28 April 2020
EMA/CHMP/251895/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Taltz

International non-proprietary name: ixekizumab

Procedure No. EMEA/H/C/003943/II/0030

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST	Aspartate aminotransferase
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EQ-5D	Euro-QoL 5-Dimension Health Status Questionnaire
HLA	Human leukocyte antigen
HLT	High level term
hsCRP	High sensitivity C-Reactive Protein
IL-17A	Interleukin-17A
IR	Inadequate responder
MACE	Major adverse cardiovascular events
MAR	Missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCS	Mental component summary score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures

MRI	Magnetic resonance imaging
MRI+	Patient with a MRI considered positive for sacroiliitis at Screening
MRI-	Patient with a MRI considered negative for sacroiliitis at Screening
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PCS	Physical component summary score
PFS	Pre-filled syringe
PsA	Psoriatic arthritis
Pso	Psoriasis
PT	Preferred term
PY	Patient years
QoL	Quality of Life
SAE	Serious adverse event
SF-36	Short Form-36
SI-joint	Sacroiliac joint
SMQ	Standardized MedDRA Query
SOC	System organ class
SpA	Spondyloarthritis
TNF	Tumor Necrosis Factor
TNF-IR	TNF-alpha inhibitor inadequate responder
ULN	Upper limit of normal
VAS	Visual analog scale

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 24 August 2019 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 treatment of adult patients with active axial spondyloarthritis; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC and relevant section of the PL are updated. Furthermore, the PI is brought in line with the latest QRD template version 10.1. In addition, an updated RMP version 6.1 has also been submitted.

The variation requested 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 PIP P/0280/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0280/2019 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 MAH 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 MAH sought Scientific Advice at the CHMP 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: Peter Kiely

Timetable	Actual dates
Submission date	24 August 2019
Start of procedure:	14 September 2019
CHMP Rapporteur Assessment Report	8 November 2019
CHMP Co-Rapporteur Assessment Report	8 November 2019
PRAC Rapporteur Assessment Report	15 November 2019
PRAC members comments	20 November 2019
Updated PRAC Rapporteur Assessment Report	21 November 2019
PRAC Outcome	28 November 2019
CHMP members comments	2 December 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 December 2019
Request for supplementary information (RSI)	12 December 2019
CHMP Rapporteur Assessment Report	26 February 2020
PRAC Rapporteur Assessment Report	28 February 2020
PRAC members comments	4 March 2020
PRAC Outcome	12 March 2020
CHMP members comments	16 March 2020
Updated CHMP Rapporteur Assessment Report	19 March 2020
Request for supplementary information (RSI)	26 March 2020
PRAC Rapporteur Assessment Report	15 April 2020
CHMP Rapporteur Assessment Report	15 April 2020
PRAC members comments	20 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	N/A
Updated PRAC Rapporteur Assessment Report	N/A
Opinion	28 April 2020

2. Scientific discussion

2.1. Introduction

Ixekizumab is an immunoglobulin G subclass 4 monoclonal antibody that binds IL-17A, a key proinflammatory cytokine in the pathophysiology of plaque Ps, psoriatic arthritis (PsA), and axSpA. Animal studies established the role of IL-17 signalling in ankylosing enthesitis and bone remodelling and prophylactic administration of anti-IL-17 antibodies blocked the development of ankylosis in spontaneous ankylosis mouse model. Compelling scientific information to date suggests an important role of the IL-17 pathway in the pathogenesis of axSpA by driving inflammation leading to erosive bone damage and pathological new bone formation In patients with axSpA, increased numbers of IL-17A-producing cells are present in the peripheral blood, as well as elevated levels of IL-17 in the serum and synovium Neutralisation of IL-17A has been shown to inhibit the aforementioned pathological cellular events, as well as mitigate disease activity in patients with axSpA The demonstration of increased IL-17-producing Th17 lymphocyte numbers and serum IL-17 levels in axSpA is consistent with a direct role of Th17 lymphocytes in this disease. Interleukin-17 secreting cells have also been detected in situ in the bone marrow of facet joints obtained from patients with axSpA.

Taltz was first approved in Europe on 25 April 2016 for the treatment of adults with moderate-to-severe plaque Ps. An extension of indication was approved on 18 January 2018 for ixekizumab alone or in combination with methotrexate to include 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.

The submitted Type II variation application was for a proposed new indication and associated posology as follows:

Ixekizumab is indicated for the treatment of adult patients with active axial spondyloarthritis, comprising:

Radiographic Axial Spondyloarthritis: Adult patients with active radiographic axial spondyloarthritis.

Nonradiographic Axial Spondyloarthritis: Adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation.

The recommended dose is 80 mg by subcutaneous injection every 4 weeks.

To support this variation, the efficacy and safety of ixekizumab in axSpA were assessed in 3 pivotal, randomised, double-blind, placebo-controlled, Phase III studies (RHBV, RHBW, RHBX). Each study included separate patient populations to address the efficacy and safety profile in bDMARD-naive patients with r-axSpA (RHBV), TNF-inhibitor-experienced patients with r-axSpA (RHBW) and bDMARD-naive patients with nr-axSpA (RHBX).

The ixekizumab clinical development programme for axSpA 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 for the treatment of ankylosing spondylitis, CPMP/EWP/4891/03).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Ixekizumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for ustekinumab is required. The CHMP considered this acceptable

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

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

2.3. Clinical aspects

2.3.1. Introduction

The applicant has conducted 3 pivotal studies in 960 adult patients with axial spondyloarthritis: 2 studies in patients with radiographic axial spondyloarthritis (r-axSpA) (RHBV and RHBW) and 1 study in patients with non-radiographic axial spondyloarthritis (nr-axSpA) (RHBX).

GCP

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

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: Summary of the Pivotal Phase 3 Studies Supporting the AxSpA Indication

Study	Description	N	Treatment	Primary Endpoint
I1F-MC-RHBV	Efficacy and safety in bDMARD-naive patients with active r-axSpA.	341	IXE: 160 mg or 80 mg at Week 0; then 80 mg Q2W or Q4W until Week 52. PBO[a]: Q2W until Week 16. ADA[b]: 40 mg Q2W until Week 16.	ASAS40 at Week 16
I1F-MC-RHBW	Efficacy and safety in TNFi-experienced patients[c] with active r-axSpA.	316	IXE: 160 mg or 80 mg at Week 0; then 80 mg Q2W or Q4W until Week 52. PBO[a]: Q2W until Week 16.	ASAS40 at Week 16
I1F-MC-RHBX	Efficacy and safety in bDMARD-naive patients with active nr-axSpA.	303	IXE[d]: 160 mg or 80 mg at Week 0; then 80 mg Q2W or Q4W until Week 52. PBO[d]: Q2W until Week 52.	ASAS40 at Week 16

Abbreviations: ADA = adalimumab; ASAS40 response = a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain; bDMARD = biologic disease-modifying anti-rheumatic drug; ITT = intent to treat; IXE = ixekizumab; N = number of patients in ITT population; nr-axSpA = nonradiographic axial spondyloarthritis; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; r-axSpA = radiographic axSpA; TNFi = tumour necrosis factor inhibitor.

a At Week 16, patients on PBO were re-randomised at a 1:1 ratio to IXE 80 mg Q2W or 80 mg Q4W, with a 160-mg starting dose. Patients remained on IXE Q2W or IXE Q4W until Week 52.

b At Week 16, patients on ADA were re-randomised (1:1 ratio) to IXE 80 mg Q2W or 80 mg Q4W with an 80-mg starting dose. Patients underwent a 6-week washout period prior to receiving ixekizumab at Week 20. Adalimumab was included as an active reference group. Study RHBV was not powered to test equivalence or noninferiority of IXE versus ADA. Patients remained on IXE Q2W or IXE Q4W until Week 52.

c TNFi-experienced patients are those who have had prior treatment with 1 to 2 TNFi and discontinued at least 1 TNFi due to intolerance *or*, in the opinion of the investigator, an inadequate response following at least 12 weeks of treatment.

d Beginning at Week 16 and up to Week 44, any patient could be identified by the investigator as an inadequate responder. At such time, changes in background therapy and/or transition to biologic rescue therapy (ixekizumab 80 mg Q2W) could be made while remaining blinded to the original randomisation treatment assignment.

2.3.2. Pharmacokinetics

The objectives of the clinical pharmacology programme supporting this application for axSpA are as follows:

- characterize ixekizumab pharmacokinetics (PK) in patients with r-axSpA and nr-axSpA and determine if the PK are consistent with the PK in patients with Ps and PsA
- evaluate the exposure-response relationship in patients with r-axSpA and nr-axSpA on efficacy (Assessment of Spondyloarthritis International Society [ASAS] endpoints of ASAS20 [an improvement of at least 20%] and ASAS40 [an improvement of at least 40%]) and on select adverse events of special interest (AESI)

- determine the incidence of antidrug antibodies (ADAs), including neutralizing antibodies (NAbs), characterize the ADA kinetics, evaluate the relationship between immunogenicity and PK, and summarize the impact of immunogenicity on the efficacy and safety of ixekizumab
- support the commercial dosing regimen justification for patients with r-axSpA and nr-axSpA through population PK and exposure-response analyses of data from the Phase3 r-axSpA and nr-axSpA studies.

Analytical method

- **ELISA for the determination of ixekizumab concentration.**

Serum samples collected in clinical studies were analysed for ixekizumab concentrations using a validated enzyme-linked immunosorbent assay method. The method was validated at ALTA Analytical Laboratory (subsequently renamed Intertek Pharmaceutical Services), San Diego, CA, and then (prior to the axial spondyloarthritis clinical studies) the method was transferred, redeveloped and validated at ICON Laboratory Services, Inc., Whitesboro, NY. Details on the Intertek validation were provided in the application for psoriasis (Ps). A summary of the ICON validation is provided in the current submission.

The methods used to quantify ixekizumab in axial spondyloarthritis (axSpA) in support of this application are listed in Table 2. A summary of method validation is provided in Table 3. .

Table 2: Summary Table for the Serum Bioanalytical Methods

Study Identifier and Report	Analytical Laboratory (Method Report ID)	Quantification Range	Analyte
I1F-MC-RHBV Supplemental Intertek Bioanalytical Contributor Report	Intertek Pharmaceutical Services[a] (San Diego, CA) ELISA (AR1827, AR1827-2[c])	7.5 to 300 ng/mL[b]	Ixekizumab
Supplemental ICON Bioanalytical Contributor Report	ICON Laboratory Services, Inc. (Whitesboro, NY) ELISA (184959)	6.3 to 400 ng/mL[d]	Ixekizumab
I1F-MC-RHBW Supplemental Intertek Bioanalytical Contributor Report	Intertek Pharmaceutical Services[a] (San Diego, CA) ELISA (AR1827, AR1827-2[c])	7.5 to 300 ng/mL[b]	Ixekizumab
Supplemental ICON Bioanalytical Contributor Report	ICON Laboratory Services, Inc. (Whitesboro, NY) ELISA (184959)	6.3 to 400 ng/mL[d]	Ixekizumab
I1F-MC-RHBX Supplemental Intertek Bioanalytical Contributor Report	Intertek Pharmaceutical Services[a] (San Diego, CA) ELISA (AR1827, AR1827-2[c])	7.5 to 300 ng/mL[b]	Ixekizumab
Supplemental ICON Bioanalytical Contributor Report	ICON Laboratory Services, Inc. (Whitesboro, NY) ELISA (184959)	6.3 to 400 ng/mL[d]	Ixekizumab

Abbreviations: ELISA = enzyme-linked immunosorbent assay; ID = identification.
[a] Previously known as ALTA Analytical Laboratory.

[b] Assay dynamic range is 1.5 to 60 ng/mL with a minimum required dilution of 1:5 resulting in a quantification range of 7.5 to 300 ng/mL.
[c] Contains Addenda E, F, and G.
[d] Assay dynamic range is 1.26 to 80 ng/mL with a minimum required dilution of 1:5 resulting in a quantification range of 6.3 to 400 ng/mL.

Table 3: Clinical Method Validation Data

Method/Validation Method Date	Matrix	Validation Range (ng/mL) Dilution Factor	Inter-Assay Precision (%RSD)	Inter-Assay Accuracy (%RE)	Stability data
Intertek Pharmaceutical Services[a] AR1827	Human serum (Ixekizumab)	Validation range 7.5 to 300 ng/mL Dilution factor Up to 32000-fold	11.8 to 17.3	-5.8 to 3.4	Room temperature: 4 hours Long-term stability: 365 days at -20°C and -70°C Freeze/thaw: 8 cycles at -70°C
Intertek Pharmaceutical Services[a] AR1827-2	Human serum (Ixekizumab)	7.5 to 300 ng/mL Dilution factor Up to 32000-fold[b]	11.8 to 17.3[b]	-5.8 to 3.4[b]	Room temperature: 4 hours[b] Long-term stability: 365 days at -20°C[b] and 36 months at -70°C Freeze/thaw: 8 cycles at -70°C[b]
ICON Laboratory Services, Inc. 184959	Human serum (Ixekizumab)	Validation range 6.3 to 400 ng/mL Dilution factor Up to 20000-fold	4.1 to 7.3	-1.0 to 1.6	Room temperature: 25 hours Long-term stability: 36 months at -70°C[c] Freeze/thaw: 6 cycles at -70°C

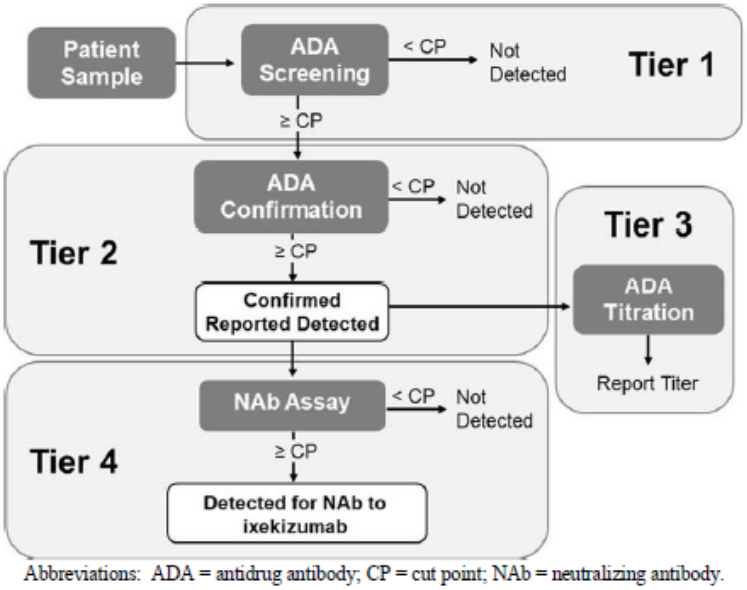
Abbreviations: RE = relative error; RSD = relative standard deviation.
[a] Previously known as ALTA Analytical Laboratory.
[b] Previously determined in method AR1827.
[c] Long-term stability was determined at Intertek Pharmaceutical Services.

Following validation of the assay at ICON, a cross-validation experiment was performed in which samples were prepared at Intertek Laboratory Services, Inc. and were assayed at ICON Laboratory Services, Inc. The acceptance criteria required at least 67% of samples within ±30% incurred sample re-analysis. Between ICON and Intertek, at least 91% of the samples met the acceptance criteria.

- **Anti-Drug Antibody Assay**

Immunogenicity samples were evaluated using a 4-tiered approach described in the regulatory application for psoriasis (Figure 1.).

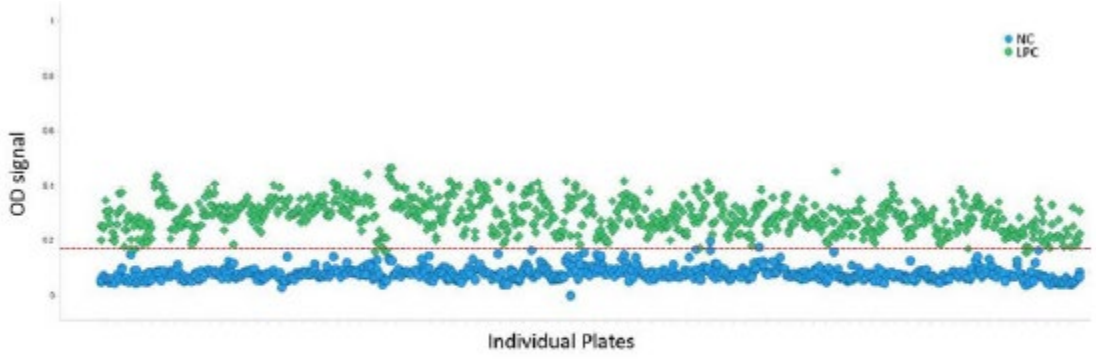
Figure 1. Flowchart for antidrug antibody assessments



Abbreviations: ADA = antidrug antibody; CP = cut point; NAb = neutralizing antibody.

All samples were assessed in Tier 1 (screening). A fixed cut point approach was found to have acceptable assay precision. The negative control (NC) and low positive control (LPC) remained consistent in their Tier 1 signal (Figure 2.). The stability of the NC and LPC, which closely bracket the cut point, demonstrate minimal plate-to- plate variability and supports the adequacy of a fixed cut point.

Figure 2. Tier 1 signals of negative control and low positive control in Studies RHBV, RHBW, and RHBX.



Abbreviations: LPC = low positive control; NC = negative control; OD = optical density.
Note: Red dotted line represents "Tier 1 cut point" (0.169).

Serum samples are added to an ELISA plate coated with ixekizumab allowing ADAs to bind. ADAs are then eluted by acid treatment. On a second ELISA plate, samples are allowed to bind and are detected using a biotin-labeled ixekizumab and HRP-labelled streptavidin and enzyme substrate.

Those samples screened in Tier 1, which produce an optical density (OD) greater / above the axSpA-specific assay cut point were assessed in Tier 2 (confirmation).

The base method assay format was also used in Tier 2 testing (confirmation) with a slight modification involving addition of excess non-labeled ixekizumab at the biotinylated ixekizumab step. This modification was utilized to confirm the specificity of presumed ADA identified during Tier 1 screening. If samples were confirmed as specific to the therapeutic in Tier 2, they were reported as "detected." All samples below the assay cut point in Tier 1 or not confirmed in Tier 2 were reported as "not detected." All samples that were confirmed in Tier 2 were further evaluated in Tier 3 (titer assessment) and Tier 4 (NAb assay).

The ADA screening assay has not changed from its original format, and a series of confirmatory validations were performed to further strengthen the overall validation package (Table 4.).

Table 4: Individual Validation Reports for the Ixekizumab Screening Anti-Drug Antibody Assay

Date of Report	Report Designation
13 October 2008	08-011 VALIDATION REPORT[a]
24 February 2011	08-011 VALIDATION REPORT ADDENDUM 1[a]
24 October 2013	08-011 VALIDATION REPORT AMENDMENT 1[a]
21 November 2013	12-196A VALIDATION REPORT ADDENDUM[a]
15 October 2014	12-196A VALIDATION REPORT ADDENDUM 2[a]
05 November 2014	12-196A VALIDATION REPORT ADDENDUM 3[a]
20 June 2016	12-196A VALIDATION REPORT ADDENDUM 2 AMENDMENT 1[a]
13 April 2017	12-196A VALIDATION REPORT ADDENDUM 4

Abbreviations: Ps = plaque psoriasis; PsA = psoriatic arthritis.
[a] Included in Section 5.3.1.4 of the Ps and PsA applications.

The current application contains validation report addendum 4, all other reports have been included in the Ps application.

Screening Cut point was determined to be 0.172 OD using 219 (225 minus 6 outliers) baseline AxSpA patient samples. A 5% false positive rate was applied. The Ps cut-point of 0.169 was applied as the difference between the two cut-points was not found to be statistically significant (Figure 3. and Figure 4.).

Figure 3. Overlaid histograms of baseline screening OD values for Ps patients (cyan) and axSpA patients (salmon). Disease state cut points of 0.169 and 0.172 indicated by the vertical lines for the Ps and axSpA disease states, respectively.

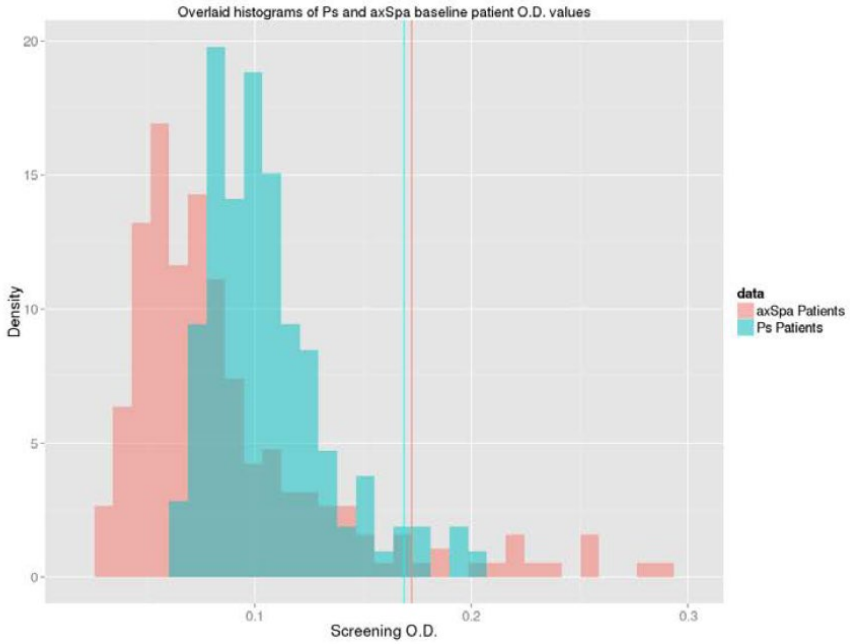
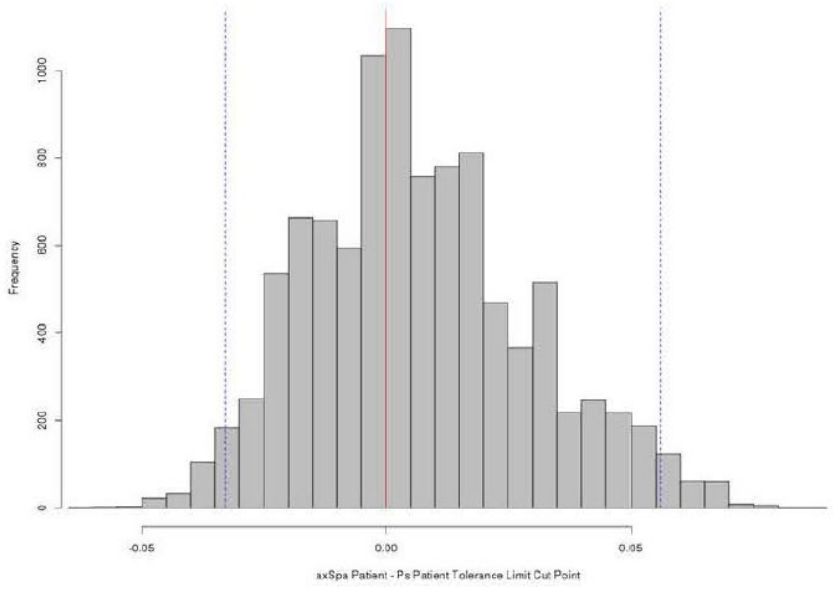


Figure 4. Distribution of cut point differences (axSpA - Ps) for 10,000 samplings of a bootstrap hypothesis test. Empirical 95% confidence interval denoted by blue dashed lines. Zero difference (red vertical line) falls within the confidence interval so we conclude that the two disease specific cut point estimates are not statistically significantly different (p>0.05).



