekizumab group (driven by the Q4W group), and decreased by approximately 2.1% in the placebo group. Median increases of 1.0 were seen in the ixekizumab 80 mg Q4W group and were 0.0 in all other treatment groups. Overall, these mean changes were not considered clinically meaningful.

The table below presents a comparison of proportions of patients in each treatment group with elevated post-baseline hepatic laboratory test values by abnormal baseline category and by using pre-specified elevation cutoffs for each parameter.

The results do not indicate clinically important changes related to ixekizumab treatment in patients with PsA.

Table 51: Elevations in Hepatic Laboratory Tests Totals by Categories Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Parameter	Placebo N=224 Nx=223 n (%)	80 mg Q4W N=229 Nx=229 n (%)	80 mg Q2W N=225 Nx=225 n (%)	Total IXE N=454 Nx=454 n (%)
Alanine aminotransferase (ALT)				
≥20xULN	0	0	0	0
≥10xULN	1 (0.4%)	0	0	0
≥5xULN	3 (1.3%)	2 (0.9%)	1 (0.4%)	3 (0.7%)
≥3xULN	5 (2.2%)	7 (3.1%)	5 (2.2%)	12 (2.6%)
Aspartate aminotransferase (AST)				
≥20xULN	0	0	0	0
≥10xULN	0	1 (0.4%)	0	1 (0.2%)
≥5xULN	2 (0.9%)	2 (0.9%)	0	2 (0.4%)
≥3xULN	4 (1.8%)	4 (1.7%)	3 (1.3%)	7 (1.5%)
Bilirubin				
≥2xULN	1 (0.4%)	0	0	0
≥1.5xULN	3 (1.3%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Alkaline phosphatase (ALP)				
≥1.5xULN	3 (1.3%)	1 (0.4%)	1 (0.4%)	2 (0.4%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; Nx = number of patients having ≥1 postbaseline measurement; PsA = psoriatic arthritis; ULN = upper limit of normal from Covance reference limits.

Note: Results are totals that include all patients with ≥1 postbaseline measurement, including patients who have missing baseline data. Percentage is calculated by n/Nx*100%.

Source: Table AP2.2.7.4.241

The number and percentage of hepatic-related TEAEs are presented in the table below. There were no differences for any ixekizumab treatment group compared with placebo with respect to the proportions of patients reporting ≥1 hepatic-related TEAE, whether considered by SMQ or by individual PT.

The company presents many tables of analyses. In order to assist understanding, the company was requested to provide shift figures of (i) baseline AST versus peak AST and (ii) baseline ALT versus peak ALT. A difference in pattern of serum liver enzyme activities in response to exposure compared between placebo and Taltz was not evident by this analysis.

Table 52: Hepatic-Related TEAEs - Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

SMQ *Classification* Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Patients with ≥1 hepatic-related TEAE (narrow terms only)	9 (4.0%)	7 (3.1%)	11 (4.9%)	18 (4.0%)
Patients with ≥1 hepatic-related TEAE (broad terms and narrow terms)	10 (4.5%)	7 (3.1%)	11 (4.9%)	18 (4.0%)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)				
Narrow	2 (0.9%)	2 (0.9%)	0	2 (0.4%)
Hepatic steatosis	1 (0.4%)	1 (0.4%)	0	1 (0.2%)
Non-alcoholic steatohepatitis	0	1 (0.4%)	0	1 (0.2%)
Liver disorder	1 (0.4%)	0	0	0
Hepatitis, non-infectious (SMQ)				
Narrow	1 (0.4%)	1 (0.4%)	0	1 (0.2%)
Non-alcoholic steatohepatitis	0	1 (0.4%)	0	1 (0.2%)
Hepatitis	1 (0.4%)	0	0	0
Liver-related investigations, signs and symptoms (SMQ)				
Narrow	7 (3.1%)	5 (2.2%)	11 (4.9%)	16 (3.5%)
ALT increased	1 (0.4%)	3 (1.3%)	5 (2.2%)	8 (1.8%)
AST increased	2 (0.9%)	3 (1.3%)	4 (1.8%)	7 (1.5%)
Hepatic enzyme increased	1 (0.4%)	2 (0.9%)	3 (1.3%)	5 (1.1%)
GGT increased	2 (0.9%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Liver function test abnormal	1 (0.4%)	0	1 (0.4%)	1 (0.2%)
Transaminases increased	1 (0.4%)	0	1 (0.4%)	1 (0.2%)
Hypertransaminasaemia	0	0	1 (0.4%)	1 (0.2%)
Blood bilirubin increased	1 (0.4%)	0	0	0
Broad	8 (3.6%)	5 (2.2%)	11 (4.9%)	16 (3.5%)
Liver function test increased	1 (0.4%)	0	0	0

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities; N = the number of patients randomized to a treatment group; n = the number of patients with an event in that category; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Note: The results of the broad term search are displayed only for terms that are identified only via the broad term search criteria. Patients may have reported >1 event within an SMQ.

Source: Table AP2.2.7.4.237

In the **All PsA Analysis Set**, among patients having≥1 postbaseline ALT and total bilirubin measurement (n=1112), there were no patients who met the laboratory screening criteria for potential drug-induced hepatotoxicity (maximum ALT ≥3xULN and maximum total bilirubin ≥2xULN). Based on the percentage and exposure-adjusted IR of hepatic-related TEAEs by 12-week intervals to Week 84, there was no indication of an increased risk for these events with increasing durations of exposure to ixekizumab.

In the **All Psoriasis Analysis Set** among ixekizumab-treated psoriasis patients having ≥1 postbaseline ALT and total bilirubin values (n=5634), 3 patients (<0.05%) met the laboratory screening criteria for potential drug-induced hepatotoxicity (maximum ALT ≥3xULN and maximum total bilirubin ≥2xULN). All 3 cases were previously reported in the plaque psoriasis MAA. There have been no additional cases since that time. Three hundred nine ixekizumab-treated psoriasis patients (309/5689 [5.4%]) had ≥1 hepatic-related TEAE according to the narrow term search. The hepatic-related TEAE preferred terms with a frequency ≥1.0% were Hepatic steatosis (1.4% [n=79]), GGT increased (1.4% [n=80]), and ALT increased (1.4% [n=77]).

Seven ixekizumab-treated psoriasis patients (7/5689 [0.1%]) had a serious hepatic-related AE. The preferred terms for these SAEs were Cholestasis, Drug-induced liver injury (verbatim term: “atorvastatin-induced hepatitis”), Hepatic steatosis, Hepatotoxicity, Hepatitis (verbatim term: “chronic

nutritive-toxic damage of the liver"), Hepatic function abnormal, and International normalized ratio increased.

Fourteen ixekizumab-treated psoriasis patients (14/5689 [0.2%]) discontinued study drug due to a hepatic-related AE defined by narrow term search; 3 additional patients (a total of 17 patients [0.3%]) discontinued due to an event defined by the broad term search. The PTs given as the reason for discontinuation of 2 or more patients were ALT increased (3 patients), Hepatic enzyme increased (3 patients), Liver function test increased (3 patients), and Hepatic steatosis (2 patients).

The table below presents the percentage and exposure-adjusted IR of hepatic-related TEAEs by 12-week intervals to Week 156. Overall, there was no indication of an increased risk of these events with increasing durations of ixekizumab exposure.

Table 53: Hepatic-Related TEAEs - Frequency and Incidence Rate by 12-Week Intervals All Psoriasis Ixekizumab Exposures Integrated Analysis Set

Interval	Nx	Frequency n (%) [CI]	Total PY	Incidence Rate n (IR) [CI]
Weeks 0 to 12	5689	45 (0.8%) [0.6, 1.0]	1272.0	45 (3.5) [2.6, 4.7]
Weeks 12 to 24	5520	59 (1.1%) [0.8, 1.3]	1232.7	59 (4.8) [3.7, 6.2]
Weeks 24 to 36	5244	59 (1.1%) [0.8, 1.4]	1176.0	59 (5.0) [3.9, 6.5]
Weeks 36 to 48	5041	50 (1.0%) [0.7, 1.3]	1075.2	50 (4.7) [3.5, 6.1]
Weeks 48 to 60	4216	18 (0.4%) [0.2, 0.6]	829.2	18 (2.2) [1.4, 3.4]
Weeks 60 to 72	3421	29 (0.8%) [0.5, 1.2]	774.5	29 (3.7) [2.6, 5.4]
Weeks 72 to 84	3367	14 (0.4%) [0.2, 0.6]	759.1	14 (1.8) [1.1, 3.1]
Weeks 84 to 96	3296	20 (0.6%) [0.3, 0.9]	744.2	20 (2.7) [1.7, 4.2]
Weeks 96 to 108	3243	15 (0.5%) [0.2, 0.7]	729.7	15 (2.1) [1.2, 3.4]
Weeks 108 to 120	3182	26 (0.8%) [0.5, 1.1]	707.0	26 (3.7) [2.5, 5.4]
Weeks 120 to 132	3021	10 (0.3%) [0.1, 0.5]	646.9	10 (1.5) [0.8, 2.9]
Weeks 132 to 144	2707	14 (0.5%) [0.2, 0.8]	537.2	14 (2.6) [1.5, 4.4]
Weeks 144 to 156	2275	10 (0.4%) [0.2, 0.7]	437.9	10 (2.3) [1.2, 4.2]

Abbreviations: CI = confidence interval; IR = incidence rate per 100 patient-years; Nx = number of patients entered each time interval; n = number of patients with ≥1 event in the specified category; PY = patient-years (total time patients were in each interval); TEAE = treatment-emergent adverse event.

Sources: Table AP2.2.7.4.4; Table AP2.2.7.4.3

Overall, as also concluded in the plaque psoriasis MAA, there appears to be no increased risk of hepatotoxicity associated with ixekizumab treatment.

Depression and Suicide/Self-Injury

Treatment with ixekizumab did not worsen depression when compared with treatment with placebo as assessed by the QIDS-SR16 (Quick Inventory of Depressive Symptomatology-Self Report) total score in the placebo-controlled PsA studies. Also, in comparison to patients treated with placebo, there were no differences among ixekizumab-treated patients in the percentages that improved, worsened, or stayed the same for maximum postbaseline QIDS-SR16 Item 12 score (thoughts of death or suicide) in the placebo-controlled PsA studies.

There was no difference between the total ixekizumab treatment group compared with placebo with respect to the proportions of patients reporting ≥1 TEAE in the Depression (excluding suicide and self-injury) sub-SMQ. Likewise, neither the ixekizumab 80 mg Q2W nor Q4W group was different from placebo. No suicide attempts or self-injury-related events were identified.

Table 54: Depression- and Suicide/Self-Injury–Related Events Double-Blind Treatment Period (Weeks 0 to 24) Primary PsA Placebo-Controlled Integrated Analysis Set

Patients with ≥1 TEAE SMQ or Sub-SMQ *Term Type* Preferred Term	Placebo N=224 n (%)	80 mg Q4W N=229 n (%)	80 mg Q2W N=225 n (%)	Total IXE N=454 n (%)
Depression *excluding* suicide and self-injury				
Narrow	3 (1.3%)	4 (1.7%)	4 (1.8%)	8 (1.8%)
Depression	3 (1.3%)	4 (1.7%)	3 (1.3%)	7 (1.5%)
Adjustment disorder with depressed mood	0	0	1 (0.4%)	1 (0.2%)
Broad	3 (1.3%)	4 (1.7%)	4 (1.8%)	8 (1.8%)
Depression	3 (1.3%)	4 (1.7%)	3 (1.3%)	7 (1.5%)
Adjustment disorder with depressed mood	0	0	1 (0.4%)	1 (0.2%)
Suicide/self-injury	0	0	0	0
Depression *and* suicide/self-injury				
Narrow	3 (1.3%)	4 (1.7%)	4 (1.8%)	8 (1.8%)
Depression	3 (1.3%)	4 (1.7%)	3 (1.3%)	7 (1.5%)
Adjustment disorder with depressed mood	0	0	1 (0.4%)	1 (0.2%)
Broad	3 (1.3%)	4 (1.7%)	4 (1.8%)	8 (1.8%)
Depression	3 (1.3%)	4 (1.7%)	3 (1.3%)	7 (1.5%)
Adjustment disorder with depressed mood	0	0	1 (0.4%)	1 (0.2%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; N = the number of patients randomized to a treatment group; n=the number of patients with an event in that category; PsA = psoriatic arthritis; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Note: Patients could have reported >1 event within an SMQ or sub-SMQ.

Source: Table AP2.2.7.4.259

In the **All PsA Analysis Set**, a total of 1.3% of patients (n=15) had ≥1 TEAE in the Depression (excluding suicide and self- injury) sub-SMQ. There were no serious depression- related events. No suicide attempts or self-injury-related events were identified by analyses of the Depression and Suicide/Self-injury SMQ.

Overall, there were no suicide/self-injury-related events reported across the PsA studies.

In the updated **All Psoriasis Analysis Set**, the percentage of patients with depression-related events was low. A total of 2.0% of patients (n=114) had ≥1 TEAE identified by narrow terms in the Depression (excluding suicide and self-injury) sub-SMQ. A total of 0.2% of patients (n=10) had a serious depression-related event identified by narrow terms (excluding suicide and self-injury). The frequency and exposure-adjusted IR for such events in this analysis set was consistent up to 156 weeks of ixekizumab treatment exposure, with no increase over time.

Cumulatively, there have been 13 events identified by narrow terms in the Depression and Suicide/Self-injury SMQ, which include suicide attempt (9 patients), suicidal ideation (3 patients), intentional overdose (1 patient, who also reported suicide attempt), and intentional self-injury (1 patient). Ten of these events have been reported previously during the submission and review of the plaque psoriasis MAA. There were no completed suicides. All patients with suicide/self-injury-related events had multiple risk factors.

Overall, the data do not suggest an increased risk of depression and suicide/self-injury behavior associated with ixekizumab use.

Inflammatory Bowel Disease

There was one case of IBD in the ixekizumab 80 mg Q2W group in the Primary PsA Analysis Set. This patient was not discontinued from study drug for either event.

In the All PsA Ixekizumab Exposures Analysis Set (N=1118), there were 2 additional cases (0.1%). One ixekizumab-treated PsA patient (0.1%) had an SAE of ulcerative colitis. Study drug was not discontinued.

The event reported for the other patient was mild and not serious. Upon evaluation, the sponsor considered that this was not a true case of IBD. This can be agreed. The event was discovered during surgery for intestinal neoplasm/polyp.

Overall, there were no significant differences between the ixekizumab groups and placebo, or between the ixekizumab 80 mg Q4W and Q2W groups, with respect to the frequency of IBD in patients with PsA.

In the updated **All Psoriasis analysis set** (N=5689), a total of 18 (0.3%) patients had ≥1 TEAE of IBD as identified by narrow terms. For 6 patients, the event was serious. For 11 patients, the event caused the patient to discontinue study drug.

With respect to possible IBD cases identified by nonspecific terms, 16 patients (0.3%) had ≥1 such event. For 6 patients, the event was serious. For one patient, the event caused the patient to discontinue study drug. Upon evaluation of the cases identified by nonspecific MedDRA terms in the All Psoriasis Ixekizumab Exposures Integrated Analysis Set, the sponsor considers that 3 of the 16 cases identified by nonspecific terms represent true IBD. A review of preexisting conditions or historical illnesses suggestive of IBD in psoriasis patients showed that, of 19 patients with such diagnoses, 3 patients experienced an exacerbation during the study.

As also noted in the plaque psoriasis MAA, studies in the literature demonstrate an increased prevalence of IBD among patients with psoriasis (some including PsA) when compared with a matched control population. Possibly, this association between psoriasis, PsA, and IBD may be due to shared inflammatory pathways.

The current data in the PsA population are consistent with the known safety profile of ixekizemab. The fact that cases of new or exacerbations of IBD have been reported is already covered in the SmPC and IBD (Crohn's disease and ulcerative colitis) is included in the RMP as a potential risk.

Interstitial Lung Disease

There have been documented cases suggestive of a potential association between the use of immunomodulatory agents and an increased risk of ILD. No safety signal for ILD in relation to ixekizumab was identified in the data submitted for the plaque psoriasis MAA.

There were no cases of ILD in the Primary PsA Analysis Set.

There was one PsA patient (1 of 1118 patients [0.1%]) with an ILD-related TEAE in the All PsA Analysis Set. The patient was in the ixekizumab 80 mg Q2W group, and the event occurred after the patient had been on Q2W more than 24 weeks. The day and month of the event were not recorded. The event (preferred term: Pulmonary granuloma, actual term: 6 mm pulmonary right lung base calcified granuloma) was mild in severity, was not serious, and did not cause the patient to discontinue study drug.

Nine ixekizumab-treated psoriasis patients (9 of 5689 [0.2%]) had ≥1 ILD-related TEAE. The most frequently reported ILD-related preferred term was Bronchiolitis (3 patients, [0.1%]). The other reported preferred terms were Interstitial lung disease, Pulmonary fibrosis, Pulmonary sarcoidosis, Pulmonary toxicity, and Sarcoidosis.

There were no cases of ILD in the Primary PsA Analysis Set. The reported events in the All PsA Analysis Set (1) and in the All Psoriasis Analysis Set (9) were non-serious. In the latter, one of the patients was reported to have died during his participation in the study due to the SAE of acute on chronic hypoxemic respiratory failure secondary to ILD. However, the specifics of this diagnosis seem unclear from the narrative and the patient had also suffered multiple episodes of pneumonia. Overall, a new safety signal has not been evoked.

2.5.1.1. Discontinuations due to AEs

In the Primary PsA Analysis Set, key findings included the following:

- The proportions of patients who prematurely discontinued study treatment due to any AE were as follows: 3.6% (n=8) of patients in the placebo group; 3.1% (n=7) of patients in the ixekizumab 80 mg Q4W group; 5.3% (n=12) of patients in the Q2W group; 4.2% (n=19) of patients in the total ixekizumab group. Thus, the proportion of patients who discontinued due to an AE was numerically higher in the ixekizumab 80 mg Q2W group than in the Q4W or placebo groups.
- The SOCs in which discontinuations due to AEs were most frequently reported were the General disorders and administration site conditions SOC (1.2%, n=8; 6 of which were injection site reactions) and the Infections and infestations SOC (0.6%, n=4).
- Individual PTs as the reason for early discontinuation (≥2 patients) were Injection site reaction (ixekizumab 80 mg Q4W, 1 patient; Q2W, 2 patients) and Interferon gamma release assay positive (ixekizumab 80 mg Q4W, 1 patient; Q2W, 1 patient).

Patients with no evidence of past infection with tuberculosis (TB) were required to undergo yearly testing and to discontinue study drug if postbaseline TB testing was positive.

In an analysis of clusters of particular PTs − such as for infections, for ISRs, and for other AESIs and preferred terms of interest− there were no clinically important differences between the ixekizumab groups compared with placebo, or between the ixekizumab 80 mg Q2W group compared with the Q4W group, with respect to the proportions of patients who discontinued due to such AEs except for the Injection Site Reactions cluster. In this cluster, the ixekizumab 80 mg Q2W group had 4 (1.8%) TEAEs that resulted in study treatment discontinuation, as compared with 1 (0.4%) in the Q4W group and 1 (0.4%) in the placebo group, which consistent with the findings in the psoriasis MAA.

In the All PsA Analysis Set, 5.7% (n=64) of ixekizumab-treated PsA patients had an AE which led to discontinuation of study drug. Discontinuations due to AEs were most frequently reported in the Infections and infestations SOC (1.3%, n=14; 6 of 14 due to Latent tuberculosis) and the Investigations SOC (1.3%, n=14; 13 of 14 due to Interferon gamma release assay positive or Tuberculin test positive).

In the All Psoriasis Analysis Set, 6.7% (n=379) of ixekizumab-treated psoriasis patients had an AE which led to discontinuation of study drug. Discontinuations due to AEs were most frequently reported in the Investigations SOC (1.1%, n=63; 41 of 63 due to Mycobacterium tuberculosis complex test positive or Tuberculin test positive); Infections and infestations SOC (1.0%, n=58); and Neoplasms benign, malignant, and unspecified SOC (0.9%, n=53).

Looking at reasons for discontinuation over a longer follow-up period, the All PsA and All Psoriasis Analysis Sets showed consistency. In the All PsA Analysis Set (N=1118), a total of 1.3% of patients (n=14) discontinued due to an infection-related AE, most commonly latent tuberculosis (n=6, 0.5%). In the updated All Psoriasis Analysis Set (N=5689), a total of 1.0% of patients (n=58) discontinued due to an infection-related AE (latent tuberculosis 0.3%).