Tier 3 (Titration) of the ADA approach outlined in Figure 1. was evaluated. The ability to dilute a positive sample to a level which falls below the AxSpA assay cut point by titration was studied using the low positive control which was run at five additional dilutions with the titre at the 1:10 dilution (**Table 5**).

Table 5: Tier 3 Titration Assessment

	Run	1	2	3	4	5	6			
	Assay Number	16PR121337			16PR121338			Mean	Std Dev	%CV
Dilution of Low Positive Control	1:5 (MRD)	[a]0.425	0.316	0.281	0.309	0.277	0.297	0.296	0.017	5.8
	1:10	0.211	[a]0.312	0.175	0.170	0.148	0.150	0.171	0.025	14.8
	1:20	0.111	0.114	0.111	[a]0.136	0.106	0.099	0.108	0.006	5.2
	1:40	0.088	0.087	0.079	0.078	0.077	0.082	0.082	0.005	5.8
	1:80	0.078	0.065	0.083	0.056	0.059	0.057	0.066	0.011	17.2
	1:160	[a]0.155	0.074	0.068	0.066	0.061	0.057	0.065	0.007	10.3

[a] High %CV, result excluded from cumulative statistics

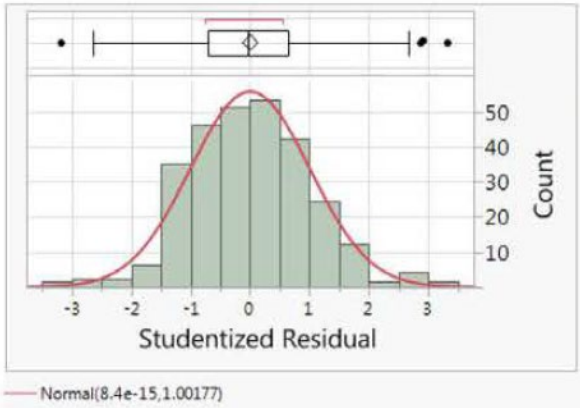
- **Neutralising Antibody Assay**

Validation Reports for the Ixekizumab Neutralizing Anti-Drug Antibody Assay (Tier 4) have been submitted as part of the Ps application. One updated addendum report has been included in this application.

The assay detects NAb by direct competition between the binding of the therapeutic target (IL-17) and binding of ADA at the active site of ixekizumab using a MesoScale Discovery® (MSD) platform. Serum samples containing ADA and free drug are incubated on a streptavidin plate coated with biotinylated ixekizumab, allowing ADA to bind. ADAs are eluted off the plate and transferred to a streptavidin plate that has been coated with biotinylated ixekizumab, allowing for ADA to bind. The plate is then challenged with ruthenium-labeled target protein (Ru-IL-17). Excitation of the Ru-IL-17 results in a measurable electrochemiluminescence (ECL) signal.

If the Ru-IL-17 is unable to bind to the ixekizumab on the plate because active binding sites are occupied by ADA, the ECL signal is decreased. To identify this decrease in signal, a percent inhibition value is calculated by comparing the patient sample with a non-ADA containing matrix control. Any patient sample that demonstrates an inhibition (knockdown of assay signal) greater than the assay inhibition threshold (cut point) is considered positive for NAb. A neutralizing assay cut point for was established for the AxSpA disease-state population. 70 AxSpA baseline serum samples were utilized. For each sample, two analytical runs were performed by two analysts. 6 analytical outliers were removed (Figure 5.). No biological outliers were identified.

Figure 5. Distribution of Studentized residuals resulting from the fixed effects model: log(Yt) - Sample/D + Analyst+ Plate[Analyst] + e. Six analytical outliers were identified and excluded from subsequent analyses.



Quantiles

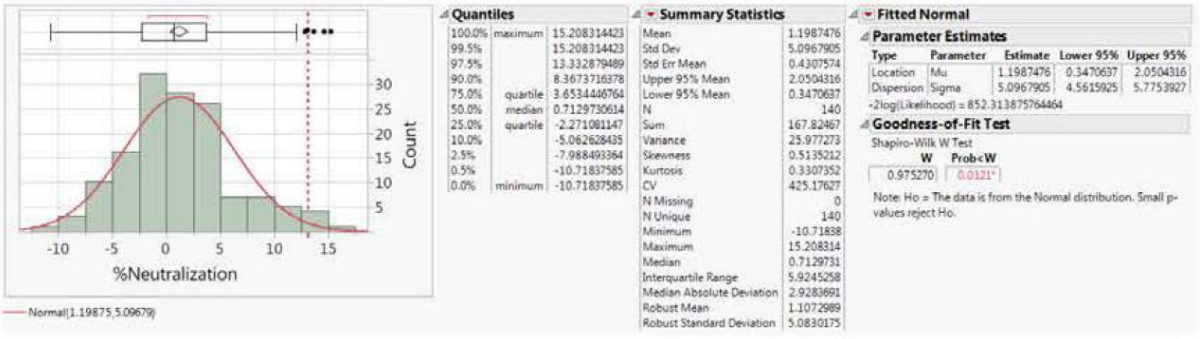
100.0%	maximum	3.3195870497
99.5%		3.1535097682
97.5%		1.9334744066
90.0%		1.2428305515
75.0%	quartile	0.6407779908
50.0%	median	-0.041189174
25.0%	quartile	-0.707153499
10.0%		-1.246140811
2.5%		-1.71149978
0.5%		-2.960939457
0.0%	minimum	-3.173520294

Summary Statistics

Mean	8.373e-15
Std Dev	1.0017742
Std Err Mean	0.0598675
Upper 95% Mean	0.1178493
Lower 95% Mean	-0.117849
N	280
Sum	2.345e-12
Variance	1.0035516
Skewness	0.2209237
Kurtosis	0.4272531
CV	1.196e+16
N Missing	0
N Unique	280
Minimum	-3.17352
Maximum	3.319587
Median	-0.041189
Interquartile Range	1.3479315
Median Absolute Deviation	0.6720832
Robust Mean	-0.00752
Robust Standard Deviation	0.9849919

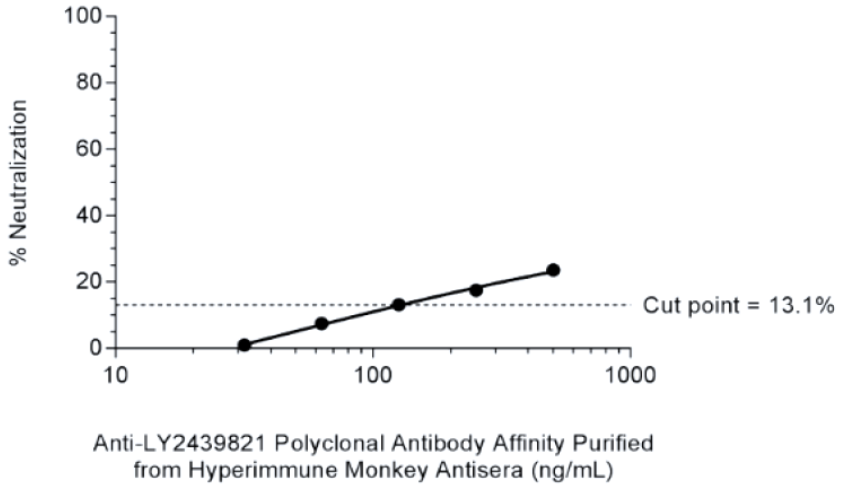
The axial spondyloarthritis NAb cut point was estimated to be 13.1% inhibition for a 1% false positive rate (Figure 6.).

Figure 6. Distribution of data used to estimate the NAb cut point. A tolerance limit to yield a 1% false positive rate with 90% confidence was used to estimate the cut point. The cut point was estimated to be 13.1% inhibition (red dashed line).



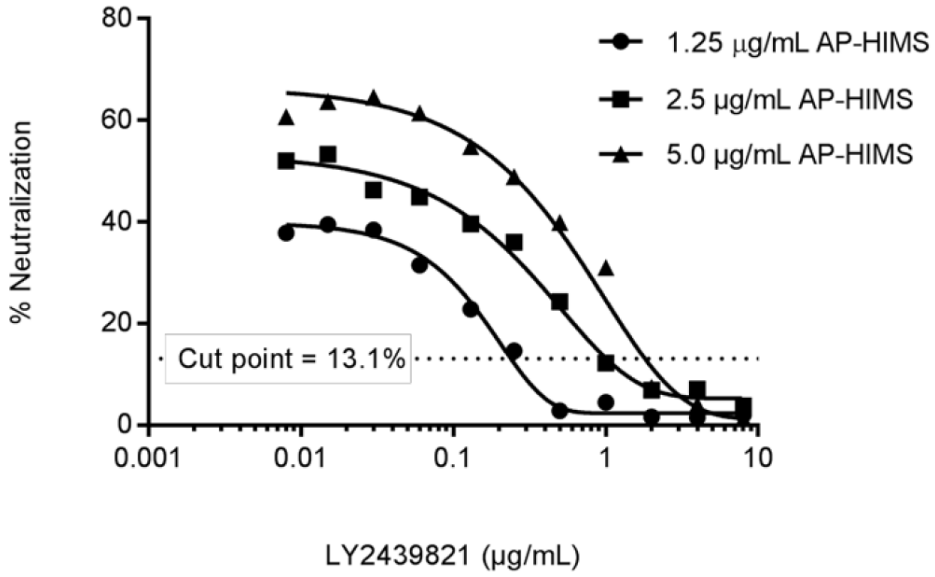
With the updated cut-point, sensitivity was determined to be 121.97 ng/mL using anti- Ixekizumab polyclonal antibody affinity purified from hyper-immune monkey sera (Figure 7.). This is more sensitive than for Ps (253.4 ng/ml).

Figure 7. Sensitivity Graph. From the mean of 3 assays. The interpolation of the cut point (13.1%) from the curve yielded a sensitivity of 121.97 ng/mL.



Assay drug tolerance was evaluated using the updated cut-point. The highest concentration of ixekizumab the NAb assay can tolerate yet detect anti- ixekizumab positive samples was proven to be 1.55 µg/mL (for the detection of 5.0 µg/mL affinity-purified, hyper-immune monkey serum (AP-HIMS)) (Figure 8.).

Figure 8. Drug Tolerance Data at all levels of AP-HIMS.



	Curve Parameter Coefficients					Cut Point (%)	Tolerance (µg/mL)
AP-HIMS (µg/mL)	A	B	C	D	G		
1.25	37.875	1.637	0.87	1.786	10.000	13.1	0.24
2.5	49.802	1.486	0.37	3.592	0.955	13.1	0.99
5.0	61.131	1.691	0.82	0.674	1.160	13.1	1.55
Curve Formula: $F(x) = D+(A-D)/((1+(x/C)^{B})^{G})$.							

Population pharmacokinetic analysis

The MAH submitted two population pharmacokinetic reports (Protocols I1F-MC-RHBV and I1F-MC-RHBW, Date 9 oct 2018; Protocol I1F-MC-RHBX, Date 17 Jul 2019). The models will be referred to as rad-axSpA (patients with radiographic axial spondyloarthritis, studies RHBV and RHBW) model and nr-axSpA (patients with nonradiographic axial spondyloarthritis, study RHBX) model.

The base population PK model in both reports was based on the final population PK models in patients with psoriasis (Ps) and Ps/psoriatic arthritis (PsA), i.e. the nr-axSpA and r-axSpA PK model was structurally similar to the Ps and Ps/PsA models. The existing base PK model is a 2-compartment linear model with first-order absorption. As part of the parameter re-estimation procedure, the same covariates that were retained in the final Ps and Ps/PsA PK models were evaluated (i.e., weight on clearance and volume terms, ADA titer and NAb status on clearance, and site of injection on bioavailability) and only retained in the base PK model if the effects remained significant. The additional covariate effects that were significant only in the r-axSpA or nr-axSpA PK model were tested in the second stage of this analysis.

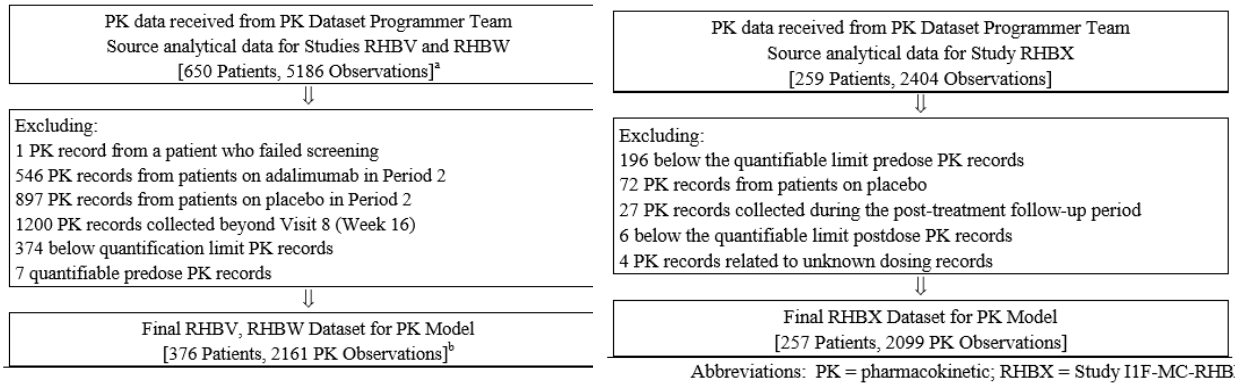
Several covariates were listed in the analysis plan to be tested; however, if there were insufficient patients in any of the subgroups to support the evaluation, they were not tested. The covariates bodyweight, injection site, ADA titer, concomitant corticosteroid use, concomitant NSAIDs, concomitant cDMARD use, race, baseline disease activity (BASDAI or ASDAS), disease duration and

baseline hs-CRP level were assessed. In addition, screening MRI/hs-CRP status was assessed for nr-axSpA (study RHBX) and prior TNFi use and study (TNFi-experienced versus bDMARD-naïve) were assessed for rad-axSpA (studies RHBV and RHBW). In both the nr-axSpA and r-axSpA model, only concomitant use of the cDMARD, hydroxychloroquine, was not tested individually as only 0.0476% and 0.266% of patients in the PK dataset were taking it, respectively.

Study RHBV and RHBW (Rad-axSpA) Population pharmacokinetic model

The population PK dataset included data from 376 patients (**Table 6**). Median age and weight were 43 years and 77.0 kg and the majority of patients were male (79.3%) and white (72.6%). Regarding concomitant medication, 82.2% had NSAIDs, 22.6% had COX-2 inhibitors, 10.4% had oral corticosteroids, 30.9% had all cDMARDs, 22.1% had Sulfasalazine, 9.0% had Methotrexate and 0.3% had Hydroxylchloroquine.

Table 6: Pharmacokinetic Analysis Data



Abbreviations: PK = pharmacokinetic; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW.

[a] 341 patients and 2732 PK observations from Study RHBV; 309 patients and 2454 PK observations from Study RHBW.

[b] 164 patients and 970 PK observations from Study RHBV; 212 patients and 1191 PK observations from Study RHBW.

The effect of a patient being bDMARD-naive (Study RHBV) versus TNFi-experienced (Study RHBW) was evaluated on clearance through inclusion of a study effect. In the final model, ADA (titer), weight and baseline hs-CRP, study effect were the covariates retained in the model (**Table 7**).

For the population PK analysis of data in patients with r-axSpA in Studies RHBV and RHBW combined, the effect of fixing the exponents to 0.75 for CL terms and 1 for V terms has subsequently been conducted, and there was an increase in the objective function value of 15 points compared with the model where exponents were estimated and an increase in interindividual variability (IIV) of V3 from 33.1% to 37.0%. Therefore, the model with estimated exponents seems most appropriate. When the *post hoc* PK parameter estimates from the models with estimated and fixed exponents were compared there was essentially no difference in individual CL parameters between the 2 models and a small difference in the total volume of distribution (Vd) estimates. In the final population PK model in patients with radiographic axial spondyloarthritis (r-axSpA) using data from Studies RHBV and RHBW, shrinkage was 4.53% for clearance (CL) and 36.4% for volume of distribution of the peripheral compartment (V3).

Visual predictive check of the final population pharmacokinetics model in patients with rad-axSpA are provided in Figure 9. Concentrations at Week 1 are non-troughs for both the Q2W and Q4W regimens and concentrations at Week 2 are non-troughs for the Q4W regimen; all other time points are Ctrough.

Table 7: Pharmacokinetic and Covariate Parameters in the Final Population Model in Patients with Rad-axSpA

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-Patient Variability (%SEE)[b]
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.00816 (0.00673 – 0.0124, 11.1)	---
Clearance		
Parameter for CL (L/hr)	0.0161 (0.0152 – 0.0170, 2.76)	29.0% (25.9% - 31.3%, 8.86)
Effect of baseline hs-CRP on CL[c]	0.00875 (0.00627 – 0.0114, 15.0)	
Titer effect on CL[c]	0.0838 (0.0406 – 0.148, 30.9)	
Study effect on CL[c]	-0.148 (-0.197 – (-0.0947), 17.6)	
Parameter for Q (L/hr)	0.0274 (0.0194 – 0.0440, 20.3)	---
Weight effect on CL and Q[c, d]	0.813 (0.653 – 0.977, 10.2)	---
Volume of Distribution		
Parameter for V_2 (L)	2.50 (1.56 – 3.94, 22.2)	---
Parameter for V_3 (L)	4.23 (3.44 – 4.83, 7.80)	33.1% (20.7% - 46.8%, 31.0)
Weight effect on V_2 and V_3[e]	0.673 (0.499 – 0.844, 12.6)	---
Bioavailability		
Parameter for F	0.72 (FIXED)[f]	---
Residual Error (proportional)	20.1% (17.9% - 22.2%, 5.67)	

Abbreviations: ADA = antidrug antibody; hs-CRP = high-sensitivity C-reactive protein; CI = confidence interval; CL = clearance; F = bioavailability; IV = intravenous; Ka = absorption rate constant; LOG_e = natural logarithm; Ps = plaque psoriasis; PsA = psoriatic arthritis; Q = inter-compartmental clearance; r-axSpA= radiographic axial spondyloarthritis; SEE = standard error of the estimate; V_2 = volume of distribution of the central compartment; V_3 = volume of distribution of the peripheral compartment.

a The CI was estimated by bootstrap.

b Inter-individual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects (for CL and V_3): $\%IIV = 100 \times \sqrt{(exp^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the relevant parameter.

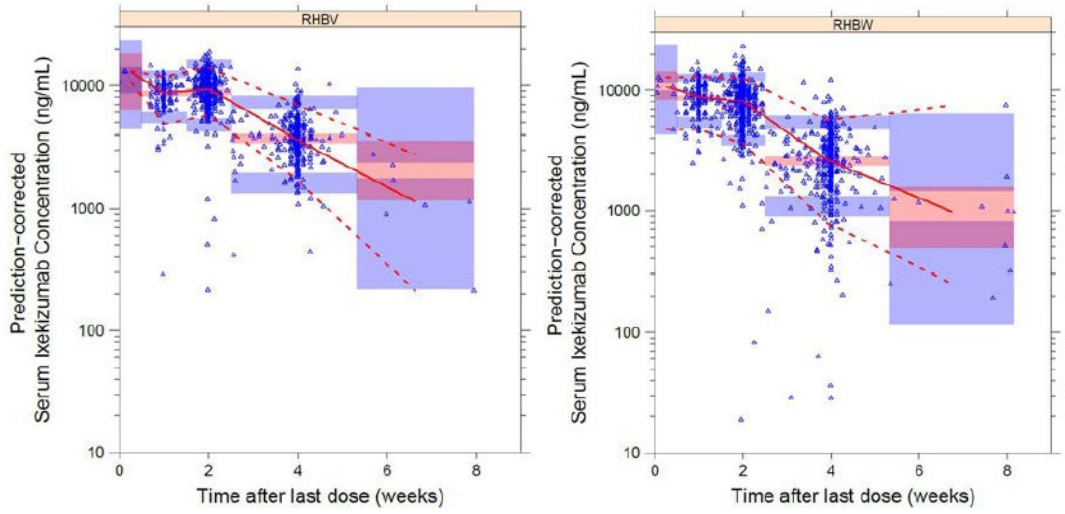
c The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{individual}$ = CL*(bodyweight/89.9)$^{0.813}$*(1+0.00875*(hs-CRP-8.32))*(1+0.0838*LOG_e(ADA titer))*(1+STDY*-0.148) where 8.32 is the median baseline hs-CRP of the population given ixekizumab as treatment in Period 2 and STDY is 1 for Study RHBV and 0 for Study RHBW.

d $Q_{individual}$ = Q * (bodyweight/89.9)$^{0.813}$.

e $V_{2,individual}$ = V_2 * (bodyweight/89.9)$^{0.673}$, $V_{3,individual}$ = V_3 * (bodyweight/89.9)$^{0.673}$

f Bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the r-axSpA analysis.

Figure 9. Visual predictive check of the final population pharmacokinetics model in patients with rad-axSpA [Study RHBV (top panel) and Study RHBW (lower panel)].



Abbreviations: RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW. The blue triangles are observations. The solid red line depicts the median of the observed data, and the red dashed lines represent the 5th and 95th percentiles of the observed data. The pink shaded area defines the 95% confidence interval around the median of the simulated data. The blue shaded areas are the model predicted 95% confidence intervals of 5th and 95th percentiles of the simulated data.

Study RHBX (Nr-AxSpA) population PK model

A total of 2105 post-dose concentrations from 257 patients were available up to and including Week 52 in Study RHBX. Of the total 2105 PK observations, 6 (0.285%) were below the quantifiable lower limit of the PK assay and were excluded from the population PK analysis. Therefore, there were a total of 2099 post-dose samples, approximately 8 samples per patient on average, available for the population PK analysis. The following concomitant medications were used: NSAIDs (89.1% of patients were taking them including COX-2 inhibitors), oral corticosteroids (14.8%), and cDMARDs (sulfasalazine, methotrexate, and hydroxychloroquine) evaluated as a single group (40.5%) and sulfasalazine (24.9%) and methotrexate (16.3%).

Ixekizumab concentration-time data are summarized over 2 time periods:

1. from Week 0 to 16, during which no changes were permitted to the study treatment (placebo or ixekizumab)
2. from Week 0 to 52, which includes the period from Week 16 to 44 when patients could be switched to ixekizumab 80 mg Q2W rescue treatment and therefore their treatment may have changed over time. To summarize the PK data by treatment group meaningfully over the full 52 weeks of the study, the change in ixekizumab dose or change from placebo to ixekizumab needs to be taken into account.

The effects of body weight on clearance terms and ADA titer on clearance were the covariates retained in the nr-axSpA base model. Once the base structural model was established, potentially significant covariates were evaluated using the SCM procedure. No additional covariates were significant. There was no change from the final base model, therefore it is considered the final model (**Table 8** ,Figure 10.).

For the population PK analysis of data in patients with nr-axSpA in Study RHBX, the effect of fixing the exponents to 0.75 for CL terms and 1 for V terms has subsequently been conducted, and there was an increase in the objective function value of 10 points compared with the model where an exponent on CL terms was estimated and an increase in IIV of V3 from 87.3% to 89.8%. Therefore, the model with estimated exponents on CL only seems most appropriate. When the post hoc PK parameter estimates from the models with estimated and fixed exponents were compared, there was essentially no difference in individual CL parameters between the 2 models and a small difference in the Vd estimates.For Study RHBX, shrinkage from the final model was 3.69% for CL and 22.1% for V3.

Table 8: Pharmacokinetic Parameters in the Base Population Model in Patients with nr-axSpA (Base and Final Models are the Same)

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-Individual Variability (95%CI, %SEE)[a,b]
Rate of Absorption		
Parameter for Ka (hr-1)	0.00447 (0.00388 – 0.0650, 12.7)	---
Clearance		
Parameter for CL (L/hr)	0.0149 (0.0140 – 0.0157, 2.83)	32.2% (29.0% - 35.5%, 9.64)
Titer effect on CLc	0.0557 (0.0204 – 0.102, 34.8)	---
Parameter for Q (L/hr)	0.0171 (0.0135 – 0.0252, 17.0)	---
Weight effect on CL and Q[c,d]	0.845 (0.673 – 1.04, 11.3)	---
Volume of Distribution		
Parameter for V2 (L)	1.33 (0.611 – 2.13, 23.2)	---
Parameter for V3 (L)	3.77 (3.29 – 4.25, 6.31)	87.3% (54.8% - 117%, 26.1)
Bioavailability		
Parameter for F1	0.72 (FIXED)[e]	---
Residual Error (proportional)	21.2% (19.3% - 23.0%, 4.34)	

Abbreviations: ADA = antidrug antibody; CI = confidence interval; CL = clearance; F = bioavailability; IV = intravenous; Ka = absorption rate constant; LOG_e = natural logarithm; Ps = plaque psoriasis; PsA = psoriatic arthritis; Q = inter-compartmental clearance; nr-axSpA = non-radiographic axial spondyloarthritis; SEE = standard error of the estimate; V_2 = volume of distribution of the central compartment; V_3 = volume of distribution of the peripheral compartment.

[a] The CI was estimated by bootstrap.

[b] Inter-individual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects (for CL and V_3): $\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the relevant parameter.

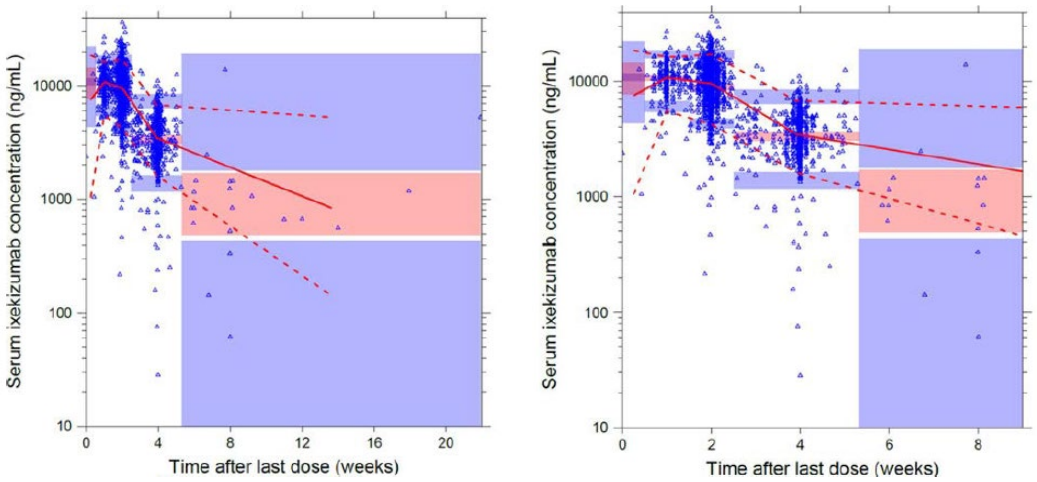
[c] The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{individual}$ = CL*(bodyweight/89.9)$^{0.845}$*(1+0.0557*LOG_e[ADA titer]).

[d] $Q_{individual}$ = Q * (bodyweight/89.9)$^{0.845}$

[e] Bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the nr-axSpA analysis.

Note: The final population model is the same as the base population model

Figure 10. Prediction-corrected Visual predictive check of the final population pharmacokinetic model in patients with nr-axSpA (full time axis – top plot; truncated time axis – bottom plot).



The blue triangles are observations. The solid red line depicts the median of the observed data, and the red dashed lines represent the 5th and 95th percentiles of the observed data. The pink shaded area defines the 95% confidence interval around the median of the simulated data. The blue shaded areas are the model predicted 95% confidence intervals of 5th and 95th percentiles of the simulated data.

Comparison of Model-Estimated Ixekizumab Pharmacokinetic Parameters between Patient Populations

Table 9. shows the comparison of the model-estimated PK parameters in different populations (nr-axSpA, r-axSpA, Ps and PsA).

Table 9: Comparison of Model-Estimated Ixekizumab Pharmacokinetic Parameters between Patients with Nonradiographic and Radiographic Axial Spondyloarthritis, Psoriasis, and Psoriatic Arthritis[a]

PK Parameter	nr-axSpA PK Analysis	r-axSpA PK Analysis	Ps PK Analysisb	PsA PK Analysisc
CL (L/hr)	0.0129 (36%)	0.0144 (38%)	0.0161 (37%)	0.0147 (33%)
Vss (L)	5.28 (46%)	6.13 (19%)	7.11 (29%)	6.02 (18%)
t1/2 (days)	12 (61%)	12 (36%)	13 (40%)	12 (32%)
%F (range)	72 FIXEDd	72 FIXEDd	60 to 90	61 to 84d
Median BW (kg)	76.6	77.0	89.9	83.1 – 87.6

Abbreviations: BW = body weight; CL = clearance; F = bioavailability; IV = intravenous; nr-axSpA = nonradiographic axial spondyloarthritis; %CV = percent coefficient of variation; PK = pharmacokinetics; r-axSpA = radiographic axial spondyloarthritis; Ps = plaque psoriasis; PsA = psoriatic arthritis; SC = subcutaneous; $t_{1/2}$ = half-life calculated as $0.693*(V_2+V_3)/(CL*24)$; V_{ss} = volume of distribution at steady state calculated as V_2+V_3; V_2 = volume of distribution of the central compartment; V3 = volume of distribution of the peripheral compartment.

[a] Data are summarized using the first occurrence of time-varying post hoc individual PK parameters in each analysis. Data are reported as geometric mean (geometric CV%).

[b] Parameters were estimated using data from 3 Ps studies (I1F-MC-RHAG [RHAG], I1F-MC-RHAJ [RHAJ], and I1F-MC-RHAZ [RHAZ]) for analysis (reported in the Ps submission).

[c] The data from the 2 PsA studies (I1F-MC-RHAP and I1F-MC-RHBE) were combined with data from 3 Ps studies (RHAG, RHAJ, and RHAZ) for analysis, parameters were calculated and summarized using post hoc values from patients in the 2 PsA studies.

[d] Only SC administration was evaluated in Studies I1F-MC-RHBV, I1F-MC-RHBW, and I1F-MC-RHBX; therefore the typical value of bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the nr-axSpA and r-axSpA analyses.

2.3.3. Pharmacodynamics

Mechanism of action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis as well as in the pathogenesis of psoriatic arthritis. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F. The pharmacological class for ixekizumab is 'interleukin-17A antagonist'. Interleukin-17A, a member of the IL-17 family, is produced mainly by inflammatory Th17 cells, a subset of T helper cells, but also by other T cells, neutrophils, and mast cells.

Primary and secondary pharmacology

In patients with axSpA, increased numbers of IL-17A-producing cells are present in the peripheral blood, as well as elevated levels of IL-17 in the serum and synovium. Neutralisation of IL-17A has been shown to inhibit the pathological cellular events, as well as mitigate disease activity in patients with axSpA. The demonstration of increased IL-17-producing Th17 lymphocyte numbers and serum IL-17 levels in axSpA is consistent with a direct role of Th17 lymphocytes in this disease. Interleukin-17 secreting cells have also been detected in situ in the bone marrow of facet joints obtained from patients with axSpA.

2.3.4. PK/PD modelling

Analyses of exposure-response relationships were conducted using both exploratory graphical approaches and model-based approaches. Post hoc PK parameters from the final population PK model were merged with dosing records and ASAS20/40 data to carry out sequential PK/PD modelling.

Table 10: Index of Studies and Analyses Supporting the Summary of Clinical Pharmacology

Analysis	Studies included	Patient populations included	Time course of evaluation
Population PK	RHBV/RHBW integrated	r-axSpA	Up to Week 16
	RHBX	nr-axSpA	Up to Week 52
Population PK/PD (exposure-efficacy)	RHBV/RHBW integrated	r-axSpA	Static time point model: Week 16 only

Analysis	Studies included	Patient populations included	Time course of evaluation
			Time course model: Up to Week 16
	RHBX	nr-axSpA	Static time point model: Week 16 only Time course model: Up to Week 52
Population PK/PD (exposure-safety)	RHBV/RHBW/ RHBX integrated	r-axSpA and nr-axSpA	Up to Week 16

2.3.4.1. Exposure-efficacy

The primary efficacy endpoint, ASAS40, was measured at Week 16, and also week 52 in study RHBX. The secondary efficacy endpoint ASAS20 was also measured at the same time points as ASAS40.

The ASAS20/40 Week 16 static time point logistic regression model was used to explore the potential relationship between ixekizumab trough concentration (Ctrough) and ASAS20/40 responses at Week 16. Patients were required to have an ASAS20 and/or ASAS40 response recorded at Week 16 and a Week 16 Ctrough as a measure of their steady-state drug exposure. All covariate effects were tested on baseline disease parameter (B1) and drug effect (DRUG) in the ASAS20/40 Week 16 static time point PK/PD model (except starting dose for the nr-axSPA model), which was tested only on the drug effect.

Efficacy data were also evaluated using the time-course model. This model describes the temporal profile of the ASAS20/40 responses and uses all data at all time points of the study, thus observed data were used rather than non-responder imputation (NRI) for ASAS20/40 response. Covariate effects were tested on B1, EFF, and PLA in the ASAS20/40 time-course PK/PD model.

Stepwise covariate modelling was used to evaluate covariates. The covariates bodyweight, age, gender, race, baseline disease activity (BASDAI or ASDAS), baseline hs-CRP, disease duration, baseline HLA B27 status, concomitant corticosteroid use, concomitant NSAIDs, concomitant cDMARD use and starting dose were tested. In addition screening MRI/hs-CRP status was assessed for nr-axSpA (study RHBX) and ADA titer and study (TNFi-experienced versus bDMARD-naive) were assessed for rad-axSpA (studies RHBV and RHBW). Neutralizing antibody status was not tested in either model due to the low incidence reported.

ASAS20/40 Week 16 Static Time Point Model

The range of exposures obtained in this study supported use of a simple slope model as follows:

EFF=SLP* LOGe(CMIN+1)

LGE1 = B1 + EFF

LGE2 = B1 - B2 + EFF

Where EFF represents drug effect (Slope model); CMIN is the Ctrough at Week 16; LGE1 and LGE2 are the logits for DV≥1 (ASAS20/40) and DV≥2 (ASAS40) respectively; and B1 and B2 correspond to the

baseline disease activity (in this model, this is a combination of baseline and placebo effects) used for the calculation of the logits for DV≥1 (ASAS20/40) and DV≥2 (ASAS40).

- ***Studies RHBV and RHBW (rad-axSpA)***

The final data set contained 312 patients on ixekizumab and 180 patients on placebo.

The effect of study (bDMARD-naive versus TNFi-experienced) was evaluated in the base model and found to be significant and, therefore, it was incorporated in the selected base model in order to avoid biases in the quantification of the drug effect. The effect of study was best described by including an additive parameter on B1 for study RHBV in the bDMARD-naive population.

After forward inclusion and backward elimination using the SCM procedure in PsN, the only additional covariate that was significant and retained in the ASAS20/40 Week 16 static time point model was age on B1, indicating that older patients have higher disease activity at baseline compared to younger patients, best described using a linear relationship.

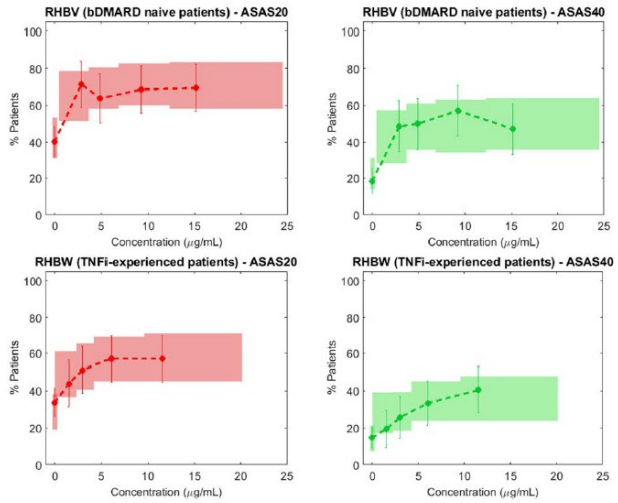
Table 11: Pharmacodynamic Parameter Estimates from the Final Population ASAS20/40 Week 16 Static Time Point Model

Parameter	*Population Estimate (%RSE*)	*95% CI from Bootstrap*
B1 (TNFi-experienced)	-0.795 (21.89)	-1.11 – -0.472
B1 (bDMARD-naive)[a]	-0.322 (37.42)	-0.983 – 0.373
B2	0.953 (9.171)	0.797 – 1.136
SLP	0.125 (17.44)	0.084 – 0.169
Age Effect on B1	-0.0291 (24.88)	-0.044 – -0.0115

Abbreviations: %RSE = relative standard error; ASAS = Assessment of Spondyloarthritis International Society; B1 = Baseline disease response for ASAS20 (DV ≥1); B2 = Baseline disease response for ASAS40 (DV ≥2); bDMARD = biological disease-modifying antirheumatic drug; CI=confidence interval; DV = 0 corresponds to ASAS20=0, DV = 1 to ASAS20=1 but ASAS40=0, DV = 2 to ASAS40=1; LOGe = natural logarithm; SLP = Slope parameter for drug effect [SLP*LOGe(CMIN+1)] where CMIN is the observed serum trough ixekizumab concentration at Week 16; TNFi = tumor necrosis factor inhibitor; Age effect on B1: B1Age = (0 -0.0291 *(Age – 43.0)).

[a] B1 (bDMARD-naive) = B1(TNFi-experienced) + 0.473 = -0.322

Figure 11. Visual predictive check of ASAS20/40 Week 16 final static time point model (rad-axSpA).



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; bDMARD = biological disease-modifying antirheumatic drug; RHBV = Study I1FMC- RHBV; RHBW = Study I1F-MC-RHBW; TNFi = tumor necrosis factor inhibitor. Circles with dashed lines represent the observed percentage of patients achieving ASAS20 (red) and ASAS40 (green) in each quartile of Week 16 Ctrough (number of patients in each bin N=35 [RHBV] and N=42 [RHBW]) or for placebo (number of patients in each bin N=86 [RHBV] and N=94 [RHBW]). The first point in the plots corresponds to concentration of 0 µg/mL representing observed response rate in placebo patients. The shaded area is the predicted 90% confidence interval of response from the model. Symbols represent the observed response rates at Week 16 and the error bar represents the 90% confidence interval of the observed response.

- ***Studies RHBX (nr-axSpA)***

The ASAS20/40 Week 16 time point analysis dataset included 280 patients who received ixekizumab (N=181) or who received placebo (N=99) in Period 2.

After forward inclusion and backward elimination using the SCM procedure in PsN, the only additional covariate that was significant in the ASAS20/40 Week 16 static time point model was age on SLP, however, the standard error of the SLP-Age effect was found to be very high (81.8%RSE), indicating poor precision in estimation of the parameter and therefore the age effect on SLP was removed from the final model. Therefore, the base model is also the final model.

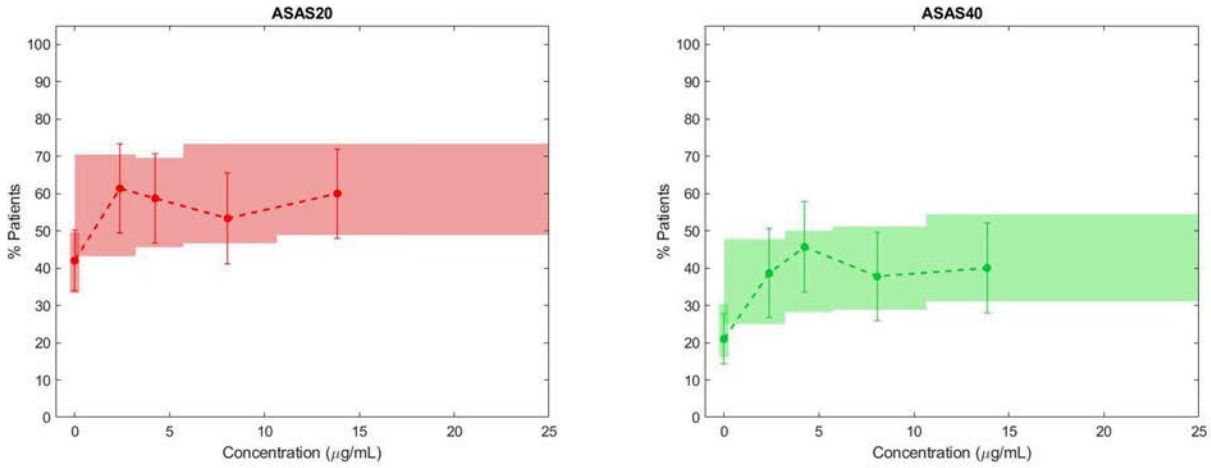
Table 12: Pharmacodynamic Parameter Estimates from the Final Population ASAS20/40 Week 16 Static Time Point PK/PD Model

Parameter	Population Estimate (%RSE)	95% CI from Bootstrap
B1	-0.382 (16.4a)	-1.02 – 0.200a
B2	0.808 (12.6)	0.610 – 1.03
SLP	0.0886 (30.3)	0.0331 – 0.151

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; B1 = baseline disease response for ASAS20 (DV ≥1); B2 = baseline disease response for ASAS40 (DV ≥2); CI = confidence interval; DV = dependent variable (DV = 0 corresponds to ASAS20=0, DV = 1 to ASAS20=1 but ASAS40=0, DV = 2 to ASAS40=1); LOGe = natural logarithm; PD = pharmacodynamics; %RSE = relative standard error; PK = pharmacokinetics; SLP = slope parameter for drug effect (SLP*LOGe[CMIN+1]) where CMIN is the observed serum trough ixekizumab concentration at Week 16.

a %RSE and 95% CI for B1 correspond to a secondary parameter that equals B1 – B2, which was needed to improve model stability.

Figure 12. Visual predictive check of Final ASAS20/40 Week 16 static time point PK/PD model.



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; Ctrough = trough concentration; N = number of patients; PD = pharmacodynamics; PK = pharmacokinetics. Circles with dashed lines represent the observed percentage of patients achieving ASAS20 (red) and ASAS40 (green) in each quartile of Week 16 Ctrough (number of patients in each bin N=44 to 45) or for placebo (number of patients N=99). The first point in the plots corresponds to a concentration of 0 µg/mL representing observed response rate in patients who received placebo. The shaded area is the predicted 90% confidence interval of response from the model. Symbols represent the observed response rates at Week 16 and the error bar represents the 90% confidence interval of the observed response.

ASAS20/40 Time-Course PK/PD Model

Dataset preparation for the ASAS20/40 time course PK/PD model is presented in **Table 13**. The final data set contained time course information on 376 patients on ixekizumab and 190 patients on placebo.