Laboratory findings

Cytopenias (neutropenia, thrombocytopenia) and hepatic evaluations are discussed in section 4.5.2.5 above.

The findings from all other analyses of treatment-emergent (TE) abnormal high or low laboratory values and analyses of mean changes from baseline in the Primary PsA Analysis Set generally did not demonstrate clinically important changes in haematology and chemistry parameters.

Clinically important cases of clinical laboratory changes comprised those related to treatment-emergent CK levels above 5000 IU/L. These cases were either transient and/or apparently associated with skeletal muscular contractions, exercise, or exertional-induced rhabdomyolysis.

There were 4 patients (2 in each ixekizumab group) with a treatment-emergent CK value >5000, occurring during the Double-Blind Treatment Period. Based on the provided narratives, these findings appeared to be incidental and transient.

Overall, the observations for laboratory findings were consistent across the 3 integrated analysis sets and similar to the findings from the initial plaque psoriasis MAA submission.

Immunogenicity

Patients in all ixekizumab clinical studies were tested for the presence of ixekizumab ADA.

In the Primary PsA Analysis Set, preexisting ADA were observed in 10 of 208 patients (4.8%) in the placebo group, 10 of 220 patients (4.5%) in the Q4W treatment group, and 11 of 218 (5.0%) in the Q2W treatment group. All patients who were ADA positive at baseline were classified as low ADA titer (<1:160). None of the patients with preexisting ADA had a 4-fold increase in titer after baseline, and therefore, none were considered treatment-emergent (TE)-ADA positive.

In the Primary PsA Analysis Set, the incidence of TE-ADA from Weeks 0 to 52 was 11% in patients receiving ixekizumab Q4W and ixekizumab Q2W treatment. The immunogenicity results from patients receiving ixekizumab Q4W was similar to those receiving ixekizumab Q2W.

The majority of patients with positive TE-ADA were classified as low titer.

The incidence of NAb was 8% and 6% in patients receiving ixekizumab Q4W and ixekizumab Q2W treatment, respectively.

No serious allergic reaction/hypersensitivity or injection site reaction TEAEs were reported in PsA patients.

In the immunogenicity evaluable population of the All PsA Analysis Set, among ixekizumab-treated PsA patients, 54 (5.9%) TE-ADA negative patients had ≥1 nonanaphylaxis TEAE (immediate or nonimmediate), and 4 (4.7%) TE-ADA positive PsA patients had such events. Also, 173 (18.9%) ixekizumab-treated PsA TE-ADA negative patients had ≥1 ISR TEAE and 24 (28.2%) TE-ADA positive patients had ≥1 ISR TEAE.

Overall, the results showed no association between TE-ADA status and allergic reaction/hypersensitivity or injection site reaction AEs.

The MAH concludes that there is no association between TE-ADA status and allergic reaction/hypersensitivity or injection site reaction AEs. As shown in the table below, the proportions of patients who experienced injection site reactions was consistently higher in TE-ADA positive patients as compared to TE-ADA negative patients. However, the number of TE-ADA positive patients was

relatively small and the appearance of the reported events not limited to TE-ADA positivity. Thus, it can be agreed that the association is not fully clear.

Table 55: Injection Site Reactions by ADA Status - Patients with TE-ADA Across Analysis Sets (Immunogenicity Evaluable Patients)

Injection Site Reactions HLT TE-ADA Status Group	Primary PsA Placebo-Controlled Integrated Analysis Set (RHAP and RHBE) Weeks 0 to 24				All PsA Ixekizumab Exposures Integrated Analysis Set (RHAP, RHBE, RHBF)	All Psoriasis Ixekizumab Exposures Integrated Analysis Set (Updated)
	Placebo Nx=218 n (%)	80 mg Q4W Nx=225 n (%)	80 mg Q2W Nx=222 n (%)	Total IXE Nx=447 n (%)	Pooled IXE Nx=1002 n (%)	Pooled IXE Nx=4118 n (%)
TE-ADA Negative Patients, Ns	**217**	**211**	**213**	**424**	**917**	**3222**
Patients reporting ≥1 ISR HLT TEAE	10 (4.6%)	35 (16.6%)	52 (24.4%)	87 (20.5%)	173 (18.9)	468 (14.5%)
TE-ADA Positive Patients, Ns	**1**	**14**	**9**	**23**	**85**	**896**
Patients reporting ≥1 ISR HLT TEAE	0	5 (35.7%)	4 (44.4%)	9 (39.1%)	24 (28.2%)	201 (22.4%)
ISR HLT TEAE occurred when:						
Only when TE-ADA positive	0	2 (14.3%)	2 (22.2%)	4 (17.4%)	8 (9.4%)	71 (7.9%)
Both when TE-ADA positive and when TE-ADA negative	0	2 (14.3%)	1 (11.1%)	3 (13.0%)	6 (7.1%)	48 (5.4%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; HLT = high level term; ISR = injection site reaction; IXE = ixekizumab; n = number of patients with ≥1 TEAE; Ns = number of patients in the subgroup; Nx = number of immunogenicity evaluable patients; PsA = psoriatic arthritis; TE-ADA = treatment-emergent anti-drug antibodies; TEAE = treatment-emergent adverse event.

Notes: Percentages are based on the number of immunogenicity evaluable patients and are calculated by n/Ns. This table summarizes events by time-varying titer at the start time of the event.

Sources: Table AP2.2.7.4.144; Table AP2.2.7.4.165; Table AP2.2.7.4.185

Safety supplementary analyses

In the 24-week Placebo-Controlled Treatment Period of Studies RHAP and RHBE, patients in the placebo group who were inadequate responders (placebo-IR) at Week 16 were re-randomized in a 1:1 ratio to 1 of the 2 ixekizumab treatment groups. These placebo-IR patients were included in the denominator of the placebo and ixekizumab treatment groups in supplementary analyses. In these supplementary analyses, the TEAEs occurring while the patient was receiving placebo were counted as TEAEs in the placebo group, and the TEAEs occurring while the patient was treated with ixekizumab were counted as TEAEs in the ixekizumab group. The actual placebo exposure time and ixekizumab exposure time were reflected in the total patient-years for the actual time the patient was on each treatment. Overall, findings from these analyses were consistent with findings for the Primary PsA Placebo- Controlled Integrated Analysis Set (Weeks 0 to 24).

Safety in patient subgroups and special populations

TEAEs from the Primary PsA Analysis Set were evaluated according to subgroups based on patient demographics (sex, age, weight, BMI, race, ethnicity, geographic region); disease severity (CRP, baseline DAS28-CRP score); previous therapy (cDMARD use at baseline, MTX use at baseline, corticosteroid use at baseline, inadequate response to 1 or more DMARDs, previous use of bDMARDs); and other characteristics (smoking, baseline psoriasis, baseline moderate-to-severe psoriasis). Additionally, there was no difference in the TEAE profile due to concomitant use of a cDMARD (MTX, leflunomide, SSZ, or hydroxychloroquine) compared to those patients not concomitantly receiving a cDMARD. Approximately 57% of patients were receiving concomitant cDMARDs during the Double-Blind Treatment Period; of those patients, 83% were receiving MTX.

Body weight appeared to interact with treatment for the occurrence of ISRs; these latter were more common with ixekizumab (total group) vs placebo in the <80 kg group (23.4% versus 0%

respectively) and the [≥80 and <100] group (24.2% vs 5.4%), but not in the ≥100 kg group (12.5% vs 9.8%) (as compared to 23.7% vs. 2.9% for the <100 kg group). See truncated table below (AP1.2.7.4.139 – injection site reactions, High-Level Term):

High Level Term Preferred term	Weight	PBO (N=224) n (%)	IXE80Q4W (N=229) n (%)	IXE80Q2W (N=225) n (%)	Total IXE (N=454) n (%)	Total (N=678) n (%)
Ns	<80 kg	81	88	109	197	278
Ns	>=80 kg - <100 kg	92	84	77	161	253
Ns	>=100 kg	51	57	39	96	147
Patients with >=1 TEAE - Injection Site Reactions	<80 kg	0	20 (22.7%)	26 (23.9%)	46 (23.4%)	46 (16.5%)
	>=80 kg - <100 kg	5 (5.4%)	14 (16.7%)	25 (32.5%)	39 (24.2%)	44 (17.4%)
	>=100 kg	5 (9.8%)	6 (10.5%)	6 (15.4%)	12 (12.5%)	17 (11.6%)

The frequency of ISRs was higher with ixekizumab versus placebo in all BMI categories, but these differences tended to be higher in the patients with BMI <30 than in those with BMI ≥30.

In section 4.8 of the current SmPC, it is stated that in the plaque psoriasis studies, injection site reactions were more common in subjects with a body weight <60 kg compared with the group with a body weight ≥ 60 kg (25% vs. 14% for the combined Q2W and Q4W groups). This was not clearly the case for the <60 kg vs. ≥60 kg subgroups in the Primary PsA Analysis Set (both subgroups showed more ISRs in the ixekizumab group as compared to placebo, see truncated table below):

High Level Term Preferred term	Weight	PBO (N=224) n (%)	IXE80Q4W (N=229) n (%)	IXE80Q2W (N=225) n (%)	Total IXE (N=454) n (%)	Total (N=678) n (%)
Ns	<60 kg	10	17	20	37	47
Ns	>=60 kg	214	212	205	417	631
Patients with >=1 TEAE - Injection Site Reactions	<60 kg	0	4 (23.5%)	6 (30.0%)	10 (27.0%)	10 (21.3%)
	>=60 kg	10 (4.7%)	36 (17.0%)	51 (24.9%)	87 (20.9%)	97 (15.4%)

Given the overall trends towards more events of ISR in subjects with lower bodyweight for the PsA studies, consistent with the plaque psoriasis studies, section 4.8 has been updated accordingly to reflect this.

There was a numeric trend towards a greater proportion of patients reporting infections who were naive to conventional DMARD experience at baseline (see truncated table below –) but the numbers of patients in this category were small. There was no statistically significant interaction between the cDMARD experience groups.

System organ class Preferred term	Conventional DMARD experience at baseline	PBO (N=224) n (%)	IXE80Q4W (N=229) n (%)	IXE80Q2W (N=225) n (%)	Total IXE (N=454) n (%)	Total (N=678) n (%)
Ns	Naïve	14	16	17	33	47
Ns	Past Use	89	85	72	157	246
Ns	Current use	121	128	136	264	385
Patients with >=1 TEAE	Naïve	7 (50.0%)	12 (75.0%)	11 (64.7%)	23 (69.7%)	30 (63.8%)
	Past Use	57 (64.0%)	57 (67.1%)	54 (75.0%)	111 (70.7%)	168 (68.3%)
	Current use	63 (52.1%)	84 (65.6%)	91 (66.9%)	175 (66.3%)	238 (61.8%)
Infections and infestations	Naïve	2 (14.3%)	8 (50.0%)	6 (35.3%)	14 (42.4%)	16 (34.0%)
	Past Use	28 (31.5%)	29 (34.1%)	27 (37.5%)	56 (35.7%)	84 (34.1%)
	Current use	32 (26.4%)	40 (31.3%)	39 (28.7%)	79 (29.9%)	111 (28.8%)

Discussion:

As stated above, approximately 57% of patients were receiving concomitant cDMARDs during the Double-Blind Treatment Period. The vast majority of those patients, 83% were receiving MTX. However, the proposed indication is broader, allowing for 'combination with conventional DMARDs'. This broad wording is considered of concern and insufficiently justified at current. The MAH has conducted subgroup analyses with regards to previous therapy groups (cDMARD use at baseline, MTX use at baseline, corticosteroid use at baseline – yes/no) but not with respect to other cDMARDs. In the

first RSI, the MAH was requested to discuss the comparative safety profile of combining ixekizumab with other cDMARDs (e.g. sulfasalazine, leflunomide or hydroxychloroquine) as compared to the combination with MTX and to justify the broad wording in the proposed indication from a safety point of view. The MAH provided summary tables with comparative TEAE data for patients with concomitant MTX use versus the other cDMARDs. Taken together, the summary tables provided by MAH did not show any notable differences in safety profile for concomitant cDMARDs other than MTX vs. placebo (as compared to concomitant MTX vs. placebo). However, given the small numbers of patients treated with each of the compounds other than MTX, it was not possible to draw conclusions and the broad indication initially submitted for patients treated with conventional DMARD could not be supported from a safety point of view. In response to CHMP concerns, the MAH has now revised the proposed indication to restrict it and include only the combination with MTX, as recommended by the CHMP.

Use in pregnancy and lactation

Cumulatively as of the data cutoff date for this submission (30 Sep 2016), there were 44 women who became pregnant during their study participation (45 total pregnancies).

Table 56:Cumulative Summary of Pregnancies: Female Study Participants Exposed to Ixekizumab

Outcome	Number of Events n (%)
Overall Cumulative Exposures Total (pregnancies exposed/total number of female patients exposed to ixekizumab)	**45/2449 (1.8%)**
Exposure/Event	**N=45**
Exposure during pregnancy (normal outcome)	13 (28.9%)
Premature birth [a]	2 (4.4%)
Exposure during pregnancy (other maternal/infant events)	3 (6.6%)
Terminated pregnancy [b]	11 (24.4%)
Abortion spontaneous (5); abortion missed (1); miscarriage (2) [c]	8 (17.8%)
Exposure during pregnancy: outcome pending	7 (15.6%)
Unknown or lost to follow-up [d]	1 (2.2%)

Abbreviations: N = number of pregnancies possibly exposed to ixekizumab at various doses, reported as of 15 Sep 2016; n = number of events.

[a] One patient delivered a healthy baby at 36 weeks. One patient experienced a premature birth estimated at 29 weeks' gestation with polyhydramnios and possible fetal chromosomal abnormalities identified in utero that were inconclusive. (At first trimester, this patient experienced a serious adverse event of pulmonary embolism, and at second trimester, this patient experienced ulcerative colitis.)

[b] One patient experienced endometritis 1 day after termination of pregnancy.

[c] All events occurred in the first trimester with no reports of congenital anomalies.

[d] Lost to follow-up or patient/partner refused to provide birth information.

Sources: Ixekizumab Blinded (cumulative to 15 Sep 2016).pdf, t_demo_safety_apsa.rtf, t_demo_safety_aps.rtf.

Three pregnancies were carried to term and delivered with notable infant or maternal outcomes: one patient underwent cesarean section performed due to cephalopelvic disproportion and fetal tachycardia; one patient underwent cesarean section due to placenta previa and breech presentation; and one patient experienced pre-eclampsia/arterial hypertension with Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome and subsequently delivered a healthy infant at 37 weeks.

There were 68 pregnancies in partners of male patients exposed to ixekizumab during their participation in a study. Of the 68 pregnancies, 38 were carried to term and delivered without evidence of fetal adverse effect, 3 were electively terminated, 3 were abortion spontaneous, and 8 outcomes are still pending. Four pregnancies were carried to term and delivered with notable infant outcomes: 1 infant was born with fetal pyelocaliecstasis right kidney; one with congenital widening of the right renal pelvis; one with webbed left and middle finger; and one was born prematurely (36 weeks of gestation) who had no evidence of fetal adverse effects.

Overall, safety data on pregnancy in relation to ixekizumab exposure is still very limited. This is reflected in the current SmPC. Of note, the RMP states that study I1F-MC-B005 is an observational study (Category 3 – current status: planned) to assess maternal and fetal outcomes following exposure to ixekizumab.

Table Overview of Adverse Events by Age Category All Treatment Periods All PsA Ixekizumab Exposures Integrated Analysis Set

	<65 Years	65-74 Years	75-84 Years	≥85 Years
Event Category	Pooled IXE N=996 n (%)	Pooled IXE N=116 n (%)	Pooled IXE N=5 n (%)	Pooled IXE N=1 n (%)
Total TEAEs	645 (64.8%)	84 (72.4%)	4 (80.0%)	1 (100.0%)
SAEs	59 (5.9%)	14 (12.1%)	0	0
Fatal	2 (0.2%)	0	0	0
Hospitalization	54 (5.4%)	13 (11.2%)	0	0
Life-threatening	1 (0.1%)	0	0	0
Disability	1 (0.1%)	1 (0.9%)	0	0
Other	8 (0.8%)	1 (0.9%)	0	0
AE leading to drop-out	54 (5.4%)	9 (7.8%)	1 (20.0%)	0
Psychiatric disorders (SOC)	28 (2.8%)	4 (3.4%)	0	0
Nervous system disorders (SOC)	79 (7.9%)	8 (6.9%)	0	0
Accidents and injuries (SMQ)	60 (6.0%)	12 (10.3%)	0	0
Cardiac disorders (SOC)	15 (1.5%)	5 (4.3%)	1 (20.0%)	0
Vascular disorders (SOC)	38 (3.8%)	8 (6.9%)	0	0
Cerebrovascular disorders (SMQ)	7 (0.7%)	1 (0.9%)	0	0
Infections and infestations (SOC)	365 (36.6%)	47 (40.5%)	3 (60.0%)	1 (100.0%)
Quality of life decreased (PT)	0	0	0	0
Hypotension, falls, fractures (LSC)	14 (1.4%)	2 (1.7%)	0	0
Fractures (LSC)	0	0	0	0

Abbreviations: AE = adverse event; IXE = ixekizumab; LSC = Lilly-Specified Category; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with ≥1 AE in the specified category; PsA = psoriatic arthritis; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event.

2.5.1.2. Safety related to drug-drug interactions and other interactions

See Clinical Pharmacology Section. Ixekizumab is not anticipated to affect the metabolism or transport of other drugs commonly used in patients with PsA. Based on both population PK analyses and graphical assessments, it was concluded that MTX and corticosteroids have no impact on the PK of ixekizumab.

Although no cytochrome P450 (CYP)-mediated drug interactions with ixekizumab are anticipated, drug-drug interaction study I1F-MC-RHBU (RHBU) is being conducted in patients with psoriasis to evaluate the hypothesis. No other drug interaction studies are planned.

2.5.1.3. Post-marketing experience

The first marketing approval for ixekizumab occurred on 22 Mar 2016 (International Birth Date) when FDA approved ixekizumab for the treatment of adults with moderate-to-severe plaque psoriasis.

In the post-marketing setting, a signal for serious immediate hypersensitivity reactions (3 reports of serious immediate hypersensitivity consistent with anaphylaxis) consistent with anaphylaxis was identified as a rare event (frequency ≥0.01% to <0.1%). This has been assessed within Periodic Safety Update Report (PSUR 01) in December 2016 (reporting period of 22 March 2016 through 22 September 2016) and is reflected in the updated SmPC.

2.5.2. Discussion on clinical safety

The safety profile for ixekizumab in the treatment of PsA is as expected and consistent with the known safety profile from studies in plaque psoriasis. During the Double-Blind Treatment Period (Weeks 0 to 24) of the PsA studies RHAP and RHBE, the most frequently reported preferred terms (occurring in≥5% of total ixekizumab-treated patients) were Injection site reaction and Injection site erythema (greater frequency in each ixekizumab group compared to placebo) and Upper respiratory tract infection (similar frequency across treatment groups). Of note, in RHAP, the most frequent TEAEs in patients treated with the active comparator adalimumab included Nasopharyngitis and Upper respiratory tract infection.

The majority of injection site reactions (ISRs, defined as high-level term) were mild or moderate in severity, 0.7% (n=5) were rated as severe, and none were reported as an SAE. Six patients (0.9%) discontinued treatment due to injection site reactions (defined as high-level term) (1 placebo, 1 ixekizumab 80 mg Q4W, and 4 ixekizumab 80 mg Q2W). The frequency of ISRs was significantly higher in the ixekizumab 80 mg Q2W group than in the Q4W group. However, the rates of ISRs per 100 active injections were comparable between the groups which may suggest that the higher rate in the Q2W treatment group is due to the greater number of injections. Also, no clear relationship between the development of ISRs and treatment-emergent ADA positivity could be observed.