Table 13: Data disposition: data included in the ASAS20/40 time-course PK/PD model analysis (left panel Studies RHBV and RHBW; right panel: Study RHBX).

ASAS20/40 data received from PK Dataset Programmer Team Source analytical data for Studies RHBV and RHBW [656 Patients, 7619 ASAS20/40 Observations] [a]	ASAS20/40 data received from PK Dataset Programmer Team Source analytical data for Study RHBX [301 patients, 3747 ASAS20/40 observations]
⇓	⇓
Excluding: 1119 ASAS20/40 records from patients on adalimumab in Period 2 3194 ASAS20/40 records collected beyond Visit 8 (Week 16)	Excluding: 11 ASAS20/40 records collected from 4 patients after these patients were initiated on treatment with a TNFi 1 ASAS20/40 record collected during the post-treatment follow-up period
⇓	⇓
Final RHBV, RHBW Dataset for ASAS20/40 Time Course PK/PD Model [566 Patients, 3306 ASAS20/40 Observations] [b]	Final RHBX Dataset for ASAS20/40 Time Course PK/PD Model 301 Patients, 3735 ASAS20/40 Observations; including at Week 0 randomization: 103 on placebo; 102 on Q2W; and 96 on Q4W]

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society response; PD=pharmacodynamic; PK = pharmacokinetic; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F- MC-RHBW; RHBX = Study I1F- MC-RHBX; TNFi=tumor necrosis factor inhibiotr.
[a]340 patients and 4233 ASAS20/40 observations from Study RHBV; 316 patients and 3386 ASAS20/40 observations from Study RHBW.
[b]250 patients and 1487 ASAS20/40 observations from Study RHBV; 316 patients and 1819 ASAS20/40 observations from Study RHBW.

- ***Studies RHBV and RHBW (rad-axSpA)***

The drug effect was found to be best described by a slope function using log-transformed drug concentrations predicted by the population PK model as the exposure input. The effect of study (bDMARD-naïve versus TNFi-experienced) was evaluated in the base model on the baseline disease activity parameter, B1, and found to be significant. After forward inclusion and backward elimination from the SCM procedure in PsN, the covariate effects that were retained in the final ASAS20/40 time-course PK/PD model were age and study/population on B1 (the baseline disease effect) and baseline hs-CRP and gender on SLP (the drug effect parameter).

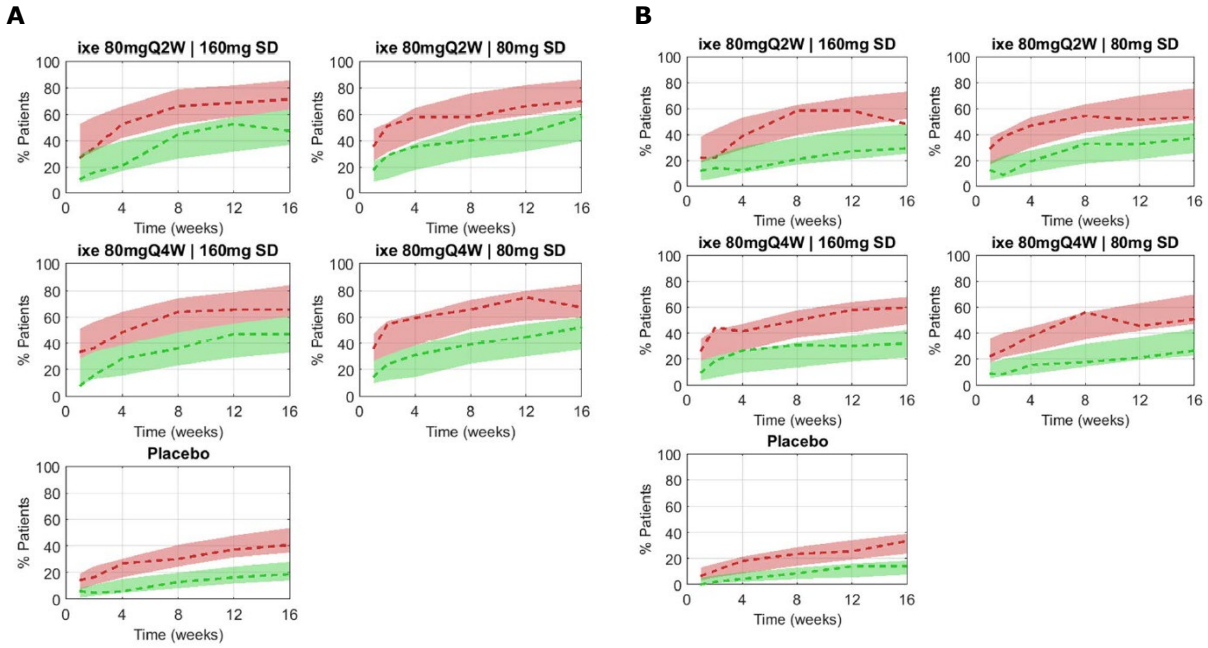
Table 14: Parameter Estimates from the Final Population Ixekizumab ASAS20/40 Week 16 Time Course Model

Parameter	**Population Estimate (%RSE)**	**95% CI from Bootstrap**
B1 (TNFi-experienced)	-2.95 (6.51)	-3.35 – -2.61
B1 (bDMARD-naive)[a]	-2.457 (29.2)	-3.14 – -1.81
B2	1.14 (4.97)	1.05 – 1.26
SLP	0.163 (12.2)	0.122 – 0.202
SLPpla	0.778 (6.44)	0.676 – 0.887
Age effect on B1	-0.0253 (23.5)	-0.038– -0.013
Baseline hs-CRP on SLP	0.198 (29.6)	0.089 – 0.340
GEN on SLP	-0.441 (33.3)	-0.761- -0.144

Abbreviations: %RSE = relative standard error; ASAS = Assessment of Spondyloarthritis International Society; B1 = Baseline value for DV ≥1; B1 - B2 = Baseline value for DV ≥2, where DV = 0 corresponds to ASAS20=0, DV = 1 to ASAS20=1 but ASAS40=0, DV = 2 to ASAS40=1; baseline hs-CRP = baseline high sensitivity C-reactive protein; bDMARD = biological disease-modifying antirheumatic drug; CI=confidence interval; GEN = gender; LOG_e = natural logarithm; SLP = Slope parameter for drug effect [SLP* LOG_e(Conc+1)] where Conc is the model-predicted serum ixekizumab concentration; SLP_{pla} = Slope parameter for placebo effect [SLP_{pla} * LOG_e(Time+1)]; Age effect on B1: B1AGEE = -0.0253*(AGEE - 43.00); Baseline hs-CRP effect on SLP: SLPbaselinehs-CRP = ((baseline hs-CRP/8.33)**0.198; Gender on SLP: SLPGEN = (1 - 0.441) if female); TNFi = tumor necrosis factor inhibitor.

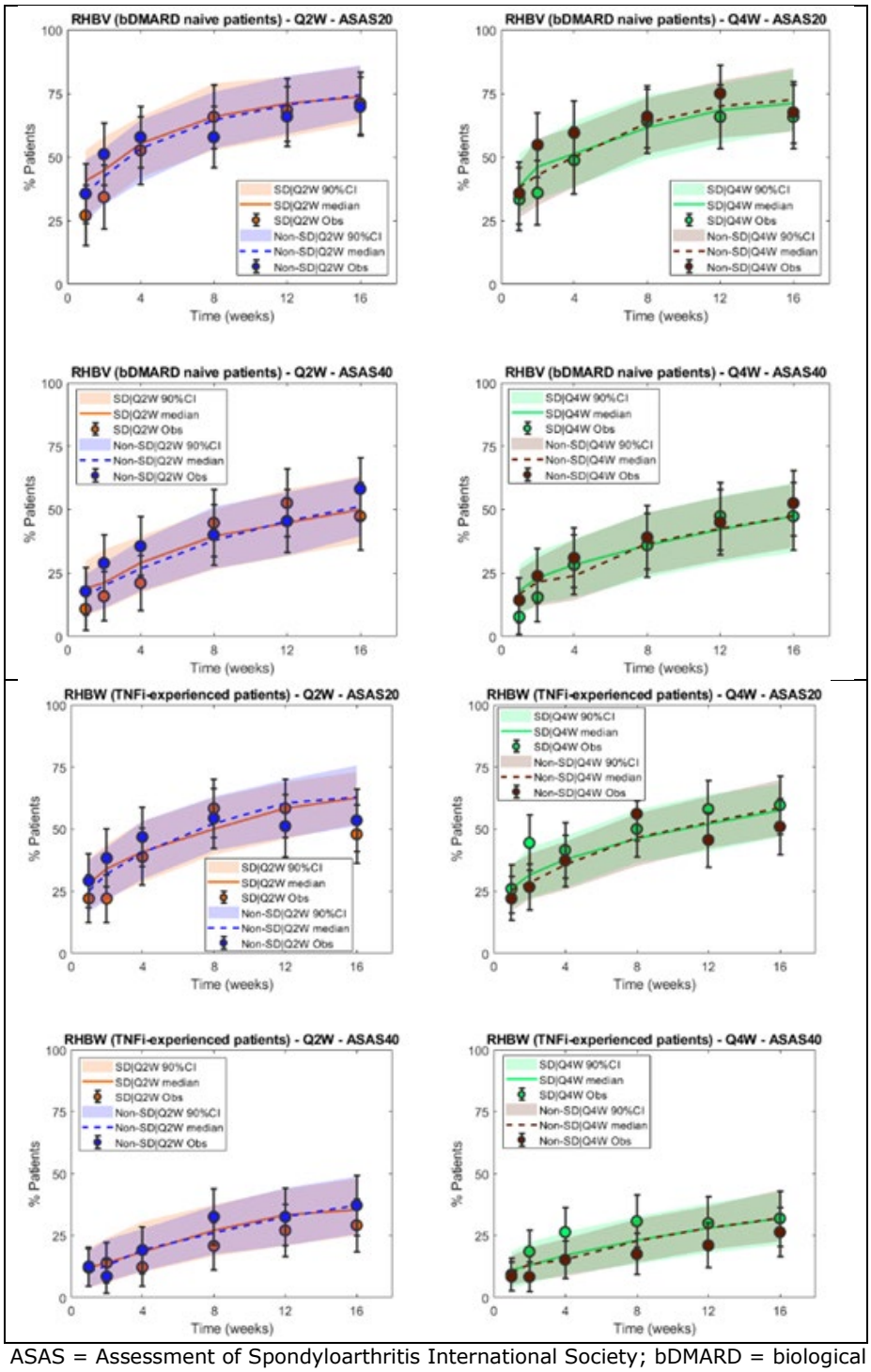
[a] B1 (bDMARD-naive) = B1(TNFi-experienced) + 0.493 =-2.457

Figure 13. Visual predictive check from the final ASAS20/40 time course PK/PD model (A: Study RHBV, B: Study RHBW).



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ixe = ixekizumab; PD = pharmacodynamic; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBV = Study I1F-MC-RHBV; SD = starting dose. Dashed lines represent the observed average percentage of patients achieving ASAS20 (red) and ASAS40 (green) by time (weeks) for ixekizumab Q2W (upper), ixekizumab Q4W (center) and placebo patients (bottom), respectively. Ixekizumab arms with the 160-mg starting dose are shown on the left. Ixekizumab arms with the 80-mg starting dose are shown on the right. The shaded area is the predicted 90% confidence interval from the model.

Figure 14. Model prediction intervals of the starting dose effect (160 mg versus 80 mg) on ASAS20/40 response per treatment arm over the 16-w eek treatment period.



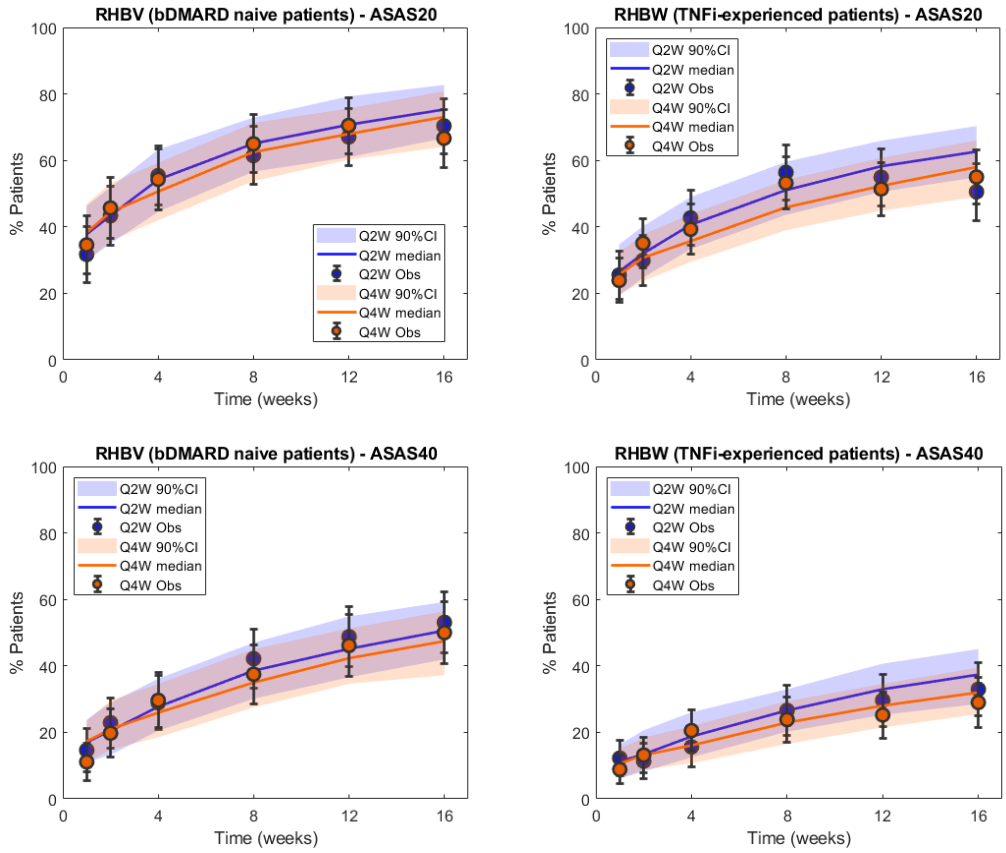
Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; bDMARD = biological disease-modifying antirheumatic drug; CI = confidence interval; non-SD = starting dose of 80 mg; Obs = observed; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; SD = starting dose of 160 mg; TNFi = tumour necrosis factor inhibitor.

Notes:

The shaded area is the predicted 90% CI from the model for percentage of patients achieving ASAS20 (plots in rows 1 and 3) and ASAS40 (plots in rows 2 and 4) by time (weeks) for ixekizumab 80 mg Q2W (blue/orange; left hand side) and 80 mg Q4W (green/brown; right hand side).

Solid lines correspond to the median response of simulated arms with the 160-mg starting dose (orange for Q2W; green for Q4W). Dashed lines represent median response of the simulated arms with the 80-mg starting dose (blue for Q2W; brown for Q4W).
The points are the observed percentage of patients achieving ASAS20 and ASAS40 at all time points up to Week 16.
Error bars represent the observed 90% CI of the response.

Figure 15. Model simulations of the ASAS20/40 response rates with the ixekizumab 80-mg Q2W versus 80-mg Q4W dosing regimens over the 16-week treatment period.



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; bDMARD = biological disease-modifying antirheumatic drug; CI = confidence interval; Obs = observed; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; TNFi = tumour necrosis factor inhibitor.
Note: The shaded area is the predicted 90% CI from the model for percentage of patients on ixekizumab Q2W (blue) and ixekizumab Q4W (orange) achieving ASAS20 (upper panels) and ASAS40 (lower panels) responses over time. Dosing regimens are not separated out by starting dose in these plots. Solid lines correspond to the median response of the simulated Q2W and Q4W arms. Symbols represent the observed response rates at all time points up to Week 16 and the error bar represents the observed 90% CI of the response.

Simulations were conducted to evaluate the impact of age, baseline hs-CRP, gender and baseline bodyweight on ASAS20/40 response rates, for the Q2W versus the Q4W dosing regimen for each population. The data were divided into 2 categories based on being lower or higher than the median of each covariate of the patients in the PK/PD dataset. Younger patients had consistently higher rates of response over the 16-week period compared to older patients. The slopes of the response rates were similar for each age group which is consistent with the higher disease activity observed at baseline in older patients compared with younger patients and a lack of an effect of age on the drug effect

parameter. Although patients with lower baseline hs-CRP levels achieved lower levels of ASAS20/40 response at Week 16 compared with patients with higher baseline hs-CRP levels, the rates of ASAS20/40 response were similar for each sub-group over the 16-week treatment period as shown by similar slopes over time. This suggests the covariate had a small overall impact on the drug effect. Although female patients achieved lower levels of ASAS20/40 response by Week 16 compared with males, they achieved ASAS20/40 responses at broadly similar rates over the 16-week period compared with male patients indicating that the covariate had a small overall impact on the drug effect. With regard to baseline bodyweight, there was an overlap in predicted response rates between higher and lower weight patients indicating the effect of weight on PK did not translate into an impact on ASAS20/40 response rates. The lack of effect of body weight was consistent across dosing regimens and in both patient populations.

- ***Study RHBX (nr-axSpA)***

The drug effect was found to be best described by a slope function using log-transformed drug concentrations predicted by the population PK model as the exposure input. The dataset used in the ASAS20/40 time-course PK/PD model included all observed ASAS20/40 response data up to and including Week 52. The dataset consisted of data from 301 patients who received ixekizumab from Week 0 (N=198) or who received placebo from Week 0 (N=103). Individual post hoc PK parameters from the final PK model were used as the exposure input for this model.

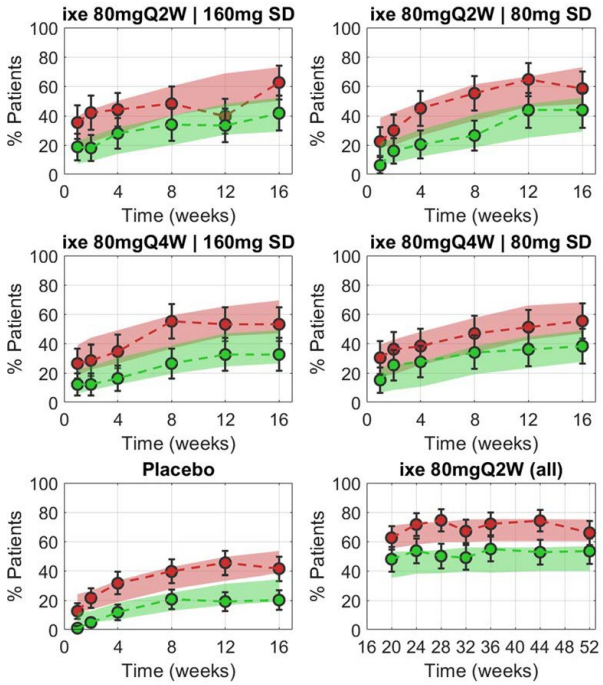
After forward inclusion and backward elimination from the SCM procedure in PsN, the only covariate effect that was retained in the final ASAS20/40 time-course PK/PD model was age on B1 (the baseline disease effect).

Table 15: Parameter Estimates from the Final Population Ixekizumab ASAS20/40 Time Course PK/PD Model

Parameter	Population Estimate (%RSE)	95% CI from Bootstrap
B1	-4.02 (8.68)	-4.94 – -3.24
B2	1.93 (5.07)	1.74– 2.14
SLP	0.154 (20.4)	0.0775 – 0.245
SLPLA	4.38 (6.48)	3.84 – 5.02
KT	0.11 (12.0)	0.0852 – 0.145
Age effect on B1	-0.0712 (22.5)	-0.110– -0.0355
ISV logit	10.4 (11.5)	8.31 – 13.1

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; B1 = baseline value for DV ≥1; B2 = baseline disease response for ASAS40 (DV ≥2); CI = confidence interval; DV = dependent variable (DV = 0 corresponds to ASAS20=0, DV = 1 to ASAS20=1 but ASAS40=0, DV = 2 to ASAS40=1); CI=confidence interval; ISV = inter-subject variability; LOG_e = natural logarithm; PD = pharmacodynamics; %RSE = relative standard error; PK = pharmacokinetics; SLP = slope parameter for drug effect (SLP* LOG_e[Conc+1]) where Conc is the model-predicted serum ixekizumab concentration; SLPLA = parameter for maximum placebo effect; KT = first-order rate to reach the maximum placebo effect [SLPLA*(1-EXP(-KT*t))]; Age effect on B1: B1AGEE = –0.0712 *(AGEE - 40.00)

Figure 16. Visual predictive check from the final ASAS20/40 time course PK/PD model (Study RHBX).



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ixe = ixekizumab; PD = pharmacodynamics; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBX = Study I1F-MC-RHBX; SD = starting dose. Dashed lines represent the observed average percentage of patients achieving ASAS20 (red) and ASAS40 (green) by time (weeks) for ixekizumab Q2W (upper), ixekizumab Q4W (center), patients who received placebo (bottom left) and ixekizumab Week 16 to 52 for the Q2W regimen (bottom right), respectively. Ixekizumab dosing regimen groups with the 160 mg starting dose are shown on the left. Ixekizumab dosing regimen groups with the 80 mg starting dose are shown on the right. The shaded area is the predicted 90% confidence interval from the model.

Simulations were conducted with the final ASAS20/40 time-course PK/PD model to determine the impact of ixekizumab dosing regimen frequency and starting dose on the probability of a patient achieving an ASAS20/40 response at Week 16. Model-predicted CIs for ASAS20 and ASAS40 response rates over 16 weeks of treatment overlapped substantially between the Q4W and Q2W dosing regimens (Figure 17.), with the median response rate being numerically higher for the 80 mg Q2W regimen compared to the 80 mg Q4W regimen (approximately 6% at Week 16 predicted from the time course model). The substantial overlap in predicted responses suggests that the 2 dosing regimens have similar efficacy. The impact of the 160 mg versus the 80 mg starting dose on ASAS20/40 response rates in both the 80 mg Q2W and 80 mg Q4W dosing regimen groups was evaluated. There was substantial overlap in the CIs of the predicted ASAS20/40 response rates irrespective of the starting dose administered at Week 0 (Figure 18.).