A known risk for patients treated with ixekizumab is infection, including *Candida* infection. In the Primary PsA Analysis Set, there was a difference in the frequency of infection-related SAEs between the ixekizumab 80 mg Q2W (n=5) group and the Q4W (n=1) and placebo (n=0) groups. Also, the proportion of patients with an opportunistic infection (OI) or potential OI (narrow terms) was greater in the ixekizumab 80 mg Q2W (n=10; 4.4%) and Q4W treatment groups (n=5; 2.2%) as compared to placebo (n=1; 0.4%). Predefined OIs included mucocutaneous *Candida* infections and herpes zoster. Treatment-emergent serious infections considered as opportunistic included 1 case of Oesophageal candidiasis and 1 case of Herpes zoster (ophthalmic branch of trigeminal nerve). There were numerical differences between the ixekizumab treatment groups vs. placebo with respect to mucocutaneous Herpes Simplex. This is reflected in section 4.8 of the product information.

Otherwise, the profile of infections in the Primary PsA Analysis Set for the current application is considered consistent with the prior experience of ixekizumab. There were no cases of invasive herpes simplex, viral hepatitis, confirmed active or reactivated TB, endemic mycoses, invasive *Aspergillus*, or other deep fungal infections. Infections are already included as identified risk in the current RMP with the objective to monitor the incidence rate and nature of rare and clinically relevant infections through submission of additional safety data from ongoing studies, a post-marketing safety registry (the Corrona Registry), as well as routine pharmacovigilance.

Of note, one of the pivotal PsA studies (RHAP) included an active reference group, with adalimumab. Within RHAP, the risk of infections and serious infections was comparable between adalimumab and ixekizumab 80 mg Q4W.

Low grade neutropenia was commonly observed in patients receiving ixekizumab. However, treatment-emergent Grades 3 and 4 neutropenia were not observed during the Double-Blind Treatment Period of the PsA studies, but occurred in respectively 3 (0.3%) and 0 patients of the All PsA Exposures dataset,

and in 16 (0.3%) and 3 (0.1%) patients of the All Psoriasis Exposures dataset. No cases of Grade 4 neutropenia were associated with concomitant infection. There were no cases of Grade 2, 3, or 4 thrombocytopenia, nor was there any case of bleeding-related TEAE associated with thrombocytopenia in the Primary PsA Analysis Set.

In the postmarketing setting following MA for plaque psoriasis, a signal for serious immediate hypersensitivity reactions has been assessed within a PSUR and this is now reflected in the updated SmPC. In the Primary PsA Analysis Set, non-anaphylaxis allergic reaction/hypersensitivity TEAEs were more frequent in the ixekizumab treatment groups (Q4W: 4.4%; Q2W: 6.2%) as compared to placebo (1.8%) consistent with the initial plaque psoriasis submission. All of these TEAEs were mild or moderate in severity and none was reported as an SAE. Some additional PTs (eczema, rash, angioedema) have been added to section 4.8 of the SmPC.

Other adverse events of special interest predefined included cerebro-cardiovascular events (including MACE), malignancies, hepatic-related events, depression and suicide/self-injury, inflammatory bowel disease (IBD), and interstitial lung disease. No new safety concerns were evoked based on the current PsA submission with regards to hepatotoxicity, depression and suicidal behavior, or interstitial lung disease.

MACE, malignancies, and IBD are already included in the RMP as potential risks. The overall rates for these events were similar to the psoriasis studies and, across the ixekizumab clinical development programme for PsA and psoriasis, appear to be consistent with background rates for these populations reported in the literature. In the updated All Psoriasis Analysis Set which includes 5689 patients with 12,061.5 total patient-years of ixekizumab exposure, there was no indication of an increase in risk of these events with increasing durations of exposure to ixekizumab.

Overall, the findings from the safety analyses across the 2 ixekizumab dosing regimens, including within subgroups, were consistent with the plaque psoriasis program.

The safety profiles of the ixekizumab 80 mg Q2W and Q4W dosing regimens were sufficiently consistent with one another although there were numerically slightly more SAEs of infection and opportunistic infections in the Q2W group. Thus, the proposed dosing regimens for the PsA population can be supported from a safety point of view. This includes the recommendation to follow the dosing regimen for plaque psoriasis for those PsA patients *with concomitant moderate to severe plaque psoriasis* (160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg every 4 weeks) whereas the remaining PsA patients are recommended to receive the less frequent ixekizumab regimen of 160 mg at Week 0, followed by 80 mg every 4 weeks thereafter.

Approximately 57% of patients in the Primary PsA Analysis Set were receiving concomitant cDMARDs during the Double-Blind Treatment Period. The vast majority of those patients, 83% were receiving MTX. The data on safety of combining ixekizumab with other cDMARDs appears to be very limited. The MAH has conducted subgroup analyses with regards to previous therapy groups (cDMARD use at baseline, MTX use at baseline, corticosteroid use at baseline – yes/no) but not with respect to other cDMARDs. However, the proposed indication is broad, allowing for 'combination with (all) conventional DMARDs'. In the first RSI, the MAH was requested to discuss the comparative safety profile of combining ixekizumab with other cDMARDs (e.g. sulfasalazine, leflunomide or hydroxychloroquine) as compared to the combination with MTX and to justify the broad wording in the proposed indication from a safety point of view. The MAH provided summary tables with comparative TEAE data for patients with concomitant MTX use versus the other cDMARDs. Taken together, the summary tables provided by MAH did not show any notable differences in safety profile for concomitant cDMARDs other than MTX vs. placebo (as compared to concomitant MTX vs. placebo). However, the small numbers of patients treated with each of the compounds other than MTX were considered insufficient to evaluate

safety. Since the mode of action and potential risks vary between the different cDMARDs it is not possible to regard them as a single “class”, or to simply extrapolate safety conclusions from the combination with MTX. Thus, the broad indication could not be supported from a safety point of view. Further studies on the combination of ixekizumab and cDMARDs other than MTX would be required to justify the proposed wording of the indication. As such the indication was revised to include only the combination with MTX.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The PRAC considered that the risk management plan version 5.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	Infections Hypersensitivity Neutropenia
Important Potential Risks	Inflammatory bowel disease (Crohn’s disease and ulcerative colitis) MACE Malignancies
Missing Information	Long-term safety (such as events with a low frequency and/or long latency) Use in pregnancy and lactation Use in very elderly (≥75 years) Use in paediatrics Use in patients with severe hepatic impairment Use in patients with severe renal impairment Use in patients with active infections (human immunodeficiency virus [HIV], hepatitis B, or hepatitis C) Immune response to live and inactive vaccines

Pharmacovigilance plan

Study / Activity Type and Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports (Planned or Actual)
3-years clinical follow-through of all recipients of Taltz in the ongoing extensions of Studies RHAZ, RHBA, and RHBC (Category 3)	• Immunogenicity: (i) describe development of antibodies and neutralising antibodies to Taltz, (ii) fully describe effect of antibody titre on pharmacokinetics of Taltz, and (iii) effect of neutralising antibodies on clinical efficacy (loss of efficacy is anticipated)	Not applicable	Started	The annual reports[a] will be submitted with the PSURs: • Annual Report 1 [Containing 2-years follow-up]: PSUR #1 [~Nov 2016]. • Annual Report 2 (Final) [Containing 3-years follow-up]: PSUR #3 [~Nov 2017]
	• AEs sorted by relative risk with incidence by treatment group and relative risk of an event in active versus placebo arm • Time-dependency of AEs • All causes of withdrawal, and in addition, separate withdrawal caused by AEs • Durations of study drug exposure			• Annual Report 1 [Containing Week 60 data, and 2-years follow-up]: PSUR #1 [~Nov 2016]. • Annual Report 2 (Final) [Containing 3-years follow-up]: PSUR #3 [~Nov 2017]
A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (may include psoriatic arthritis) in the Course of Routine Clinical Care I1F-MC-RHBT	To monitor the incidence rate and nature of infections, hypersensitivity reactions, inflammatory bowel disease, MACE, and malignancies in clinical practice. To provide additional information on the long-term safety (effects which are infrequent, and/or have a longer latency period) in routine clinical practice. To monitor the incidence and nature of AEs in the	Important identified risks: infections and hypersensitivity Important potential risks: inflammatory bowel disease, MACE, and malignancies Missing information: long-term safety; use in	The study has commenced[e] Study synopsis submitted October 2015	No formal interim reports are planned. The final study report is anticipated in Q3 2029.

Study / Activity Type and Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports (Planned or Actual)
(Corrona Registry) (Category 3)	very elderly in routine clinical practice. Signal detection. To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real world setting.	the very elderly		
Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Ixekizumab I1F-MC-B005 (Category 3)	To monitor the incidence of adverse maternal and foetal outcomes following exposure to ixekizumab during pregnancy. Signal detection. To determine if the use of ixekizumab in pregnancy could lead to adverse effects.	Missing information: use in pregnancy	Planned Study synopsis submitted October 2015	An interim report is anticipated by Q2 2021.[c] The final study report is anticipated in Q2 2025.[d]
3-years clinical follow-through of all recipients of Taltz in the ongoing extensions of Studies RHAP and RHBE (Category 3)	• AEs sorted by relative risk with incidence by treatment group and relative risk of an event in active versus placebo arms • Time-dependency of AEs • All causes of withdrawal, and in addition, separate withdrawal caused by AEs • Durations of study drug exposure	Important identified risks: infections and hypersensitivity Important potential risks: inflammatory bowel disease, MACE, and malignancies Missing information: long term safety	Planned	The annual reportsf will be submitted with the PSURs: • Annual Report 1 (PsA) [Containing 3 years follow-up for Study RHAP and 2 years follow-up for Study RHBE]: PSUR #6 [~May 2019]. • Annual Report 2 (PsA; Final) [Containing 3-years follow-up for Study RHBE]: PSUR #7 [~May 2020]

Abbreviations: ~ = approximately; AE = adverse event; MACE = major adverse cerebro-cardiovascular events; PsA = psoriatic

arthritis; PSUR = periodic safety update report; Q2 = second quarter; Q3 = third quarter; RMP = risk management plan; US = United States.

[a] The content of these reports as described in "Response to CHMP Day 180 List of Outstanding Issues, Clinical Aspects, Question 18" - January 2016. The reports will be submitted with the PSURs or sooner should there be findings that warrant more expeditious communication.

[b] The final study report will be submitted with the PSUR/RMP and within 12 months of study completion.

[c] An interim analysis will be performed once one-third of targeted ixekizumab exposures have accrued. If a sufficient number of exposures have not accrued for an interim analysis by Q2 2021, available data will be summarised and reported in the PSUR according to regulated timelines.

Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

[d] If sufficient sample size can be obtained by Q2 2021 and an interim analysis is performed, the study will continue for a maximum of 8 years to obtain the targeted sample size. A final study report will be submitted with the PSUR/RMP and within 12 months of study completion (anticipated Q2 2025). If there is insufficient use among pregnant women as of Q2 2021, no additional reports will be submitted.

[e] The study is being conducted within an independent registry, the Corrona Psoriasis Registry. Corrona enrolled the first ixekizumab-exposed patient in April 2016.

[f] The reports were agreed upon in December 2017 per the request of the Rapporteur. The reports will be submitted with the PSURs or sooner should there be findings that warrant more expeditious communication.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Infections	The text in the SmPC (4.4 Special warnings and precautions for use) informs about the association of ixekizumab treatment with an increased risk of certain infections, and advises caution and monitoring in patients with clinically important chronic or active infection. The text in the SmPC (4.3.Contraindications) contraindicates the use of ixekizumab in patients with clinically important active infections (for example, active TB). The text furthermore provides information when to discontinue patients from treatment and how to manage patients with latent TB. The text in the SmPC (4.8 Undesirable effects; Tabulated list of adverse reactions; Description of selected adverse reactions) informs about the association of ixekizumab treatment with an increased risk of infections and provide further characterisation of the ADR to prescribers	None
Hypersensitivity	The text in the SmPC (4.3 Contraindications) contraindicates the use of ixekizumab in patients with known serious hypersensitivity to the active substance or to any of the excipients. The text in the SmPC (4.4 Special warnings and precautions for use) informs about cases of serious hypersensitivity reactions reported with	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	the use of ixekizumab and advises on appropriate actions if such a reaction occurs.	
Neutropenia	The text in the SmPC (4.8 Undesirable Effects; Description of selected adverse reactions) informs health care professionals about the association of ixekizumab treatment with an increased risk of neutropenia.	None
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	The text in the SmPC (4.4 Special warnings and precautions for use) informs that cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported for ixekizumab and advises caution and monitoring for patients with preexisting inflammatory bowel disease.	None
MACE	No specific measures are required for patients receiving ixekizumab; standard of care is adequate.	None
Malignancies	No specific measures are required for patients receiving ixekizumab; standard of care is adequate.	None
Long-term safety (such as events with a low frequency and/or long latency)	None	None
Use in pregnancy and lactation	The text in the SmPC (4.6 Fertility, pregnancy, and lactation) informs about the limited data available regarding the safety of ixekizumab in pregnancy and lactation and advises to avoid the use of ixekizumab during pregnancy, and to assess the benefit-risk to determine whether to continue Taltz or to continue breastfeeding.	None
Use in very elderly (≥75 years)	The text in the SmPC (4.2 Posology and method of administration) informs health care providers that there is limited information in this patient population.	None
Use in paediatrics	The text in the SmPC (4.2 Posology and method of administration) informs about the lack of data in children below the age of 18 years.	None
Use in patients with severe hepatic impairment	The text in the SmPC (4.2 Posology and method of administration) states that ixekizumab has not been studied in this patient population and no dose recommendations can be made.	None
Use in patients with severe renal impairment	The text in the SmPC (4.2 Posology and method of administration) states that ixekizumab has not been studied in this patient population and no dose recommendations can be made.	None
Use in patients with active infections (HIV, hepatitis B, or hepatitis C)	The text in the SmPC (4.3 Contraindications) contraindicates the use of ixekizumab in patients with clinically important active infections.	None
Immune response to live and inactive vaccines	The text in the SmPC (4.4 Special warnings and precautions for use; Immunisations) informs	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	health care providers that ixekizumab should not be used with live vaccines and that no data are available on the response to live vaccines and insufficient data are available for inactive vaccines. Section 5.1 provides information on a study with 2 inactive vaccines that demonstrated no safety concerns, but immunisation data were considered insufficient to conclude that there was an adequate immune response.	

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are being updated to reflect the new safety and efficacy information. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been revisions that significantly affect the overall readability and design of the package leaflet. Therefore, Lilly does not consider it necessary to conduct further consultation with target patient groups further to that performed for the initial MAA.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Efficacy data are provided from 2 pivotal phase III studies in patients with psoriatic arthritis, studies RHAP and RHBE. In Study RHAP, 417 bDMARD-naive subjects were randomised to each of the 4 treatment groups: ixekizumab 80 mg every 2 weeks (Q2W), ixekizumab 80 mg every 4 weeks (Q4W), adalimumab 40 mg every 2 Weeks or placebo. Ixekizumab treatment was started with a loading dose of 160 mg.

The primary efficacy endpoint was achieved as ixekizumab at both 80 mg Q2W and Q4W were superior to placebo for ACR20 response at Week 24 ($p<0.001$). The ACR20 response rates at Week 24 were 62.1% for ixekizumab 80 mg Q2W, 57.9% for ixekizumab 80 mg Q4W, 57.4% for adalimumab and 30.2% for placebo. Superior ACR20 response rates compared to placebo were seen already at Week 1, and response rates were maintained over time. The difference vs placebo was 31.9% for ixekizumab 80 mg Q2W, 27.8% for ixekizumab 80 mg Q4W and 27.2% for adalimumab.

Both dosing regimens of ixekizumab were superior to placebo for the secondary endpoints mTSS at Week 24, HAQ-DI at Week 24, ACR20 at Week 12 and PASI 75 at Week 12. No statistically significant responses were shown for the secondary endpoints LEI score at Week 12 or Itch NRS at Week 12, for either ixekizumab dose compared to placebo.

In the extension period (up to 52 weeks) of study RHAP, sustained therapeutic effect was observed for ACR20, HAQ-DI and PASI75.

Study RHAP included efficacy analyses in the subset of patients who were cDMARD-experienced, which is relevant according to the proposed indication. Both ixekizumab doses were superior to placebo for the primary endpoint ACR20 at Week 24 and for the major secondary endpoints HAQ-DI, mTSS, ACR20 (at Week 12), PASI 75, and Itch NRS.

In Study RHBE, 363 bDMARD-experienced subjects were randomised to each of the 3 treatment groups: ixekizumab 80 mg Q2W, ixekizumab Q4W or placebo.

The primary efficacy endpoint was achieved as ixekizumab at both dosing regimens were superior to placebo for ACR20 response at Week 24 ($p<0.001$). The ACR20 response rates at Week 24 were 48.0% for ixekizumab 80 mg Q2W, 53.3% for ixekizumab 80 mg Q4W and 19.5% for placebo. Superior ACR20 response rates compared to placebo were seen already at Week 2 for ixekizumab 80 mg Q4W and continued to improve until a plateau was reached around Week 8. The difference vs placebo was 28.5% for ixekizumab 80 mg Q2W and 33.8% for ixekizumab 80 mg Q4W. It is noted that the lower dose has higher response rates.

Both dosing regimens of ixekizumab were superior to placebo for the secondary endpoints HAQ-DI at Week 24, ACR20 at Week 12, PASI 75 at Week 12 and minimal disease activity at Week 24. No difference was shown in proportion of patients achieveing remission of enthesitis defined by LEI score=0 at Week 24, compared to placebo.

The extension period of RHBE is ongoing, and the Week 52 data are anticipated to become available in August 2017. The data will be submitted post approval.

Both phase III studies thus met the primary endpoint as ACR20 response rates with both ixekizumab doses were statistically significantly higher compared to placebo at Week 24. In the bDMARD-naive population, the proportion of patients achieving the primary endpoint ACR20 response at Week 24 were comparable to the active comparator adalimumab, though no statistical comparison was made.

There were no significant differences in treatment response between the two posologies for the pre-specified endpoints. Data from the psoriasis phase III program indicated that for patients with moderate-to-severe plaque psoriasis, following a 160 mg starting dose, a dosing regimen of ixekizumab 80 mg Q2W provided greater efficacy at Week 12 for the skin endpoints of PASI 75/90/100 and sPGA (0,1)/(0), when compared to a dosing regimen of ixekizumab 80 mg Q4W. Therefore, it is recommended that PsA patients with coexistent moderate-to-severe plaque psoriasis use the dosing approved for patients with moderate-to-severe plaque psoriasis: 160 mg at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg Q4W.

In conclusion, ixekizumab has demonstrated a positive and clinically meaningful effect on the treatment of psoriatic arthritis.

Uncertainty in the knowledge about the beneficial effects

Regarding ixekizumab's inhibitory effect on radiographic progression, it is difficult to draw safe conclusions due to the short observation time for the secondary outcome. From a clinical perspective, data on mTSS at Week 52 are more relevant. In this analysis, patients in the ixekizumab 80 mg Q4W group had a larger mTSS change from baseline compared to patients initially randomised to placebo or

adalimumab (both switched to ixekizumab at Week 16 or 24). The applicant justifies this with the fact that the progression per se was low, and mainly driven by one patient. This may be true and can hopefully be verified when data from the long-term extension (108 Weeks) arrives.

Risks

Unfavourable effects

Safety data were submitted from the 2 pivotal studies for the PsA indication, studies RHAP and RHBE. In addition, supportive safety data in PsA is provided by one ongoing double-blind, randomized withdrawal study, preceded by an Open-Label Period, in patients with active PsA who have had inadequate response to conventional disease-modifying antirheumatic drugs (cDMARD-IR) and are bDMARD-naive (I1F-MC-RHBF [RHBF]). Integrated datasets were submitted comprising data from the 2 pivotal studies (Primary PsA Analysis Set), a larger dataset containing data from ixekizumab-treated patients from all treatment periods of studies RHAP and RHBE and the open-label period of study RHBF (All PsA Analysis Set), as well as data from 11 completed or ongoing studies in psoriasis as of September 2016 (All Psoriasis Analysis Set).

During the Double-Blind Treatment Period (Weeks 0 to 24) of the PsA studies RHAP and RHBE, the most frequently reported preferred terms (occurring in≥5% of total ixekizumab-treated patients) were Injection site reaction and Injection site erythema (greater frequency in each ixekizumab group compared to placebo) and Upper respiratory tract infection (similar frequency across treatment groups). Of note, in RHAP, the most frequent TEAEs in patients treated with the active comparator adalimumab included Nasopharyngitis and Upper respiratory tract infection.