Figure 17. Model simulations of the ASAS20/40 response rates with the ixekizumab 80 mg Q2W versus 80 mg Q4W dosing regimens over the first 16 weeks of treatment.

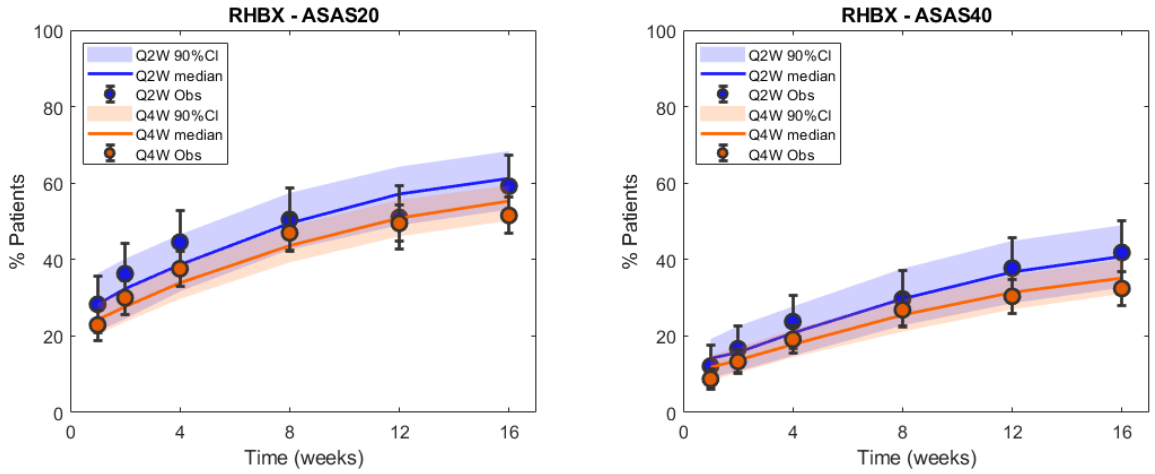
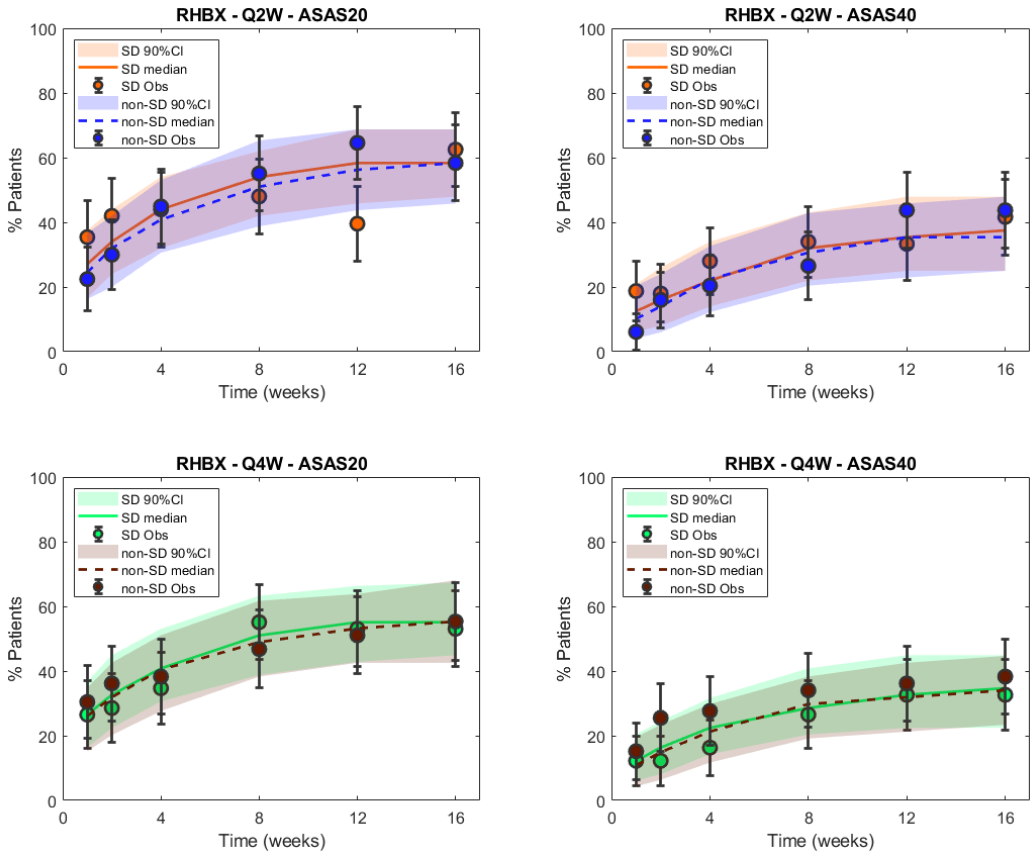


Figure 18. Model prediction intervals of the starting dose effect (160 mg versus 80 mg) on ASAS20/40 response per dosing regimen over the first 16 weeks of treatment.



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; CI = confidence interval; non-SD = starting dose of 80 mg; Obs = observed; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBX = Study I1F-MC-RHBX; SD = starting dose of 160 mg.

Notes: The shaded area is the predicted 90% CI from the model for percentage of patients achieving ASAS20 (left panels) and ASAS40 (right panels) by time (weeks) for ixekizumab 80 mg Q2W (upper row; blue and orange) and 80 mg Q4W (bottom row; green and brown).
Solid lines correspond to the median response of simulated dosing regimen groups with the 160-mg starting dose (orange for Q2W; green for Q4W). Dashed lines represent median response of the simulated dosing regimen groups with the 80-mg starting dose (blue for Q2W; brown for Q4W). The points are the observed percentage of patients achieving ASAS20 and ASAS40 at all time points up to Week 16. Error bars represent the observed 90% CI of the response.

Age at baseline was identified as a significant covariate on the baseline disease activity parameter, B1, whereby older patients had higher disease activity at baseline. The data were divided into 2 categories based on being lower or higher than the median age (40 years) of the patients in the PK/PD dataset. The response rates increased in parallel for the younger and older patients. This suggests that the effect of age was a consequence of differential disease activity at baseline and not due to a drug effect, since age was not a significant covariate on the drug effect parameter in the model. Simulations show that there is no apparent benefit of increasing the dosing frequency based on age.

Baseline body weight was identified as a significant covariate on clearance terms in the PK model where higher body weight was associated with higher CL resulting in lower ixekizumab serum concentrations. The data were divided into 2 categories based on being lower or higher than the median baseline weight (76.4 kg) of the patients in the PK/PD dataset. There was substantial overlap in predicted response rates between patients with higher and lower weight, indicating that the effect of weight on PK did not translate into an impact on ASAS20/40 response rates.

2.3.4.2. Exposure-safety

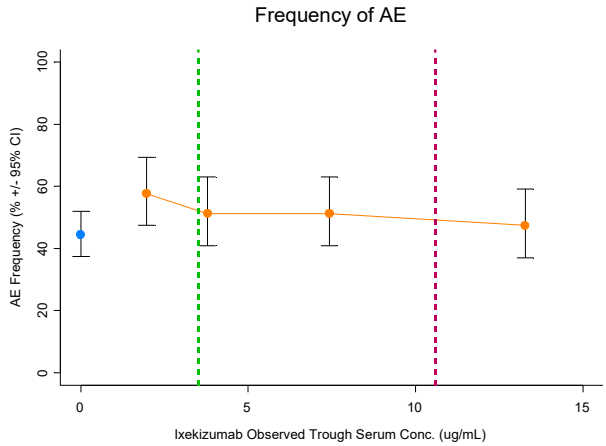
The exposure-safety analysis included data from patients (r-axSPA and nr-axSPA) receiving ixekizumab or placebo up to and including Week 16. Data were included in the analyses if patients had Ctrough measurements at Week 16 and for patients who reported TEAEs or AESIs in the first 16 weeks of treatment. For patients who received placebo who completed to Week 16, Week 16 concentrations were set to zero for plotting.

- ***Studies RHBV and RHBW (rad-axSpA)***

Ixekizumab serum concentrations used in the present analyses were observed Ctrough values from patients at Week 16 (N=181 ixekizumab patients). To summarize safety AEs, Ctrough values were divided into quartiles and the median (range) for each quartile was calculated.

An exposure-response relationship was observed for injection site reaction (ISRs). There were higher incidences of infections (all types) reported with ixekizumab in the 2 upper ixekizumab Ctrough quartiles compared to placebo and the 2 lower ixekizumab Ctrough quartiles.

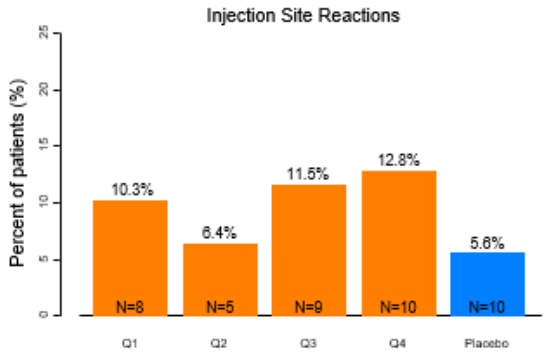
Figure 19. Incidence of treatment-emergent adverse events in the Week 0 to 16 period by ixekizumab trough concentration quartile at Week 16 (Studies RHBV and RHBX).



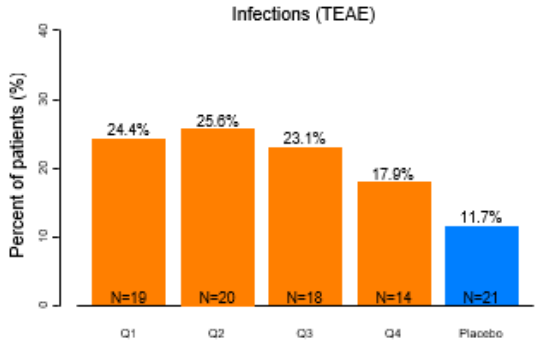
Abbreviations: AE = adverse event; CI = confidence interval; Conc = concentration; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW. Dotted line represents the mean trough concentration per dosing regimen (Red = Q2W, and Green = Q4W. Orange dots represent the incidence of adverse events at each quartile and the median concentration at each quartile. Blue dot represents placebo

Figure 20. Summary of injection site reactions (A) and all infection (B) by ixekizumab trough concentration quartile at Week 16 (Studies RHBV and RHBW combined).

A



B



Abbreviations: N = number of patients who experienced the adverse event; Q = Quartile; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; TEAE = treatment-emergent adverse events.
Trough concentration quartiles: Q1: <2.91 µg/mL. Q2: 2.91 to 5.34 µg/mL. Q3: 5.34-10.6 µg/mL.Q4:≥10.6 µg/mL

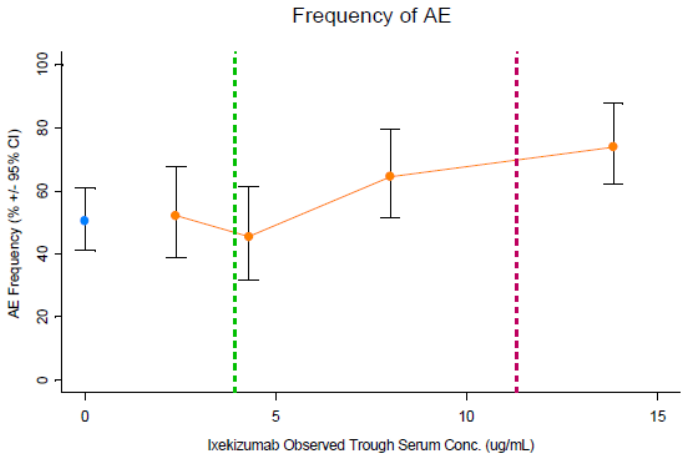
All allergic reactions/hypersensitivity events were non-anaphylactic in nature and there was no relationship with concentration. The remaining AESIs were all reported with low or no incidence in the exposure-safety analysis dataset and thus there were insufficient data to allow an evaluation of the relationship to ixekizumab Ctrough values.

- ***Study RHBX (nr-axSpA)***

Ixekizumab serum concentrations used in the present analyses were observed Ctrough values from patients at Week 16 (N=181 ixekizumab patients). Patients were included if their Week 16 concentration met the trough definition. To summarize safety AEs, Ctrough values were divided into quartiles and the median (range) for each quartile was calculated. Data beyond Week 16 were not evaluated for study RHBX due to the large proportion of patients who were deemed inadequate responders and assigned to ixekizumab 80 mg Q2W rescue treatment between Weeks 16 and 44 of the study. The change in treatment or dose confounds the assessment of the relationship with concentrations during this period and thus the analysis could not be performed. In study RHBX (nr-axSPA), a total of 144 patients (47.7% of total randomized patients) were assigned to ixekizumab 80 mg Q2W rescue treatment (41.2%, 41.7%, and 59.6% in the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W and placebo groups, respectively).

An exposure-response relationship was observed for injection site reaction (ISRs). There were higher incidences of infections (all types) reported with ixekizumab in the 2 upper ixekizumab Ctrough quartiles compared to placebo and the 2 lower ixekizumab Ctrough quartiles. For other infection AESIs (Candida, herpes, staphylococcal, or SAEs), incidence rates were low (n=0 to 8 patients per term) and no relationship with Ctrough values could be conducted. There was no relationship observed with ixekizumab trough concentrations for the few (N=4 on ixekizumab and N=2 on placebo in this dataset) reports of allergic reactions/hypersensitivity events that were non-anaphylactic in nature. The remaining AESIs were all reported with low or no incidence in the exposure-safety analysis dataset and thus there were insufficient data to allow an evaluation of the relationship to ixekizumab Ctrough values.

Figure 20. Incidence of treatment-emergent adverse events in the Week 0 to 16 period by ixekizumab trough concentration quartile at Week 16 (Study RHBX).

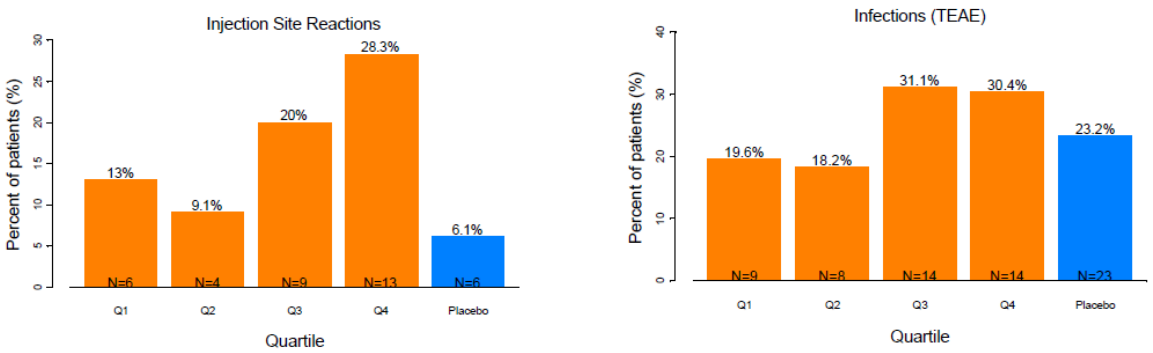


Abbreviations: AE = adverse event; CI = confidence interval; Conc = concentration; Q2W = every 2 weeks; Q4W = every 4 weeks; RHBX = Study I1F-MC-RHBX. Dotted line represents the mean trough concentration per dosing

regimen (Red = Q2W, and Green = Q4W). Orange dots represent the incidence of AEs at each quartile and the median concentration at each quartile. Blue dot represents placebo.

Figure 21 Summary of injection site reactions (A) and all infection (B) by ixekizumab trough concentration quartile at Week 16 (Studies RHBX).

A **B**



Abbreviations: N = number of patients who experienced the adverse event; Q = quartile; RHBX = Study I1F-MC-RHBX.
Trough concentration quartiles: Q1: <3.22 µg/mL; Q2: 3.22 to 5.73 µg/mL; Q3: 5.73 to 10.6 µg/mL; Q4:≥10.6 µg/mL

2.3.5. Discussion on clinical pharmacology

Analytical Method

Ixekizumab is an IgG4 mAb that binds with high affinity (<3 pM) and specificity to IL-17A, a proinflammatory cytokine. Because of the immunogenic potential for ixekizumab, patients in all ixekizumab clinical studies were tested for the presence of ixekizumab ADA. The ELISA method for analysing human serum samples was previously assessed and then originally validated by ALTA Analytical Laboratory. However, prior to the axSpA clinical studies it was transferred to ICON Laboratory Services, Inc., Whitesboro, NY. A cross-validation experiment was performed according to guideline and was deemed acceptable by CHMP.

Population Pharmacokinetic Analysis

The MAH characterized the PK of ixekizumab using population PK analysis, separately for radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis. The base population PK model in both reports was based on the final population PK models in patients with psoriasis (Ps) and Ps/psoriatic arthritis (PsA). The parameters were re-estimated, and first the significant covariates in Ps and PsA were tested and only retained in the base PK model if the effects remained significant. Subsequently, other covariate effects were tested, only in the r-axSpA or nr-axSpA PK model. Weight was not found to have a significant impact on central and peripheral volume of distribution in patients with nr-axSpA, as was done in the analyses for all other indications. This is likely due to the patient characteristics in this study or the data collection, and the MAH should have kept weight with fixed exponent on volume in the model for nr-axSpA as well. However, as it is not considered to have a major impact on the final conclusion, the issue was not further pursued by CHMP. The approach of

estimating allometric scaling exponents for CL and V terms rather than fixing to the theoretical values of 0.75 and 1 was challenged and justified. The posthoc PK parameter estimates from the models did not differ for CL, and very little for Vd estimates. The goodness-of-fit plots for the PopPK models do not show any major trends, and the pcVPCs indicate that the models can adequately predict the data. The final parameter estimates of both models were reasonable (Table 7 and Table 8), and similar to the parameter estimates of the previously developed model for Ps and PsA (Table 9). The final models are considered adequate for individual prediction of concentrations. In the final population PK model in patients with r-axSpA shrinkage was 4.53% for clearance (CL) and 36.4% for volume of distribution of the peripheral compartment (V3). For patients with nr-axSpA shrinkage was 3.69% for CL and 22.1% for V3.

PK/PD Modelling

Post hoc PK parameters from the final population PK model were merged with dosing records and ASAS20/40 data to carry out sequential PK/PD modelling. Analyses of exposure-response relationships were conducted using both exploratory graphical approaches (exposure-safety analysis) and model-based approaches (exposure-efficacy analyses).

For the exposure-efficacy analysis, the pcVPCs and parameter estimates for the static and time-course model for both indications indicate that the model is adequately predicting the observed data. The models can predict the exposure-efficacy relationship adequately. The MAH presented model-based exposure-efficacy analysis to support the 80 mg Q4W dosing regimen for both indications. While the trends in the plots may be in clear support of a 160mg SD in all subpopulations the responses overlap which render the result difficult to interpret. There are limitations to the model, which is observed in the presented stratified plots. The model suggests similar effect using the 160 mg and 80 mg starting dose. However, the benefit of a starting dose cannot be based solely on model-based predictions.

Safety data from study RHBX were analysed separately from studies RHBV and RHBW. Data up to week 16 were analysed in the latter mentioned studies, however, in study RHBX (nr-axSPA), which was conducted up to week 52, only data up to week 16 were analysed because 48% of total randomized patients switched dosing regimen (non-randomised switched) at week 16. A trend towards a slightly higher frequency of treatment emergent adverse events for the Q2W dosing regimen can be observed for the nr-axSpA patients. An exposure-response relationship was observed for injection site reaction in both analyses, and there were higher incidences of infections reported with ixekizumab in the two upper Ctrough quartiles compared to placebo and the two lower Ctrough quartiles. For other infection AESIs, incidence rates were low and no relationship with Ctrough values could be conducted.

Pharmacokinetic analyses indicate that drug clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, sulfasalazine, or methotrexate. Section 4.5 of the SmPC is updated to include this information.

2.3.6. Conclusions on clinical pharmacology

The ixekizumab pharmacokinetics (PK) in adult patients with r-axSpA and nr-axSpA has been adequately characterized and the PK determined to be consistent with the PK in patients with Ps and PsA. Section 4.5 of the SmPC is updated to indicate that pharmacokinetic analyses have shown that drug clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, sulfasalazine, or methotrexate.

2.4. Clinical efficacy

The MAH submitted results of 3 phase III studies (RHBV, RHBW, and RHBX), randomised, double-blind, placebo-controlled. Studies RHBV and RHBW were conducted in patients with active r-axSpA, respectively bDMARD naïve and TNFi-experienced patients. Study RHBX was conducted in b-DMARD naïve nr-axSpA patients. The placebo-controlled, double-blind treatment period of Studies RHBV and RHBW was **16 weeks**, whereas the placebo-controlled, double-blind treatment period of Study RHBX was **52 weeks**.

The axSpA programme also includes Study I1F-MC-RHBY (RHBY), a long-term extension study with a double-blind, placebo-controlled, randomised withdrawal–retreatment period. Patients who completed any of the 3 pivotal Phase 3 studies and meet eligibility criteria can enrol in Study RHBY. **Study RHBY** is currently ongoing.

2.4.1. Dose response studies

The dosing regimens (80 mg Q2W and 80 mg Q4W) for the pivotal Phase 3 studies were selected based on the following considerations:

- Dose-ranging data from bDMARD-naive and TNFi-inadequate responder populations in I1F-MC-RHAK (Phase 2 RA study).
- Dose-ranging data from I1F-MC-RHAJ (Phase 2 Ps study).
- Final dosing regimen selection for the pivotal Phase 3 studies in patients with moderate-to-severe plaque Ps and in patients with active PsA.
- All approved dose regimens for other indications have a 160-mg starting dose at Week 0. To evaluate the potential carryover effect of that starting dose on Week 16 response, the axSpA programme evaluated a 160-mg starting dose as well as an 80-mg starting dose at Week 0.