The majority of injection site reactions (ISRs, defined as high-level term) were mild or moderate in severity, 0.7% (n=5) were rated as severe, and none were reported as an SAE. Six patients (0.9%) discontinued treatment due to injection site reactions (defined as high-level term) (1 placebo, 1 ixekizumab 80 mg Q4W, and 4 ixekizumab 80 mg Q2W). The frequency of ISRs was significantly higher in the ixekizumab 80 mg Q2W group than in the Q4W group. There was an overall trend towards more events of ISR in subjects with lower (as compared to higher) body weight for the PsA studies, consistent with the plaque psoriasis studies.

A known risk for patients treated with ixekizumab is infection, including *Candida* infection. In the Primary PsA Analysis Set, there was a difference in the frequency of infection-related SAEs between the ixekizumab 80 mg Q2W (n=5) group and the Q4W (n=1) and placebo (n=0) groups. Also, the proportion of patients with an opportunistic infection (OI) or potential OI (narrow terms) was greater in the ixekizumab 80 mg Q2W (n=10; 4.4%) and Q4W treatment groups (n=5; 2.2%) as compared to placebo (n=1; 0.4%). Predefined OIs included mucocutaneous *Candida* infections and herpes zoster. Treatment-emergent serious infections considered as opportunistic included 1 case of Oesophageal candidiasis and 1 case of Herpes zoster (ophthalmic branch of trigeminal nerve). There were numerical differences between the ixekizumab treatment groups vs. placebo with respect to mucocutaneous Herpes Simplex.

Of note, one of the pivotal PsA studies (RHAP) included an active reference group, with adalimumab. Within RHAP, the risk of infections and serious infections was comparable between adalimumab and ixekizumab 80 mg Q4W.

Low grade neutropenia was commonly observed in patients receiving ixekizumab. However, treatment-emergent Grades 3 and 4 neutropenia were not observed during the Double-Blind Treatment Period of the PsA studies, but occurred in respectively 3 (0.3%) and 0 patients of the All PsA Exposures dataset, and in 16 (0.3%) and 3 (0.1%) patients of the All Psoriasis Exposures dataset. No cases of Grade 4 neutropenia were associated with concomitant infection. There were no cases of Grade 2, 3, or 4

thrombocytopenia, nor was there any case of bleeding-related TEAE associated with thrombocytopenia in the Primary PsA Analysis Set.

In the postmarketing setting following MA for for the approved indication of plaque psoriasis, a signal for serious immediate hypersensitivity reactions has been assessed within a PSUR and this is now reflected in the updated SmPC. In the Primary PsA Analysis Set, non-anaphylaxis allergic reaction/hypersensitivity TEAEs were more frequent in the ixekizumab treatment groups (Q4W: 4.4%; Q2W: 6.2%) as compared to placebo (1.8%) consistent with the initial plaque psoriasis submission. All of these TEAEs were mild or moderate in severity and none was reported as an SAE

Other adverse events of special interest predefined by the MAH included cerebro-cardiovascular events (including MACE), malignancies, hepatic-related events, depression and suicide/self-injury, inflammatory bowel disease (IBD), and interstitial lung disease. No new safety concerns were evoked based on the current PsA submission with regards to hepatotoxicity, depression and suicidal behavior, or interstitial lung disease.

MACE, malignancies, and IBD are already included in the RMP as potential risks. The overall rates for these events were similar to the psoriasis studies and, across the ixekizumab clinical development programme for PsA and psoriasis, appear to be consistent with background rates for these populations reported in the literature. In the updated All Psoriasis Analysis Set which includes 5689 patients with 12,061.5 total patient-years of ixekizumab exposure, there was no indication of an increase in risk of these events with increasing durations of exposure to ixekizumab.

Uncertainty in the knowledge about the unfavourable effects

The safety profile observed in the studies is similar to the previous indication. There are no recommended changes to the safety specification for ixekizumab based on the current submission. The current RMP reflects the previously agreed identified and potential risks, as well as missing information, to be addressed.

Effects Table

Table 57. Effects Table for Ixekizumab for the Treatment of Psoriatic Arthritis – Data Cut-Off: September 2016[a]

Effect	Short Description	Unit	PBO	IXE 80 mg Q4W	Difference vs. PBO (95% CI)	IXE 80 mg Q2W	Difference vs. PBO (95% CI)	ADA 40 mg Q2W [b]	Difference vs. PBO (95% CI)	Uncertainties / Strengths of Evidence
Favourable Effects										
ACR20	% achieving response at Week 24 (primary endpoint)	%	24.6 (1) 30.2 (2) 19.5 (3)	55.5 (1) 57.9 (2) 53.3 (3)	30.9 [α] (22.3, 39.5) (1) 27.8 [α] (15.0, 40.6) (2) 33.8 [α] (22.4, 45.2) (3)	54.0 (1) 62.1 (2) 48.0 (3)	29.4 [α] (20.8, 38.0) (1) 31.9 [α] (19.1, 44.8) (2) 28.5 [α] (17.1, 39.8) (3)	57.4 (2)	27.2 [α] (14.2, 40.3) (2)	Well-controlled, rigorous, multicentre designs. Similar results obtained with the more stringent ACR50 and ACR70 assessments. Higher levels of skin improvement, PASI 90 and PASI 100, favoured Q2W regimen. Each trial studied a distinct subpopulation of interest in PsA (bDMARD-naive or bDMARD-experienced patients). I1F-MC-RHAP included an adalimumab active reference group; however, the study was not powered to compare ixekizumab and adalimumab.
mTSS [c]	Change from baseline to Week 24 in mTSS; LSM (SE)	NA	0.51 (0.092) (2)	0.18 (0.090) (2)	-0.33 [β] (-.57, -.09) (2)	0.09 (0.091) (2)	-0.42 [α] (-.66, -.19) (2)	0.13 (0.093) (2)	-0.38 [β] (-.62, -.14) (2)	
HAQ-DI MCID [d]	% with ≥0.35 change from baseline in HAQ-DI score at Week 24	%	22.1 (1) 26.1 (2) 16.8 (3)	46.1 (1) 49.0 (2) 43.3 (3)	24.0 [α] (15.0, 32.9) (1) 22.9 [α] (9.6, 36.2) (2) 26.4 [α] (14.6, 38.3) (3)	47.5 (1) 57.8 (2) 39.8 (3)	25.4 [α] (16.3, 34.4) (1) 31.7 [α] (18.1, 45.3) (2) 23.0 [α] (11.4, 34.6) (3)	49.4 (2)	23.4 [β] (9.6, 37.1) (2)	

Effects Table for Ixekizumab for the Treatment of Psoriatic Arthritis – Data Cut-Off: September 2016[a]
(Favourable Effects continued)

Effect	Short Description	Unit	PBO	IXE 80 mg Q4W	Difference vs. PBO (95% CI)	IXE 80 mg Q2W	Difference vs. PBO (95% CI)	ADA 40 mg Q2W [b]	Difference vs. PBO (95% CI)	Uncertainties / Strengths of Evidence
PASI 75 [e]	% achieving response at Week 12	%	9.0 (1)	66.7 (1)	57.7 [α] (48.6, 66.9) (1)	65.4 (1)	56.4 [α] (46.8, 66.0) (1)			
			7.5 (2)	75.3 (2)	67.9 [α] (56.2, 79.6) (2)	69.5 (2)	62.0 [α] (48.7, 75.4) (2)	33.8 (2)	26.4 [α] (13.5, 39.2) (2)	
			10.4 (3)	57.4 (3)	46.9 [α] (33.1, 60.8) (3)	61.8 (3)	51.3 [α] (37.6, 65.0) (3)			
MDA	% achieving MDA at Week 24	%	8.9 (1)	28.8 (1)	19.9 [α] (12.9, 26.8) (1)	31.4 (1)	22.5 [α] (15.4, 29.6) (1)			
			15.1 (2)	29.9 (2)	14.8 [γ] (3.8, 25.8) (2)	40.8 (2)	25.7 [α] (14.0, 37.4) (2)	34.7 (2)	16.6 [β] (5.2, 27.9) (2)	
			3.4 (3)	27.9 (3)	24.5 [α] (15.9, 33.1) (3)	23.6 (3)	20.2 [α] (12.0, 28.4) (3)			

Effect	Short Description	Unit	PBO	IXE 80 mg Q4W	MH Odds Ratio vs. PBO	IXE 80 mg Q2W	MH Odds Ratio vs. PBO	ADA 40 mg Q2W [b]	MH Odds Ratio vs. PBO	Uncertainties/Strengths of Evidence
Unfavourable Effects										
Infections and infestations SOC	Incidence of Infections and infestations SOC	%	27.7 (1) 25.5 (2) 29.7 (3)	33.6 (1) 28.0 (2) 38.5 (3)	1.32 (1) NA (2) 1.49 (3)	32.0 (1) 23.5 (2) 38.2 (3)	1.22 (1) NA (2) 1.47 (3)	25.7 (2)	NA (2)	Mostly mild or moderate in severity. No imbalance in the long-term using exposure-adjusted IR.
Candida HLT Plus Clinical Terms [f]	Incidence of *Candida* HLT plus clinical terms	%	0.4 (1) NA (2) NA (3)	1.7 (1) NA (2) NA (3)	3.95 (1) NA (2) NA (3)	3.6 (1) γ NA (2) NA (3)	8.12 (1) NA (2) NA (3)	NA (2)	NA (2)	No SAEs or discontinuations were reported in the IXE 80 mg Q4W treatment group.
Urticaria	Incidence of Urticaria	%	0 (1) 0 (2) 0 (3)	0.4 (1) 0.9 (2) 0 (3)	NA (1) NA (2) NA (3)	0.9 (1) 1.0 (2) 1.6 (3)	NA (1) NA (2) NA (3)	1.0 (2)	NA (2)	These events were not SAEs, were mild or moderate in severity, and did not lead to discontinuation.
Injection Site Reactions	Incidence of Injection Site Reactions HLT	%	4.5 (1) 4.7 (2) 4.2 (3)	17.5 (1) α 24.3 (2) α 11.5 (3)	4.56 (1) NA (2) 2.93 (3)	25.3 (1) α,δ 26.5 (2) α 23.6 (3) α	7.29 (1) NA (2) 6.97 (3)	5.9 (2)	NA (2)	These events were mild to moderate in severity. No SAEs from treatment due to Injection Site Reactions were reported.
Neutro-penia Grade 2 or Worse	Incidence of treatment-emergent neutropenia Grade 2 or worse	%	0.5 (1) 0 (2) 0.9 (3)	1.7 (1) 2.8 (2) 0.8 (3)	NA (1) NA (2) NA (3)	4.0 (1) 6.9 (2) 1.6 (3)	NA (1) NA (2) NA (3)	3.0 (2)	NA (2)	Neutropenia was transient, did not require discontinuation or hospitalisation, and was not associated with an increased frequency of infections.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% response rate; ADA = adalimumab; ANCOVA = analysis of covariance; bDMARD = biologic disease-modifying antirheumatic drug; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire–Disability Index; HLT = high level term; IR = incidence rate; IXE = ixekizumab; LSM = least squares mean; MCID = minimal clinically important difference; MDA = minimal disease activity; MH = Mantel-Haenszel; mTSS = modified Total Sharp Score; NA = not calculated or not applicable; PASI 75/90/100 = Psoriasis Area and Severity Index 75%/90%/100% response rate; PBO = placebo; PsA = psoriatic arthritis; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; SE = standard error; SOC = system organ class; vs. = versus.