2.4.2. Main studies

The efficacy and safety of ixekizumab in axSpA were assessed in 3 pivotal, randomised, double-blind, placebo-controlled Phase 3 studies (**RHBV**, **RHBW**, and **RHBX**). The placebo-controlled, double-blind treatment period of Studies RHBV and RHBW was 16 weeks in length, whereas the placebo-controlled, double-blind treatment period of Study RHBX was 52 weeks in length.

2.4.2.1. Study I1F-MC-RHBV (RHBV)

Study RHBV: a Randomised, double-blind, placebo- and active controlled study in biologic disease-modifying antirheumatic drug (bDMARD)-naïve patients with active radiographic axial spondyloarthritis (r-axSpA).

Methods

Study design

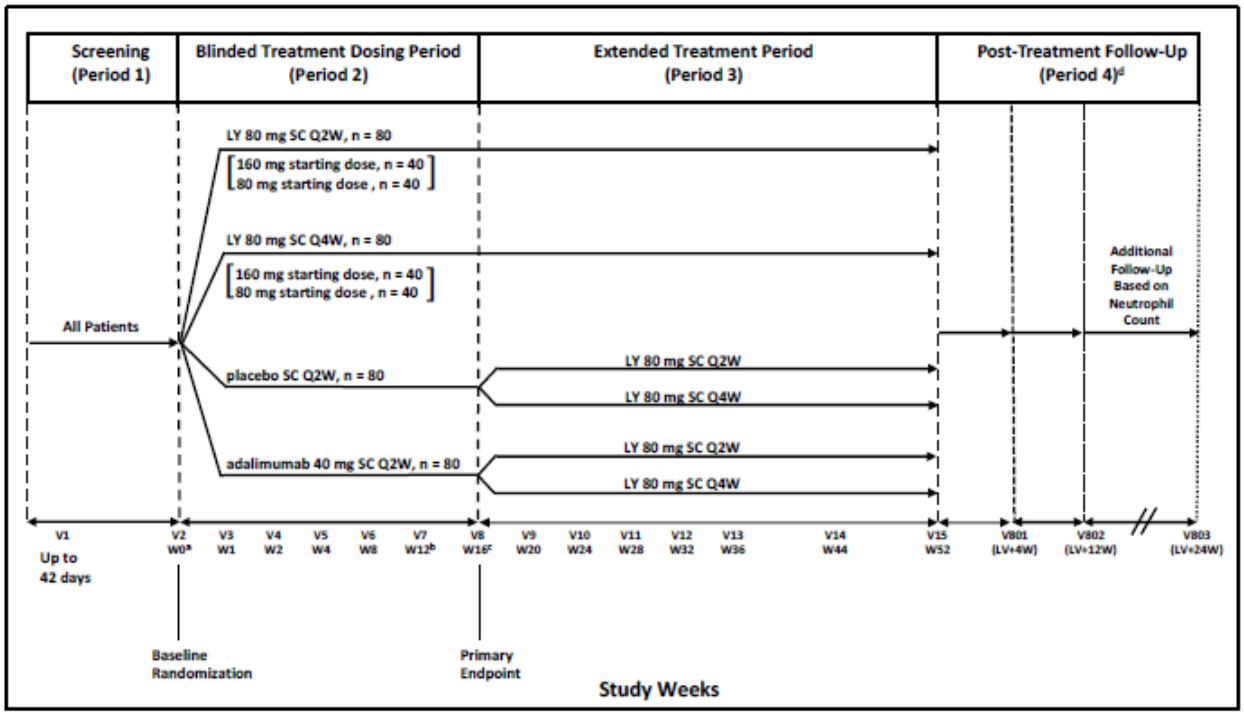
The study design is presented in Figure 21. .

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

- ixekizumab 80 mg Q2W SC
- ixekizumab 80 mg Q4W SC
- placebo
- adalimumab 40 mg Q2W SC

A starting dose of either 160mg or 80mg was given to patients with ixekizumab.

Figure 21. Study design of study RHBV.



Study participants

Key inclusion criteria:

The study population included patients aged 18 years or older who met the following criteria:

1. Have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically according to the mNY criteria (van der Linden et al. 1984) based on central reading: sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally.

   AND

   At least 1 SpA feature, according to ASAS criteria (Rudwaleit et al. 2009; Sieper et al. 2009),

- Inflammatory back pain (IBP): IBP according to experts, 4 out of 5 of the following parameters present: (1) age at onset, 40 years, (2) insidious onset, (3) improvement with exercise, (4) no improvement with rest, (5) pain at night (with improvement upon getting up).
- Arthritis: Past or present active synovitis diagnosed by a doctor.
- Enthesitis (heel): Heel enthesitis: past or present spontaneous pain or tenderness atexamination at the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus.
- Uveitis: Past or present uveitis anterior, confirmed by an ophthalmologist.
- Dactylitis: Past or present dactylitis diagnosed by a doctor.
- Psoriasis: Past or present psoriasis diagnosed by a doctor.
- Crohn's/Colitis: Past or present Crohn's disease or ulcerative colitis diagnosed by a doctor.
- Good response to NSAIDs: At 24 to 48 hours after a full dose of NSAID, the back pain was not present anymore or much better.

Note: As patients enrolling into the study should have failed 2 NSAIDs or be intolerant to NSAIDs, a doctor should assess whether patients had "good" prior response to NSAIDs.

- Family history for SpA: Presence in first-degree or second-degree relatives of any of the following: (a) AS, (b) psoriasis, (c) uveitis, (d) reactive arthritis, (e) inflammatory bowel disease.
- Note: A doctor should confirm with his/her patient there was a clear diagnosis (not selfdiagnosis) for any of these in first- or second-degree relatives.
- HLA-B27: Positive testing according to standard laboratory techniques.
- Elevated CRP: CRP >5.00 mg/L in the presence of back pain after exclusion of other causes of elevated CRP.

2. Patients have a history of back pain ≥3 months with age at onset <45 years
3. Have active rad-axSpA defined as BASDAI ≥4 and total back pain ≥4 (Sieper et al. 2009, Box 25 Spinal Pain) on an NRS at screening and baseline.
4. Must have had an inadequate response, as determined by the investigator, to 2 or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks **OR** have a history of intolerance to NSAIDs.
5. Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening. Examples of prior therapy may include but are not limited to physical therapy and NSAID treatment.
6. If taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, the dose must be stable for at least 2 weeks prior to baseline randomization.
7. Are ambulatory male or female patients ≥18 years of age at time of screening.

Exclusion criteria included

1. Have total ankylosis of the spine, as assessed locally, based on lateral radiographs of the cervical and lumbar spine.
2. Have a history of other systemic inflammatory diseases that might confound the evaluations of benefit from ixekizumab therapy
3. Have active Crohn’ s disease (CD) or active ulcerative colitis (UC).
4. Have evidence of active anterior uveitis (an acute episode) within the last 42 days prior to baseline randomization.
5. Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years prior to baseline randomization; or have active or history of malignant disease within 5 years prior to baseline randomization
6. Have a history of fluid overload, myocardial infarction (MI), uncompensated heart failure, or evidence of new-onset ischemic heart disease or in the opinion of the investigator other serious cardiac disease, within 12 weeks prior to baseline randomization.
7. Presence of significant uncontrolled cerebrocardiovascular events (for example, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident) at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
8. Presence of any comorbid respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorders, at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
9. Presence of any neurologic or neuropsychiatric disorders, at screening that, in the opinion of the investigator, poses an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
10. Presence of significant uncontrolled neuropsychiatric disorder; have recent history of a suicide attempt; or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-self report (16 items) (QIDSSR16) at screening or baseline randomization or are clinically judged by the investigator to be at risk for suicide.
11. Have presence or personal history or family history (1st degree relative) of demyelinating disorder.
12. Patients who have:

- in the past 12 weeks prior to baseline randomization: o had a serious infection, or have been hospitalized for an infection, o or have received intravenous (IV) antibiotics for an infection,
- or in the past 24 weeks prior to baseline randomization had a serious bone or joint infection
- or have ever had, or an infection of an artificial joint, o an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jirovecii pneumonia, symptomatic histoplasmosis, or coccidioidomycosis)

13. Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient
14. Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline randomization.
15. Have any other active or recent infection within 4 weeks of baseline randomization that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.
16. Have had surgical treatment of a joint that is to be assessed in the study within 8 weeks prior to baseline randomization or will require surgical treatment of a joint that is to be assessed in the study during the first 16 weeks of the trial.
17. Have had any major surgery within 8 weeks prior to baseline randomization or will require major surgery during the study that in the opinion of the investigator and in consultation with Lilly or its designee would pose an unacceptable risk to the patient.
18. Have received cDMARDs, and/or other therapies such as but not limited to: gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents within 4 weeks prior to baseline randomization. Exception: MTX (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization AND if used, must not be in any combination with other cDMARDs.
19. Use of oral corticosteroids >10 mg/day prednisone or its equivalent.
20. Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents, including investigational therapies (such as but not limited to Janus kinase (JAK) inhibitors, TNF inhibitors, IL-1, IL-6, IL-23, IL-17 (including ixekizumab), IL-17R, T cell, or B cell targeted therapies).
21. Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks prior to baseline randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the Blinded Treatment Dosing Period (Period 2) of the study.
22. Had a live vaccination within 12 weeks prior to baseline randomisation, or intend to have a live vaccination during the course of the study, or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline randomization.
23. Have evidence or suspicion of active or latent TB (refer to Section 5.3 for rescreening and Section 8.4.6 for details on determining full TB exclusion criterion.
24. Are positive for human immunodeficiency virus serology (HIV); that is, positive for human immunodeficiency virus antibody (HIVAb).
25. Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+), OR 2) anti-hepatitis B core antibody positive (HBcAb+) and are HBV DNA positive. Note: Patients who are HBcAb+ and HBV DNA negative may be enrolled in

the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 8.4.10.2.

26. Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab); and 2) positive via a confirmatory test for HCV (for example, HCV-polymerase chain reaction).
27. At screening, have a neutrophil count <1500 cells/μL (<1.50x103/μL or <1.50 GI/L).
28. At screening, have a lymphocyte count <800 cells/μL (<0.80x103/μL or <0.80 GI/L).
29. At screening, have a platelet count <100,000 cells/μL (<100x103/μL or <100 GI/L).
30. At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5xULN).
31. At screening, have a total white blood cell (WBC) count <3000 cells/μL (<3.00x103/μL or <3.00 GI/L).
32. At screening, have haemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients.

Treatments

Treatment regiments from Week 0 to Week 14 and from Week 16 to Week 50 are provided respectively in Figure 22. and Figure 23.

Figure 22. Treatment Regimens from Week 0 to Week 14 (Period 2) in study RHBV

Initial Regimen		Dose Week 0 (Day 0)		Dose Week 2 to Week 14[a] (Period 2)
	Total injections per patient	**3 injections**		**2 injections Q2W**
ixekizumab 80 mg Q2W with 160 mg starting dose	Treatment dose	2 ixekizumab 80 mg injections	→	1 ixekizumab 80 mg Q2W (Beginning at Week 2, Q2W)
	Injections to maintain blinding	1 placebo for adalimumab injection		
ixekizumab 80 mg Q2W with 80 mg starting dose	Treatment dose	1 ixekizumab 80 mg injection	→	1 placebo for adalimumab injection Q2W (Beginning at Week 2, Q2W)
	Injections to maintain blinding	1 placebo for ixekizumab injection 1 placebo for adalimumab injection		
ixekizumab 80 mg Q4W with 160 mg starting dose	Treatment dose	2 ixekizumab 80 mg injections	→	1 ixekizumab 80 mg Q4W injection (Beginning at Week 4, Q4W)
	Injections to maintain blinding	1 placebo for adalimumab injection		
ixekizumab 80 mg Q4W with 80 mg starting dose	Treatment dose	1 ixekizumab 80 mg injection	→	1 placebo for ixekizumab injection (Beginning at Week 2, Q4W) and 1 placebo for adalimumab injection Q2W (Beginning at Week 2, Q2W)
	Injections to maintain blinding	1 placebo for ixekizumab injection 1 placebo for adalimumab injection		
adalimumab 40 mg Q2W (comparator)	Treatment dose	1 adalimumab 40 mg injection		1 adalimumab 40 mg Q2W injection (Beginning at Week 2, Q2W)
	Injections to maintain blinding	2 placebo for ixekizumab injections		1 placebo for ixekizumab injection Q2W (Beginning at Week 2, Q2W)
placebo	Injections to maintain blinding	2 placebo for ixekizumab injections 1 placebo for adalimumab injection		1 placebo for ixekizumab injection Q2W (Beginning at Week 2, Q2W) and 1 placebo for adalimumab injection Q2W (Beginning at Week 2, Q2W)

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

Patients on adalimumab received their last adalimumab dose at Week 14.
Note: Shaded cells represent ixekizumab regimens with a starting dose (ixekizumab 160 mg).

Figure 23. Treatment Regimens from Week 16 to Week 50 in study RHBV.

Initial Regimen		Dose Week 16[a]	Dose Week 18 to Week 50 (Period 3)
	Total injections per patients	**2 injections**	**1 injection Q2W**
ixekizumab 80 mg Q2W	Treatment dose	1 ixekizumab 80 mg injection	1 ixekizumab 80 mg injection Q2W (Beginning at Week 18, Q2W)
	Injections to maintain blinding	1 placebo for ixekizumab injection	None
ixekizumab 80 mg Q4W	Treatment dose	1 ixekizumab 80 mg injection	1 ixekizumab 80 mg injection Q4W (Beginning at Week 20, Q4W)
	Injections to maintain blinding	1 placebo for ixekizumab injection	1 placebo for ixekizumab injection Q4W (Beginning at Week 18, Q4W)
adalimumab 40 mg Q2W (comparator)		rerandomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W[b]	
	Treatment dose	None	ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W beginning at Week 20
	Injections to maintain blinding	2 placebo for ixekizumab injections	1 placebo injection at Week 18 only (ixekizumab 80 mg Q2W regimen) or 1 placebo for ixekizumab injection Q4W beginning at Week 18 (ixekizumab 80 mg Q4W regimen)
placebo		rerandomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W	
	Treatment dose	2 ixekizumab 80 mg injections (starting dose)	ixekizumab 80 mg Q2W beginning at Week 18 or ixekizumab 80 mg Q4W beginning at Week 20
	Injections to maintain blinding	None	None (ixekizumab 80 mg Q2W regimen) or 1 placebo for ixekizumab injection Q4W beginning at Week 18 (ixekizumab 80 mg Q4W regimen)

Injections were administered subcutaneously by the patient or caregiver after training by the clinical staff. Training: At Week 0 (baseline, Visit 2) each patient was scheduled to receive 3 injections of blinded investigational product. For training purposes, the proper procedures for administration of the initial injection was to be performed by clinical staff and the second and third injections of investigational product at that visit will be administered by the patient or caregiver under the supervision of clinical staff. If additional training was necessary, an injection could be administered by the patient or caregiver under the supervision of clinical staff at Week 2 (Visit 4). If the patient was unable to perform the injection, a caregiver, who will also be trained under supervision of site staff, may administer the investigational product. All subsequent injections of investigational product were be administered, unsupervised, by the patient or caregiver.

Objectives

The primary objective was to compare ixekizumab 80 mg every 2 weeks (Q2W) and 80 mg every 4 weeks (Q4W) versus placebo in the treatment of patients with active radiographic axial spondyloarthritis (rad-axSpA) at Week 16, as measured by the proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response.

There were also a number of other objectives, see endpoints below.

Outcomes/endpoints

Primary endpoint:

ASAS40 response at week 16.

Key secondary endpoints

- ASDAS change from baseline at week 16
- BASDAI50 response at week 16
- ASAS 20 response at Week 16
- BASFI change from baseline at week 16
- ASDAS <1.3 response at Week 16
- MRI Spine SPARCC score change from baseline at Week 16
- SF-36 PCS score change from baseline at Week 16
- ASAS HI change from baseline at Week 16

Other endpoints:

- to compare ixekizumab 80 mg Q2W and 80 mg Q4W versus placebo in the treatment of patients with active rad-axSpA during the 16-week placebo-controlled period, as assessed by:
    - proportion of patients who achieve ASAS20, ASAS40, ASAS5/6, partial remission by ASAS criteria, BASDAI50, clinical-important improvement (ASDAS change from baseline≥1.1), major improvement (change of ASDAS change from baseline ≥2.0), ASDAS <2.1, or inactive disease.
    - change from baseline in the individual components of the ASAS criteria, BASDAI, ASDAS, BASFI, measure of high sensitivity C-reactive protein (hs-CRP), mobility (BASMI linear and individual components, chest expansion, occiput-to-wall distance), MRI of the SIJ (SPARCC), MRI of the spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity-Berlin Score [ASSpiMRI-Berlin]), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), SPARCC Enthesitis Score, Fatigue NRS score, ASAS HI score, Jenkins Sleep Evaluation Questionnaire (JSEQ), Work Productivity Activity Impairment– Spondyloarthritis (WPAI-SpA) scores, SF-36 (both PCS and mental component summary [MCS] scores), Quick Inventory of Depressive Symptomatology-Self Report 16 items (QIDS-SR16) score, and European Quality of Life-5 Dimensions 5-level (EQ-5D-5L)
    - incidence and severity of peripheral arthritis by tender joint count (TJC) and swollen joint count (SJC) scores of 46/44 joints
    - incidence rate of anterior uveitis flares
- to determine if the effect of either ixekizumab regimen is maintained through Week 52 for
    - all endpoints assessed at Week 16 (above) and during the 16-week placebo-controlled period (above)

    - Nonsteroidal anti-inflammatory drug (NSAID) intake, as assessed by ASAS-NSAID score and Percentage of patients taking NSAIDs.

- to explore the effect of the starting dose (160 mg versus 80 mg at Week 0) as assessed by the onset of action and treatment response (e.g., ASAS, ASDAS, CRP, and BASFI) during the 16-week placebo-controlled period
- to evaluate the incidence of anti-ixekizumab antibodies and their relationship to the efficacy of ixekizumab at Weeks 16 and 52, as assessed by proportion of patients achieving ASAS40 or ASAS20.
- to measure ixekizumab exposure and assess the relationship between exposure and efficacy and exposure and immunogenicity at Weeks 16 and 52, as assessed by serum trough concentrations of ixekizumab or ixekizumab serum trough concentrations associated with ADA titer sub groups.
- to test assay sensitivity by comparing adalimumab 40 mg Q2W with placebo in the treatment of patients with active rad-axSpA at Week 16, as measured by the proportion of patients achieving an ASAS40 response.

Definitions of endpoints:

ASAS20 and ASAS40. The ASAS20 and ASAS40 are derived from the following patient-reported assessments:

Patient Global Assessment of Disease Activity. The patient was asked to respond to the following question: "How active was your spondylitis on average during the last week?" The answer was recorded on an NRS and was rated between "0" (not active) and "10" (very active).

Spinal Pain. The patient was asked to respond to the following 2 questions (on average during the last week): "How much pain of your spine due to ankylosing spondylitis do you have?" and "How much pain of your spine due to ankylosing spondylitis do you have at night?" The answers were recorded on an NRS and were each rated between "0" (no pain) and "10" (most severe pain). The first question is used to determine the spinal pain component of the ASAS20 or ASAS40 response.

Function (BASFI). Patients were asked to rate the difficulty associated with 10 individual basic functional activities. Patients responded to each question using an NRS scale (range 0 to 10), with a higher score indicating worse function. The patient's final BASFI score is the mean of the 10 item scores completed on an NRS.

Inflammation (mean of BASDAI Questions 5 and 6)

The BASDAI is a patient-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to axSpA. The following 2 questions are used to determine the inflammation component of the ASAS20 or ASAS40 response: Intensity and Duration of morning stiffness. Patients scored each item with a score from 0 to 10 (NRS).

An ASAS20 response is defined as an at least 20% improvement and an absolute improvement from baseline of at least 1 unit (range 0 to 10) in at least 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening of at least 20% and at least 1 unit (range 0 to 10) in the remaining domain.

An ASAS40 response is defined as an at least 40% improvement and an absolute improvement from baseline of at least 2 units (range 0 to 10) in at least 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain.

hs-CRP

High-sensitivity CRP (hs-CRP) was the measure of acute phase reactant.

BASDAI

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a patient-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to axSpA (1) Fatigue, (2) Spinal pain, (3) Peripheral arthritis, (4) Enthesitis, (5) Intensity, and (6) Duration of morning stiffness. Patients needed to score each item with a score from 0 to 10 (NRS). The BASDAI50 represents an improvement of at least 50% of the BASDAI score from baseline.

ASDAS

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in axSpA). The parameters used for the ASDAS (with hs-CRP as acute phase reactant) are

- Total back pain (BASDAI Question 2)
- Patient Global Assessment of Disease Activity
- Peripheral pain/swelling (BASDAI Question 3)
- Duration of morning stiffness (BASDAI Question 6), and
- CRP in mg/L.

$ASDAS_{crp}$ = 0.121 × total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(CRP+1)

Four disease activity states have been defined by ASAS consensus:

- ASDAS <1.3 defines inactive disease
- 1.3≤ASDAS<2.1 defines low disease activity
- 2.1≤ASDAS≤3.5 defines high disease activity, and
- ASDAS >3.5 defines very high disease activity.

Clinically important improvement is defined as change of at least 1.1 units, and major improvement is defined as change of at least 2.0 units or achievement of the minimum of ASDAS score (0.6361)

BASMI

The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a combined index comprising the following 5 clinical measurements of spinal mobility in patients with axSpA

- Lateral spinal flexion
- Tragus-to-wall distance
- Lumbar flexion (modified Schrober)
- Maximal intermalleolar distance, and
- Cervical rotation.

The BASMI includes these 5 measurements that were each scaled to a score of 0 to 10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives

the BASMI linear result.

MRI SIJ and Spine (SPARCC Scores)

MRI SIJ

Both left and right SIJs were scored for bone marrow oedema. Total SIJ SPARCC scores can range from 0 to 72, with higher scores reflecting worse disease. Scoring was performed by central readers.