(1) Primary PsA Placebo-Controlled Integrated Analysis Set (I1F-MC-RHAP and I1F-MC-RHBE), Double-Blind Treatment Period.

(2) I1F-MC-RHAP Intent-to-Treat Population, Double-Blind Treatment Period.

(3) I1F-MC-RHBE Intent-to-Treat Population, Double-Blind Treatment Period.

α p<.001 vs. PBO.

β p<.01 vs. PBO.

γ p<.05 vs. PBO.

δ p<.05 vs. IXE 80 mg Q4W.

a The Week 24 database lock for I1F-MC-RHAP was 26-Feb-2015. The Week 24 database lock for I1F-MC-RHBE was 30-Sep-2016.

b ADA 40 mg Q2W was included in I1F-MC-RHAP as an active reference group. The study was not powered to test superiority or non-inferiority of ixekizumab vs. adalimumab.

c mTSS was assessed only in I1F-MC-RHAP. Treatment comparisons were conducted using ANCOVA with linear extrapolation method for missing data.

d HAQ-DI MCID was assessed in patients with baseline HAQ-DI ≥0.35.

e PASI 75 was assessed in patients with body surface area (BSA) ≥3% at baseline.

f *Candida* Medical Dictionary for Regulatory Activities (MedDRA) HLTs with MedDRA preferred terms for treatment-emergent adverse event (TEAEs) are those likely to represent *Candida* infections (Fungal oesophagitis, Oral fungal infections, Oropharyngitis fungal, Vulvovaginal mycotic infection).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Statistically significant efficacy of ixekizumab in the treatment of PsA has been demonstrated as both phase III studies met their primary endpoint. The ACR20 response rates with both ixekizumab doses were statistically significantly higher compared to placebo at Week 24. In the bDMARD-naive population, the proportion of patients achieving the primary endpoint ACR20 response at Week 24 was similar to the response for adalimumab.

There were no significant differences in treatment response between the two posologies for the pre-specified endpoints. Data from the psoriasis phase III program for patients with moderate-to-severe plaque psoriasis indicated that following a 160 mg starting dose, a dosing regimen of ixekizumab 80 mg Q2W provided greater efficacy at Week 12 for the skin endpoints of PASI 75/90/100 and sPGA (0,1)/(0), when compared to a dosing regimen of ixekizumab 80 mg Q4W. Therefore, it is recommended that PsA patients with coexistent moderate-to-severe plaque psoriasis use the dosing approved for patients with moderate-to-severe plaque psoriasis: 160 mg at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg Q4W.

Overall, the safety profile for ixekizumab in the treatment of PsA, based on the data provided, was as expected and consistent with the known safety profile from studies in plaque psoriasis. Frequently reported ADRs were Injection site reaction and Injection site erythema. However, the majority of these reactions were mild or moderate in severity and none were reported as an SAE. The frequency of ISRs was significantly higher in the ixekizumab 80 mg Q2W group than in the Q4W group. However, the rates of ISRs per 100 active injections were comparable between the groups which may suggest that the higher rate in the Q2W treatment group is due to the greater number of injections. Also, no clear relationship between the development of ISRs and treatment-emergent ADA positivity could be observed.

The profile of infections in the Primary PsA Analysis Set for the current application is also considered consistent with the prior experience of ixekizumab. There were no cases of invasive herpes simplex, viral hepatitis, confirmed active or reactivated TB, endemic mycoses, invasive *Aspergillus*, or other deep fungal infections. Treatment-emergent serious infections considered as opportunistic included 1 case of Oesophageal candidiasis and 1 case of Herpes zoster (ophthalmic branch of trigeminal nerve). There were numerical differences between the ixekizumab treatment groups vs. placebo with respect to mucocutaneous Herpes Simplex, however. This has been reflected in section 4.8 of the product information.

Low grade neutropenia was commonly observed in patients receiving ixekizumab. However, treatment-emergent Grades 3 and 4 neutropenia were not observed during the Double-Blind Treatment Period of the PsA studies, although reported in few patients in the All PsA Exposures and All Psoriasis Exposures datasets. No cases of Grade 4 neutropenia were associated with concomitant infection. There were no cases of Grade 2, 3, or 4 thrombocytopenia, nor was there any case of bleeding-related TEAE associated with thrombocytopenia in the Primary PsA Analysis Set.

Consistent with the initial plaque psoriasis submission, non-anaphylaxis allergic reaction/hypersensitivity TEAEs were more frequent in the ixekizumab treatment groups as compared to placebo. All of these events were mild or moderate in severity and none was reported as an SAE. Some additional PTs (eczema, rash, angioedema) have been added to section 4.8 of the SmPC.

Overall, the findings from the safety analyses across the 2 ixekizumab dosing regimens, including within subgroups, were consistent with the plaque psoriasis program. Also, the safety profiles of the ixekizumab 80 mg Q2W and Q4W dosing regimens were sufficiently consistent with one another although there were numerically slightly more SAEs of infection and opportunistic infections in the Q2W group. Thus, the proposed dosing regimens for the PsA population can be supported from a safety point of view.

No concerns were evoked based on the current submission with regards to potential AEs of interest including hepatotoxicity, depression and suicidal behavior, or interstitial lung disease. MACE, malignancies, and IBD are already included in the RMP as potential risks and no new safety concerns were identified.

Importantly, while the safety profile of ixekizumab in the PsA population appears to be reflective of prior experience, the initially proposed indication allowing for ‘combination with (all) conventional DMARDs’ could not be accepted from a safety perspective. Approximately 57% of patients were receiving

concomitant cDMARDs during the Double-Blind Treatment Period. The vast majority of those patients, 83%, were receiving MTX. Data supporting the safety of combining ixekizumab with other cDMARDs appears to be very limited. Thus, the available data were considered to be insufficient to justify such broad wording in terms of conventional DMARD therapy. However, the proposed indication was revised to include the combination with MTX only.

Benefit-risk balance

Ixekizumab has demonstrated a positive and clinically meaningful effect on the treatment of psoriatic arthritis. The risks identified in the pivotal Phase III studies for PsA are considered to be consistent with those previously established in the psoriasis MAA submission.

Discussion on the Benefit-Risk Balance

Clinically relevant efficacy has been shown for ixekizumab in the treatment of PsA in bDMARD-naïve and bDMARD-experienced populations.

The safety profile for ixekizumab in the current application is considered quite consistent with prior experience. Also, the safety profiles of the ixekizumab 80 mg Q2W and Q4W dosing regimens were sufficiently consistent with one another although there were numerically slightly more SAEs of infection and opportunistic infections in the Q2W group. Thus, the proposed dosing regimens for the PsA population can be supported from a safety point of view. This includes the recommendation to follow the dosing regimen for plaque psoriasis for those PsA patients *with concomitant moderate to severe plaque psoriasis* (160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg every 4 weeks) whereas the remaining PsA patients are recommended to receive the less frequent ixekizumab regimen of 160 mg at Week 0, followed by 80 mg every 4 weeks thereafter.

MACE, malignancies, and IBD are already included in the RMP as potential risks. The overall rates for these events were similar to the psoriasis studies and, across the ixekizumab clinical development programme for PsA and psoriasis, appear to be consistent with background rates for these populations reported in the literature. In the updated All Psoriasis Analysis Set which includes 5689 patients with 12,061.5 total patient-years of ixekizumab exposure, there was no indication of an increase in risk of these events with increasing durations of exposure to ixekizumab. Infections are already included as identified risk in the current RMP with the objective to monitor the incidence rate and nature of rare and clinically relevant infections through submission of additional safety data from ongoing studies, a post-marketing safety registry (the Corrona Registry), as well as routine pharmacovigilance.

In conclusion, the risks identified in the pivotal Phase III studies for PsA are considered to be consistent with those previously established in the psoriasis MAA submission. However, the initial proposed indication was broad, allowing for ‘combination with (all) conventional DMARDs’ although the vast majority of concomitant cDMARDs safety data pertain to MTX only. The small numbers of patients treated with each of the compounds other than MTX was considered insufficient to evaluate safety. Since the mode of action and potential risks vary between the different cDMARDs it is not possible to regard them as a single “class”, or to extrapolate safety conclusions from the combination with MTX.

Further studies on the combination of ixekizumab and cDMARDs other than MTX would be required to justify a broader wording as initially proposed by the MAH.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include Ixekizumab alone or in combination with methotrexate, the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated to reflect the new safety and efficacy information. The Package Leaflet and RMP (v.5.1) have been updated accordingly.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional market protection

The MAH submitted at the start of the procedure a request for consideration that the new indication brings significant benefit in comparison to existing therapies in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the assessment, the CHMP raised questions concerning the significant benefit. Prior to the adoption of the CHMP opinion, the company withdrew its request for additional market protection. As a result of the MAH withdrawal of this ancillary request, no opinion on the additional market protection is adopted by CHMP.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include Ixekizumab alone or in combination with methotrexate, the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated to reflect the new safety and efficacy information. The Package Leaflet and RMP have been updated accordingly.

Summary

Please refer to the published Assessment Report Taltz H-3943-II-09-AR.

Attachments

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 14 December 2017

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 8 January 2018. The principles to be applied for the deletion of CCI are published on the EMA website at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable)within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.