MRI spine

All 23 disco-vertebral units (DVUs) of the spine (from C2 to S1) were scored for bone marrow oedema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease. Scoring was performed by central readers.

SF-36

The 36-Item Short Form Health Survey (SF-36) is a 36-item patient-reported instrument designed to assess 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. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute version) was used, which utilises a 1-week recall period.

ASAS HI

The Assessment of Spondyloarthritis International Society Health Index (ASAS HI) is an axSpA-specific17-item patient-reported instrument designed to assess functioning, disability, and health. The ASAS HI is a reliable, valid, and responsive, axSpA-specific measure for evaluating clinically meaningful improvement in overall functioning and quality of life (QoL).

The ASAS HI has scores ranging from 0 (good health) to 17 (poor health). Each item consists of 1 question that the patient needed to respond to with either "I agree" (score of 1) or "I do not agree" (score of 0). A score of "1" was given where the item was affirmed, indicating adverse health. All item scores are summed to give a total score or index.

Sample size

The total planned sample size for study RHBV was 320 patients. With 80 patients per treatment group and assuming the Week 16 ASAS40 response rates of 16% for the placebo group and 44% for the ixekizumab 80 mg Q2W treatment group, this study was planned to have approximately 96% power to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 16. A 2-sided Fisher's exact test at an alpha level of 0.05 was assumed.

Randomisation

At Week 0 (Visit 2), eligible patients were randomised using an allocation ratio of 1:1:1:1 to receive ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab 40 mg Q2W, or placebo. The patients randomised to ixekizumab were further randomised 1:1 to a starting dose of 80 mg or 160 mg (given as 2 SC injections of 80 mg). Treatment assignments were determined by a computer-generated random sequence using an interactive web-response system (IWRS). At randomisation subjects were stratified by country and baseline CRP (non-elevated or elevated; defined as CRP>5.00 mg/L). Due to operational feasibility, stratification by CRP was based on the most recent CRP prior to randomisation,

i.e. screening CRP. Initially, it was planned to enrol approximately 50% of patients with baseline CRP elevated. Within study protocol amendment (b), approved 23 December 2016, the limitation on the enrolment of patients with elevated versus non-elevated CRP was removed so that all patients who met protocol eligibility criteria could be enrolled independent of CRP.

At Week 16, all patients on placebo were re-randomised (1:1) to either ixekizumab group, receiving a starting dose of 160 mg (2 injections of 80 mg).

At Week 16, all patients on adalimumab were re-randomised (1:1) to either ixekizumab group, receiving no starting dose.

Blinding (masking)

This was a double-blind study, with a double-dummy design. Initial randomisation (study drug administered between Weeks 0 and 16) remained blinded to study site personnel and patients until the final (i.e., end of study) clinical trial database lock has occurred. Study drug assigned during the Extended Treatment Period (Period 3) was known to the site and patient at entry to Study RHBY. Initial randomisation, as well as study drug assignment during Period 3, remained blinded to the sponsor until the clinical trial database through Week 16 had been locked. Unblinding occurred on 31 January 2018. Unblinding details are specified in the blinding/unblinding plan included. The syringes (and contents) containing either ixekizumab or placebo were visibly indistinguishable from each other and visibly different from adalimumab and its matching placebo, and the syringes (and contents) containing either adalimumab or placebo to match adalimumab were visibly indistinguishable from each other (i.e., double-dummy design). Randomisation codes were generated and emergency unblinding for AEs were allowed to be performed with IWRS, which could have supplemented or taken the place of emergency codes generated by a computer drug-labeling system. No emergency unblinding took place in this study.

Statistical methods

Blinded Treatment Dosing Period weeks 0 to 16 (Period 2)

A pre-planned interim database lock and unblinding of data occurred 31 January 2018 after the last patient had completed Visit 8 (***Week 16***) or the early termination visit (ETV). This was the primary (and final) analysis of the Blinded Treatment Dosing Period (Period 2) and included assessments of all primary and major secondary study objectives. The Statistical Analysis Plan version 1 was approved 07 April 2016 (prior to first patient visit); version 2 was approved 19-Jan-2018, i.e. before unblinding. There was one *post-hoc* analysis assessing percentage of patients achieving ASDAS <2.1 but, according to the MAH, no other changes to the prespecified statistical analysis.

Extended Treatment Period weeks 16 to 52 (Period 3)

There was also an interim database lock after all patients had completed the ***Week 52*** Visit or discontinued study drug early for analyses of efficacy and safety from the completed Extended Treatment Period (Period 3; Weeks 16 to 52). The date of Week 52 database lock was 05 Oct 2018; a version 3 of the SAP was approved after unblinding (16-Oct-2018) and included the adding of ASDAS <2.1 as a secondary endpoint. All endpoints assessed at Week 16 and during the 16-week placebo-controlled period continued to be assessed through Week 52. Efficacy, health outcomes, and safety analyses for Period 3 were conducted on the Extended Treatment Period Population defined as all patients who received at least 1 dose of ixekizumab treatment during Period 3.

Selected analyses were also provided for the combined periods 2 and 3; (Weeks 0 to 52) based on the ITT Population including all patients randomised to ixekizumab at Week 0 (Visit 2).

Primary/final analysis week 16 (Period 2)

Primary and major secondary endpoints were analysed according to a prespecified graphical multiple testing procedure. Unless otherwise specified, efficacy and health outcome analyses were conducted on the intent-to-treat (ITT) population comprising all randomised patients analysed according to the treatment group to which they had been randomised. In the primary analysis, treatment groups of ixekizumab 80 mg Q2W and Q4W were analysed without regard to starting dose.

Treatment comparisons of ***categorical efficacy variables***, including the primary, response rate week 16 based on ASAS40, were made using a logistic regression analysis with treatment, geographic region (Europe and non-Europe), and baseline CRP status (non-elevated or elevated) in the model. The odds ratio and 95% CIs were reported as was treatment difference and 95% CI. Secondary analysis was conducted using a Fisher's exact test. Patients who did not meet clinical response criteria or had missing data were considered non-responders (referred to as non-responder imputation [NRI]).

Analyses of ***continuous*** efficacy and health outcomes variables (except MRI SPARCC spine score) were based on mixed-effects models for repeated measures (MMRM) with treatment, geographic region, baseline CRP status, baseline value (except for the analysis of CRP, in which baseline CRP value was not included in the model), visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors. The primary analysis for change from baseline in MRI SPARCC spine score was an observed case (OC) analysis using ANCOVA with treatment, geographic region, baseline CRP status and baseline value in the model. Only patients with both baseline and Week 16 SPARCC spine score were included in the analysis.

Additional/sensitivity analyses

As a secondary analysis for the primary and major secondary categorical efficacy measures, a categorical, pseudo-likelihood based mixed-effects model of repeated measures (categorical MMRM) estimating the percentage of patients achieving response across postbaseline visits were used. The model included treatment, geographic region, baseline CRP status, visit, and treatment-by-visit as fixed factors. The probability of response, the corresponding 2-sided 95% CI, and the p-value for treatment comparisons at Week 16 (Visit 8) and all other postbaseline visits were reported.

For endpoints ASAS40, ASAS20, and ASDAS change from baseline at Week 16 sensitivity analyses were performed using placebo multiple imputation (***pMI***). Based on the assumption that the statistical behaviour of drug- and placebo-treated patients after discontinuing study medication becomes that of placebo-treated patients, multiple imputations (MIs) were used to replace missing outcomes for drug- and placebo-treated patients who discontinued.

For continuous major secondary endpoints secondary analyses were performed based on ANCOVA models using modified baseline observation carried forward (***mBOCF***) and last observation carried forward (***LOCF***). The modified BOCF implied that for patients discontinuing study drug due to an AE, the baseline observation was carried forward, for patients discontinuing study drug for any other reason, the last non-missing observation before discontinuation were carried forward. Patients without at least one post-baseline observation were excluded with the exception of patients discontinuing study treatment due to an AE. LOCF was identical to the mBOCF approach, with one exception: for patients discontinuing study drug due to an AE, the last non-missing post-baseline observation before

discontinuation were to be carried forward to the corresponding time point for evaluation. Randomised patients without any postbaseline observation were excluded.

To evaluate the robustness of statistical analyses of key efficacy data and assumptions inherent in missing data imputation methods, ***tipping point analyses*** were performed for ASAS40, ASAS20, and mean change from baseline in ASDAS Week 16.

Multiple Comparisons/Multiplicity

A multiple testing strategy for the primary and major secondary objectives was implemented to control the family-wise type I error rate at a 2-sided α level of 0.05 based on a graphical multiple testing procedure (Bretz et al. 2011).

The following primary and major secondary outcomes were planned to be tested for both ixekizumab 80 mg Q2W and Q4W regimen at Week 16:

Primary - proportion of patients achieving an ASAS40 response [ASAS40]

Secondary 1 - proportion of patients achieving an ASAS20 response [ASAS20]

Secondary 2 - change from baseline in ASDAS score [ASDAS CFB]

Secondary 3 - proportion of patients achieving BASDAI50 [BASDAI50]

Secondary 4 - change from baseline in BASFI [BASFI CFB]

Secondary 5 - proportion of patients achieving ASDAS inactive disease [ASDAS IN]

Secondary 6 - change from baseline in MRI of the spine [MRI spine SPARCC CFB]

Secondary 7 - change from baseline in SF-36 PCS score [SF-36 PCS CFB]

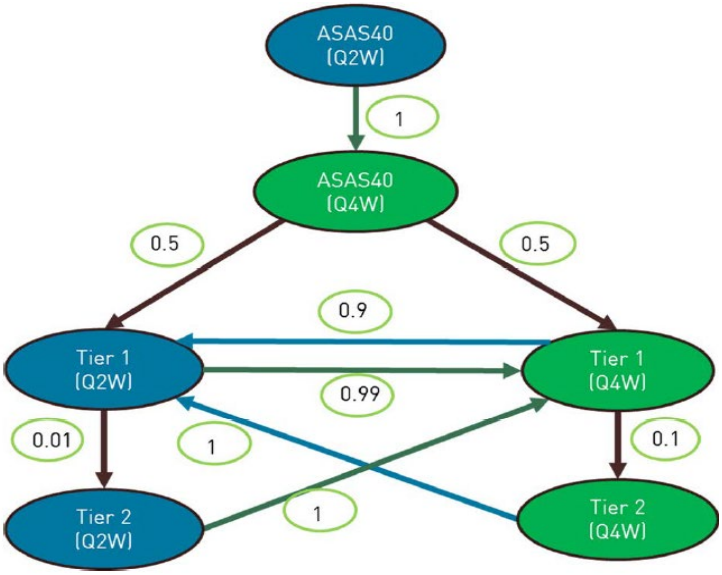
Secondary 8 - change from baseline in ASAS-HI [ASAS-HI CFB].

The 8 secondary outcomes were grouped into 2 tiers.

Tier 1: secondary hypotheses 1 to 5.

Tier 2: secondary hypotheses 6 to 8.

Figure 24. Illustration of graphical multiple testing procedure with initial α = 0.05 allocation and weights



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

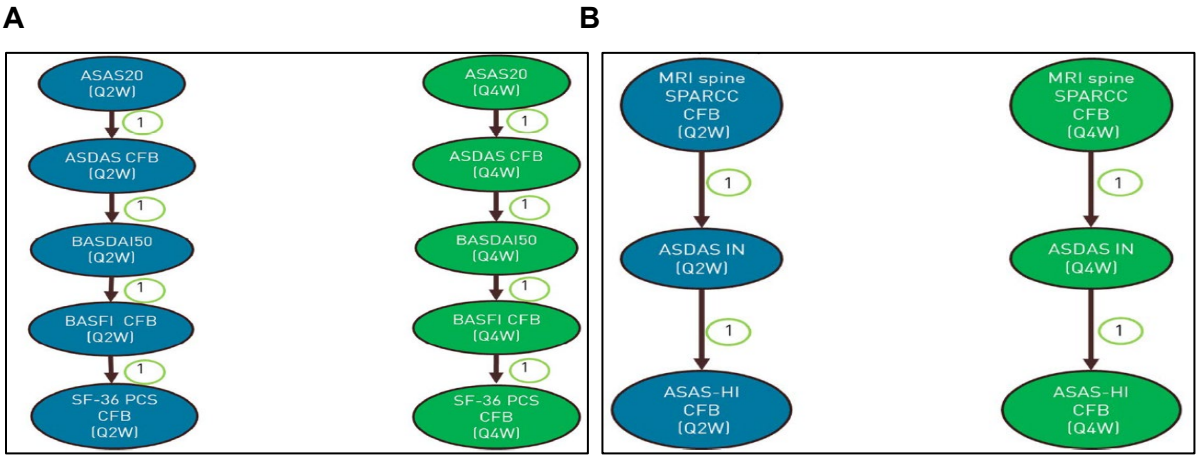
The testing steps were as described below:

Step 1: The primary outcome of ASAS40 was tested for ixekizumab 80 mg Q2W vs. placebo at a two-sided α=0.05. If the null hypothesis was rejected, then testing commenced to Step 2. If the null hypothesis could not be rejected, no further testing was to be conducted.

Step 2: The primary outcome of ASAS40 was tested for ixekizumab 80 mg Q4W vs placebo at a two-sided α=0.05. If the null hypothesis was rejected, then testing commenced to Step 3. If the null hypothesis could not be rejected, no further testing was to be conducted.

Step 3: α=0.025 was distributed to Tier 1 set of secondary outcomes for ixekizumab 80 mg Q2W (blue circles, see below), and the remaining α=0.025 was distributed to Tier 1 set of secondary outcomes for Ixekizumab 80 mg Q4W (green circles, see below).

Figure 25. Graphical multiple testing scheme used within the Tier 1 group of endpoints (A) and Tier 2 group of endpoints (B)



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; ASDAS IN = ASDAS inactive disease; ASAS-HI = ASAS Health Index; CFB = change from baseline; MRI spine SPARCC = MRI of spine Spondyloarthritis Research Consortium of Canada score; SF-36 PCS = Short Form 36 physical component score; CFB = change from baseline; Q2W = every 2 weeks; Q4W = every 4 weeks.

The major secondary endpoints for both doses were tested according to the prespecified procedure. The testing process continued for the remaining outcomes by allocating the remaining α to the next set of outcomes as long as at least one hypothesis could be rejected. Each time a hypothesis was rejected, the graph was updated to reflect the reallocation of α, which was considered "recycled" (Alosh et al. 2014). This iterative process of updating the graph and reallocating α was repeated until all major secondary hypotheses had been tested or when no remaining hypotheses could be rejected at their corresponding α level. The weights along the edges for α allocation between ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W outcomes as well as within each of the tiers were prespecified (as shown above).

There was no multiplicity adjustment for the other secondary endpoints.

Different starting doses

The impact of ixekizumab starting dose of 160 mg versus 80 mg on treatment response at Week 16 and time to onset of action were summarised and evaluated separately. Response rates in categorical variables (including ASAS40, ASAS20, ASDAS major improvement) and LS mean change in continuous efficacy measures (including CRP, BASFI) at Week 16 were presented for patients randomised to ixekizumab Q2W or Q4W treatment regimen with ixekizumab 160 mg starting dose and with ixekizumab 80 mg starting dose.

Subgroup Analyses

Subgroup analyses were conducted based on an ASAS40 response at Week 16 (NRI) and ASAS20 (NRI) at Week 16. The subgroups included patient demographics, geographic region, baseline disease severity, and other patient characteristics. A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors was used. The subgroup-by-treatment interaction was tested at the significance level of 0.10. Treatment group differences were evaluated

within each category of the subgroup using Fisher's exact test, regardless of whether the interaction was statistically significant. If any group within the subgroup was <10% of the total population, only summaries of the efficacy data were provided (that is, no inferential testing).

Results

Participant flow

A total of 781 patients signed informed consent and entered into the Screening Period of Study RHBV. In total, 341 patients were randomised to 1 of 4 treatment groups as the ITT Population.

One patient (480-20445), a screen fail, was inadvertently randomised to placebo; the patient was discontinued at Week 0 (Visit 2) prior to receiving study drug.

A total of 97.1% of randomised patients completed the Blinded Treatment Dosing Period. The two figures below summarize patient disposition from study drug.

Figure 26. Patient disposition from study drug during the Blinded Treatment Dosing Period (Week 0 to 16) for the ITT Population.

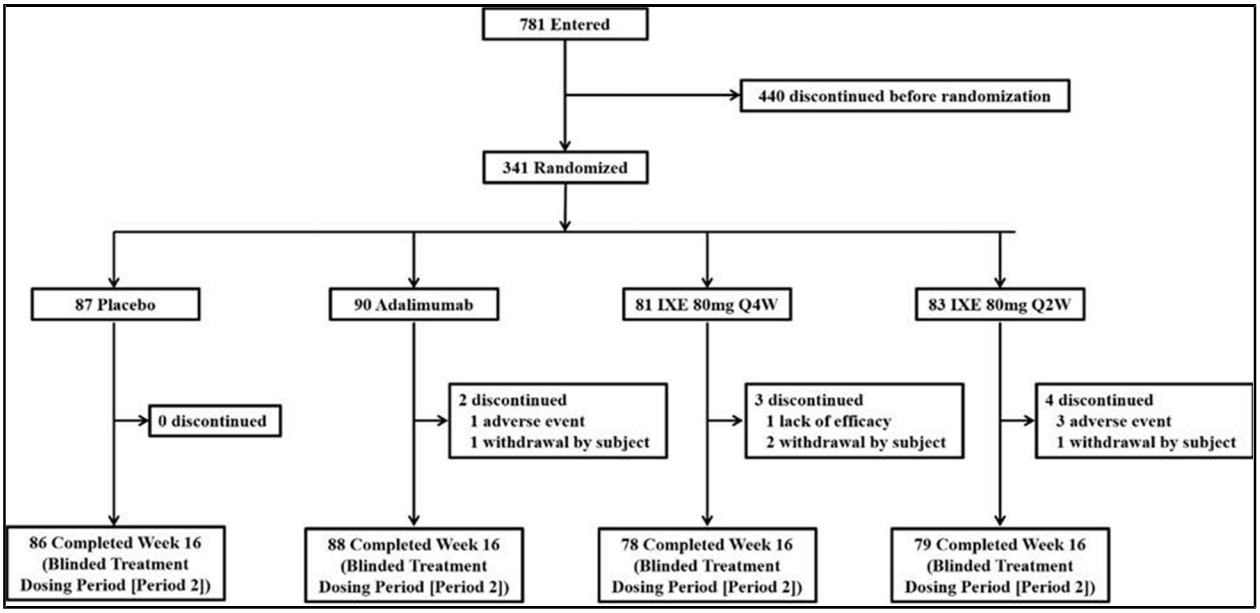
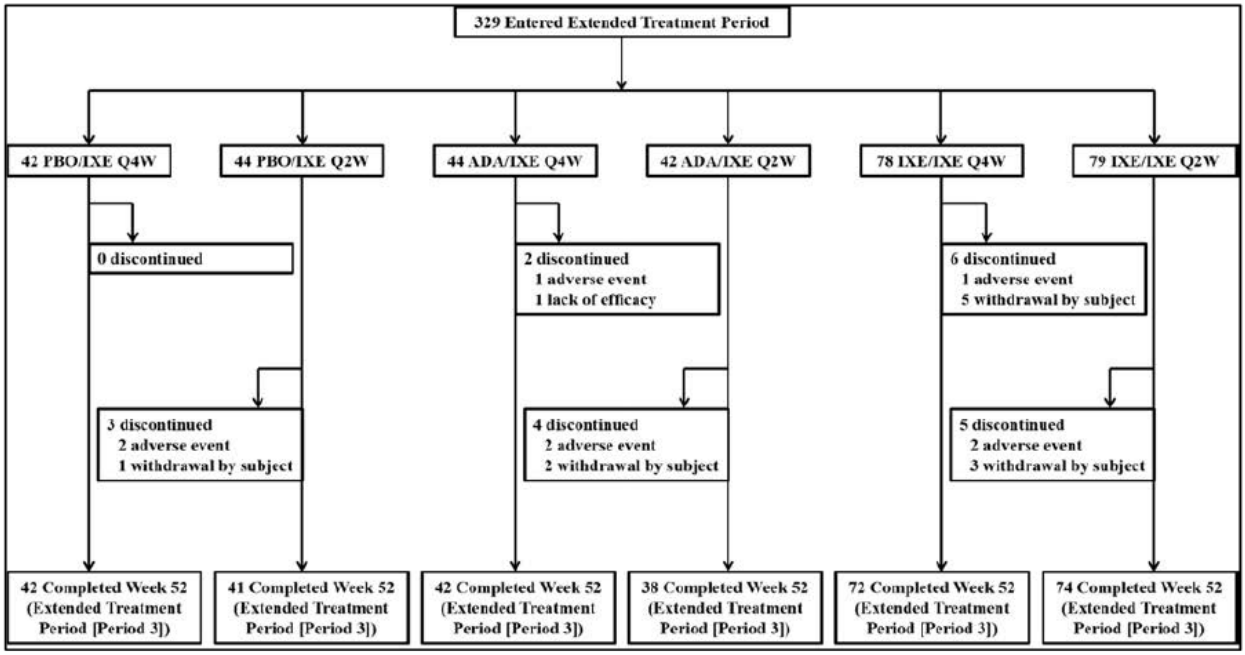


Figure 27. ***Patient disposition from study drug during the Extended Treatment Period (Weeks 16 to 52) for the Extended Treatment Period Population by treatment groups***



Protocol deviations:

Overall, 94 patients (27.6%) had at least 1 important protocol deviation.

The following categories of important protocol deviations were further reviewed:

- Violation of inclusion criterion: (no established diagnosis of rad-axSpA at screening): 17 patients (5.0%) had this protocol deviation. These patients were reclassified as not meeting mNY criteria specified in this criterion after a change in central readers early in the trial.
- Took incorrect study medication: 16 patients (4.7%) were reported to have taken incorrect study medication during the Blinded Treatment Dosing Period, with a similar percentage of patients across treatment groups. For most patients affected, the error occurred at a single visit. Most of the errors were a result of inaccurate recordings of the syringe number/suffix

Based on what study drug was dispensed, 3 errors had a meaningful impact: 2 errors (1 in the ixekizumab 80 mg Q2W group and 1 in the ixekizumab 80 mg Q4W group) likely affected the ixekizumab exposure analysis because the injections were treated as missing due to the incorrect syringe number. One error of administration of incorrect syringe order resulted in a double dose of ixekizumab (160 mg, instead of 80 mg) for a patient in the ixekizumab 80 mg Q2W group on a single day after Week 0.

- Improper informed consent: 40 patients (11.7%) had this protocol deviation. All patients provided informed consent; however, there were delays in consent updates or other minor errors in the consent, resulting in protocol deviations.

A subset of important protocol deviations that might have an impact on the primary objective were pre-specified in the SAP. Only those patients who deviated from these criteria (n=36, 10.6%) were excluded from the PPS analysis.

Recruitment

Date first patient enrolled: 20 Jun 2016

Date last patient completed Week 16 Visit: 08 Dec 2017

Date of database lock: 31 Jan 2018

This study was conducted at 84 study sites in 12 countries.

Conduct of the study

There were 2 protocol amendments. The main changes implemented were related to the conduct of the study and are as follows:

Protocol Amendment (a) - 05 August 2016

- The SPARCC scoring method for MRI of the spine replaced the ASSpiMRI-Berlin score as a major secondary endpoint. Emerging evidence indicated the SPARCC may be more discriminative than the Berlin scoring method and may provide higher inter-examiner reliability. The ASSpiMRI-Berlin scoring method was still included as an endpoint for "other" secondary objectives to allow for comparisons with other studies' data that are based on the Berlin method.
- Guidance was provided to allow rescreening of patients for Study RHBV who were ineligible for Study I1F-MC-RHBX, a Phase 3 study for ixekizumab in bDMARD-naive patients with non-axSpA.
- Adjudication of suspected IBD was added to ensure that all reported events were evaluated uniformly by a single group in an unbiased manner.
- Additional changes were made to enhance clarity of the protocol.

Protocol Amendment (b) - 23 December 2016

The main change implemented with this amendment was related to the method of treatment assignment. Specifically, the amendment removed the limitation on the enrolment of patients with elevated versus non-elevated CRP so that all patients who met protocol eligibility criteria could be enrolled independent of having elevated or non-elevated CRP.

Baseline data

Patients were enrolled in 12 countries. The majority of patients (53.2%) were from Europe, while the rest were from other parts of the world. At baseline, the mean age of patients was 41.7 years, with the majority of patients (95.9%) being <65 years of age. The mean age at onset of axSpA was 26.1 years, mean duration of axSpA symptoms was 16.0 years, and mean time since axSpA diagnosis was

7.7 years. Patients were predominantly male (81.2%), white (62.6%), and human leukocyte antigen B27 (HLA-B27) positive (90.9%). Patients had a mean weight of 78.1 kg and a mean BMI of 26.5 kg/m2. Mean baseline BASDAI and ASDAS were similar across treatment groups (6.7 to 6.8 and 3.7 to 3.9, respectively). Across all treatment groups, the mean and median baseline high sensitivity CRP (hs-CRP) levels were 13.5 mg/L and 7.6 mg/L, respectively, and 64.4% of patients had a hs-CRP level >5.00 mg/L at baseline. At baseline, 91.8% of patients were receiving NSAIDs, 36.8% of patients were receiving cDMARDs (28,5% Sulfasalazine, 8,5% Methotrexate, 0,6% Hydroxychloroquine), and 9.4% of patients were receiving oral corticosteroids.

Numbers analysed

The primary analysis population was the ITT population including all randomised patients corresponding to a total of 341 patients; 83 in the ixekizumab 80 mg Q2W arm, 81 in the ixekizumab 80 mg Q4W arm, 90 in the adalimumab 40 mg Q2W arm and 87 patients in the placebo arm. In addition, the primary analysis was repeated using the PPS.

Table 16: Patient dispostion during Blinded Treatment Period in Study RHBV

Period Population and Status	PBO n (%)	ADA40Q2W n (%)	IXE80Q4W n (%)	IXE80Q2W n (%)	Total n (%)
Period 2 - Blinded Treatment Dosing Period					
Randomized patients	87	90	81	83	341
Intent to Treat (ITT)	87	90	81	83	341
Completed Period 2 (% relative to ITT)	86 (98.9%)	88 (97.8%)	78 (96.3%)	79 (95.2%)	331 (97.1%)
Completed Period 2 and entered Period 4 directly	0	1	0	0	1
Completed Period 2 and entered Period 3	86	85	78	79	328
Discontinued from Period 2 (% relative to ITT)	0	2 (2.2%)	3 (3.7%)	4 (4.8%)	9 (2.6%)
Discontinued from Period 2 and entered Period 4	0	0	1	4	5
Discontinued from Period 2 but did not enter Period 4	0	2	2	0	4
Per Protocol Set (PPS) (% relative to ITT)	79 (90.8%)	76 (84.4%)	76 (93.8%)	74 (89.2%)	305 (89.4%)
Completed Period 2 treatment (% relative to PPS)	79 (100.0%)	75 (98.7%)	73 (96.1%)	71 (95.9%)	298 (97.7%)

Outcomes and estimation

Primary analysis - Blinded Treatment Dosing Period (Week 0 to Week 16)

Table 17 presents the nominal and multiplicity-adjusted p-values based on the graphical multiple testing procedure for the primary and major secondary endpoints. Statistically significant differences were observed for the primary endpoint and all major secondary endpoints.

Table 17: Summary of primary and major secondary analyses at Week 16 (ITT)

	Ixekizumab 80 mg Q4W vs. Placebo		Ixekizumab 80 mg Q2W vs. Placebo	
	Unadjusted Nominal p-value	Multiplicity Adjusted p-value	Unadjusted Nominal p-value	Multiplicity Adjusted p-value
Primary Objective				
ASAS40 Response	<.001	<.001	<.001	<.001
Major Secondary Objectives				
ASAS20 Response	.001	.001	<.001	<.001
ASDAS Change from Baseline	<.001	.001	<.001	<.001
BASDAI50 Response	<.001	.001	<.001	<.001
BASFI Change from Baseline	<.001	.001	<.001	<0.001
SF-36 PCS Change from Baseline	<.001	.001	<.001	<.001
MRI Spine SPARCC Change from Baseline	<.001	.001	<.001	<.001
ASDAS IN Response	.007	.008	.041	.041
ASAS HI Change from Baseline	.010	.011	<.001	.041

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASDAS IN = ASDAS inactive disease; ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; SF-36 PCS = Medical Outcomes Study 36-Item Short Form-Health Survey Physical Component Summary; vs. = versus. Note: All comparisons of ixekizumab with placebo for the primary and major secondary endpoints were statistically significant as calculated with the graphical method for multiple testing, with the family-wise type I error rate strongly controlled at a 2-sided α level of 0.05 for multiple comparisons.

Primary and major secondary endpoints

Statistically significant improvements in efficacy were observed for each of the ixekizumab treatment groups relative to placebo for the primary and for all the major secondary objectives at Week 16. There was a significantly greater percentage of patients who achieved an ASAS40 response at Week 16 for each of the ixekizumab treatment groups and for the adalimumab active reference group compared with the placebo group.

Table 18: Study RHBV: Summary of Primary and Major Secondary Endpoints at Week 16

	PBO N = 87	ADA Q2W N = 90	IXE Q4W N = 81	IXE Q2W N = 83
Primary Objective				
ASAS40 Response, n (%)	16 (18.4)	32 (35.6)[d]	39 (48.1)[c]	43 (51.8)[c]
Difference from PBO, % (95% CI)		17.2 (4.4, 30.0)	29.8 (16.2, 43.3)	33.4 (19.9, 46.9)
Major Secondary Objectives				
ASAS20 Response, n (%)	35 (40.2)	53 (58.9)[d]	52 (64.2)[b]	57 (68.7)[c]
Difference from PBO, % (95% CI)		18.7 (4.2, 33.1)	24.0 (9.3, 38.6)	28.4 (14.1, 42.8)
ASDAS Change from Baseline, LSM (SE)	-0.46 (0.099)	-1.30 (0.096)[d]	-1.43 (0.102)[b]	-1.37 (0.101)[c]
BASDAI50 Response, n (%)	15 (17.2)	29 (32.2)[d]	34 (42.0)[b]	36 (43.4)[c]
BASFI Change from Baseline, LSM (SE)	-1.16 (0.215)	-2.14 (0.209)[d]	-2.39 (0.222)[b]	-2.43 (0.219)[c]
ASDAS <1.3 Response, n (%)	2 (2.3)	14 (15.6)[d]	13 (16.0)[b]	9 (10.8)[a]
MRI Spine SPARCC Change from Baseline, LSM (SE)	-1.51 (1.147)	-11.57 (1.113)[d]	-11.02 (1.160)[b]	-9.58 (1.168)[c]
SF-36 PCS Change from Baseline, LSM (SE)	3.64 (0.753)	6.90 (0.731)[d]	7.70 (0.777)[b]	7.97 (0.767)[c]
ASAS HI Change from Baseline, LSM (SE)	-1.25 (0.300)	-2.30 (0.292)[d]	-2.36 (0.311)[a]	-2.74 (0.306)[a]

Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASDAS IN = ASDAS inactive disease; ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; CSR = clinical study report; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; LSM = least squares mean; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; N = number of patients in the ITT population; n = number of patients within each specific category; PBO = placebo; RHBV = Study I1F-MC-RHBV; SE = standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary; vs. = versus.

[a]p<.05 vs. PBO (multiplicity adjusted p-value).

[b]p<.01 vs. PBO (multiplicity adjusted p-value).

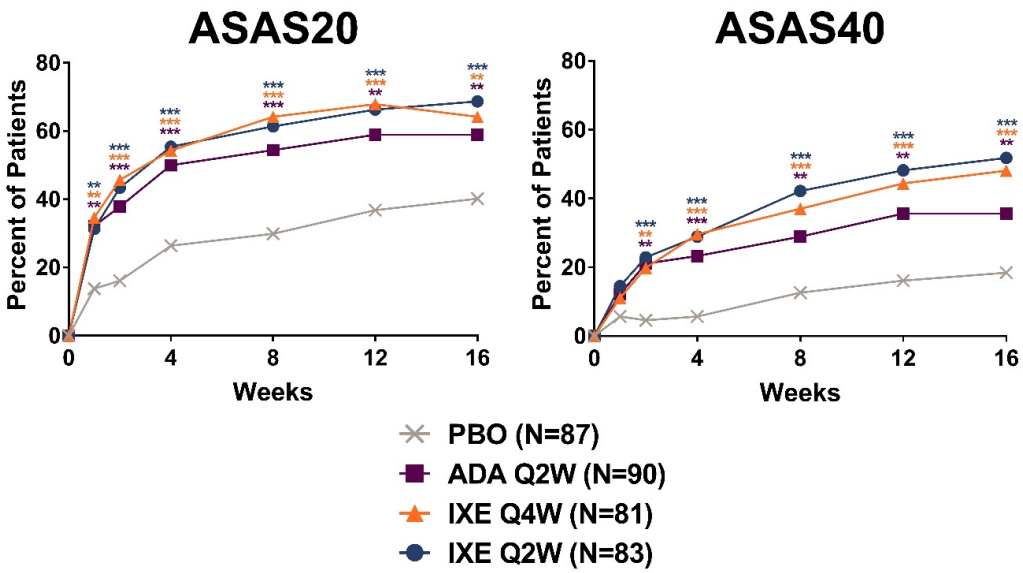
[c]p<.001 vs. PBO (multiplicity adjusted p-value).

[d]p<.05 vs. PBO (unadjusted p-value). p values for ADA vs. PBO comparisons are not multiplicity adjusted as these comparisons are not part of primary and major secondary objectives.

Note: All comparisons of ixekizumab with placebo for the primary and major secondary endpoints were statistically significant as calculated with the graphical method for multiple testing.

Greater percentage of patients achieved ASAS20/ASAS40 response (NRI) in each ixekizumab treatment group compared with the placebo group with differences appearing as early as week 1 (ASAS20) and week 2 (ASAS40), see figure below.

Figure 28. Time course of ASAS20 and ASAS40 response rates (NRI; ITT Population) up to Week 16 for Study RHBV.



Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; ASAS = Assessment of Spondyloarthritis International Society; CSR = clinical study report; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; NRI = nonresponder imputation; PBO = placebo; RHBV = Study I1F-MC-RHBV; vs. = versus.

** p<.01 vs. PBO (unadjusted p-value).

*** p<.001 vs. PBO (unadjusted p-value).

Note: ASAS40 at Week 16 was the primary endpoint for Study RHBV. ASAS20 at Week 16 was a major secondary endpoint for Study RHBV.

Other secondary endpoints

Table 19Study RHBV: Summary of other secondary endpoints at Week 16

	PBO N = 87	ADA Q2W N = 90	IXE Q4W N = 81	IXE Q2W N = 83
ASAS Components				
Patient Global Change from Baseline, LSM (SE)	-1.4 (0.24)	-2.6 (0.24)[c]	-2.5 (0.25)[b]	-2.8 (0.25)[c]
Spinal Pain Change from Baseline, LSM (SE)	-1.7 (0.24)	-2.7 (0.23)[b]	-3.2 (0.25)[c]	-3.2 (0.24)[c]
BASFI Change from Baseline, LSM (SE)	-1.16 (0.215)	-2.14 (0.209)[b]	-2.39 (0.222)[c]	-2.43 (0.219)[c]
Inflammation (BASDAI Questions 5 and 6) Change from Baseline, LSM (SE)	-1.27 (0.228)	-2.67 (0.221)[c]	-3.18 (0.235)[c]	-2.85 (0.232)[c]
BASDAI Change from Baseline, LSM (SE)	-1.39 (0.217)	-2.45 (0.211)[c]	-2.92 (0.224)[c]	-2.68 (0.220)[c]
BASMI Change from Baseline, LSM (SE)	-0.08 (0.083)	-0.45 (0.080)[b]	-0.50 (0.086)[c]	-0.41 (0.084)[b]
hs-CRP Change from Baseline, LSM (SE)	1.43 (1.924)	-7.20 (1.869)[b]	-5.21 (1.980)[a]	-6.57 (1.958)[b]
ASDAS <2.1 Response, n (%)	11 (12.6)	34 (37.8)[c]	35 (43.2)[c]	35 (42.2)[c]

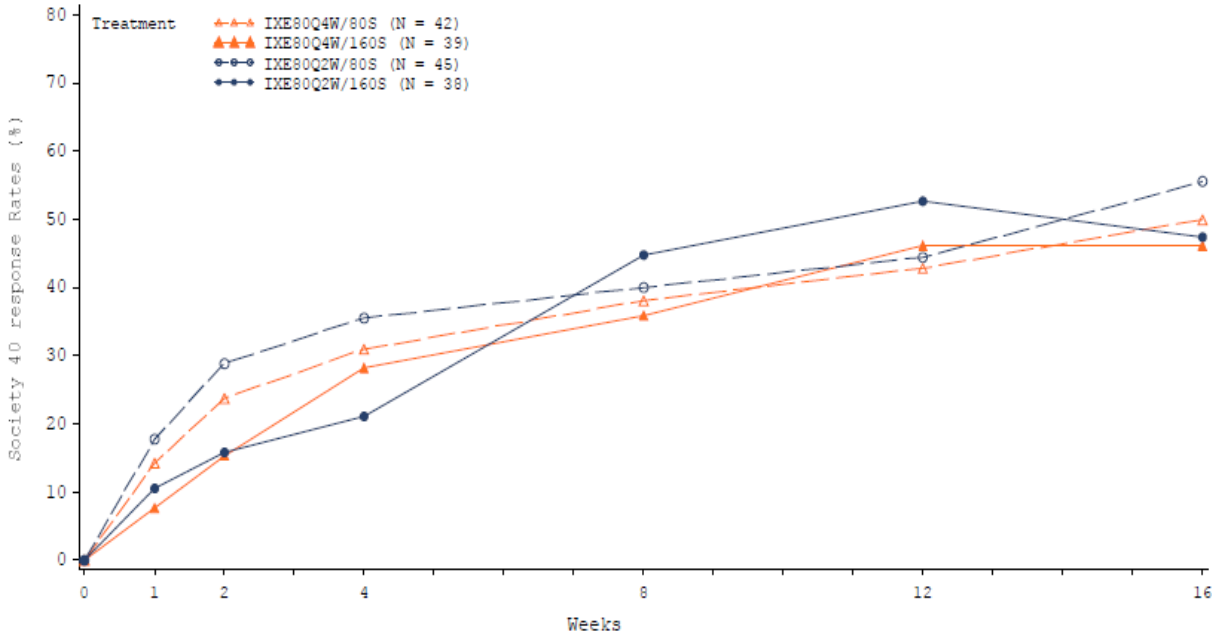
Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = 50% improvement in BASDAI; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CSR = clinical study report; hs-CRP = high-sensitivity C-reactive protein; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; LSM = least squares mean; N = number of patients in the ITT population; n = number of patients within each specific category; PBO = placebo; RHBV = Study I1F-MC-RHBV; SE= standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary; vs. = versus.

[a] p<.05 vs. PBO. [b]p<.01 vs. PBO. [c] p<.001 vs. PBO

Efficacy Starting Dose Analyses

The impact of ixekizumab starting dose (160 mg vs. 80 mg at Week 0) on treatment effect at Week 16 was assessed by ASAS20/40 response rates, the percentage of patients achieving ASDAS clinically important improvement, major improvement, or inactive disease, change from baseline in CRP, and change from baseline in BASFI.

Figure 29. ASAS40 response rates at each postbaseline visit by ixekizumab starting dose (ITT, NRI)



N = number of patients in the analysis population. Abbreviations: IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; 80S = 80 mg starting dose; 160S = 160 mg starting dose;

Extended Treatment Period (Period 3, Week 16 up to Week 52)

Table 20: Summary of Endpoints at Week 52, ITT Population Initially Randomised to Ixekizumab at Week 0

	Week 16	Week 36	Week 52
ASAS20 response, %			
Ixekizumab 80 mg Q4W (N = 81)	64.2%	71.6%	65.4%
Ixekizumab 80 mg Q2W (N = 83)	68.7%	72.3%	71.1%
ASAS40 response, %			
Ixekizumab 80 mg Q4W (N = 81)	48.1%	55.6%	53.1%
Ixekizumab 80 mg Q2W (N = 83)	51.8%	48.2%	50.6%
ASDAS Mean Change from Baseline			
Ixekizumab 80 mg Q4W (N = 81)	-1.43	-1.52	-1.65
Ixekizumab 80 mg Q2W (N = 83)	-1.39	-1.59	-1.58
BASDAI50 Response, %			
Ixekizumab 80 mg Q4W (N = 81)	42.0%	49.4%	53.1%
Ixekizumab 80 mg Q2W (N = 83)	43.4%	47.0%	45.8%
BASFI Mean Change from Baseline			
Ixekizumab 80 mg Q4W (N = 81)	-2.38	-2.82	-2.80
Ixekizumab 80 mg Q2W (N = 83)	-2.45	-2.75	-2.78
ASDAS <1.3 Response, %			
Ixekizumab 80 mg Q4W (N = 81)	16.0%	16.0%	22.2%
Ixekizumab 80 mg Q2W (N = 83)	10.8%	19.3%	19.3%
MRI Spine SPARCC Mean Change from Baseline			
Ixekizumab 80 mg Q4W (N = 81)	-8.93	NA	-8.83
Ixekizumab 80 mg Q2W (N = 83)	-8.72	NA	-8.46
SF-36 PCS Mean Change from Baseline			
Ixekizumab 80 mg Q4W (N = 81)	7.11	7.92	8.28
Ixekizumab 80 mg Q2W (N = 83)	7.37	7.98	8.06
ASAS HI Mean Change from Baseline			
Ixekizumab 80 mg Q4W (N = 81)	-2.25	-2.73	-2.65
Ixekizumab 80 mg Q2W (N = 83)	-2.84	-2.88	-3.29

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CSR = clinical study report; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; N = number of patients in the ITT population; PBO = placebo; RHBV = Study I1F-MC-RHBV; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary.

Ancillary analyses

Subgroup analyses supporting the primary endpoint (ASAS40) and the major secondary endpoint (ASAS20) were performed by patient demographics, geographic region, baseline disease severity, and other patient characteristics. The subgroup analyses were conducted with small subgroup sizes and without control for Type I error. The findings from the subgroup analyses were generally consistent

with those from the overall population. For the majority of subgroup analyses, both ixekizumab treatment groups demonstrated greater efficacy compared with the placebo group. All significant treatment-by-subgroup interactions (defined as p<.10) are summarized below.

At Week 16, the following subgroups from the Blinded Treatment Dosing Period showed significant treatment-by-subgroup interactions

- ASAS40
    - Geographic region: Europe vs. non-Europe (p=.049)
    - Geographic region: America vs. Asia vs. Europe (p=.064)
    - Baseline CRP category: ≤3.00 mg/L vs. >3.00 mg/L (p=.092)
    - Duration of symptom onset category: <10 years vs. ≥10 years (p=.020)
    - Duration of symptom onset category: <5 years vs. ≥5 years (p=.093)
- ASAS20
    - Baseline CRP category: ≤3.00 mg/L vs. >3.00 mg/L (p=.097)
    - History of enthesitis: yes vs. no (p=.083)

The applicant states that the significance and clinical meaningfulness of these potential statistically significant treatment-by-subgroup interactions needs further investigation in a larger, integrated dataset.

Comparison of Results in Subpopulations

Efficacy in Subpopulations in R-axSpA Studies

Variables analysed

Potential differences in response across patient demographic and baseline disease activity variables were examined for ASAS20 and ASAS40 response rates at Week 16 in the Primary R-axSpA Analysis Set. The most clinically relevant subgroup variables included

- patient demographics (e.g., sex, age, weight, race)
- disease-related characteristics (e.g., baseline CRP category, baseline ASDAS category, baseline BASDAI category, duration of symptoms since axSpA onset), and
- concomitant therapy use at baseline (e.g., cDMARD, oral corticosteroid, NSAIDs, analgesic).

Results of subgroup analyses

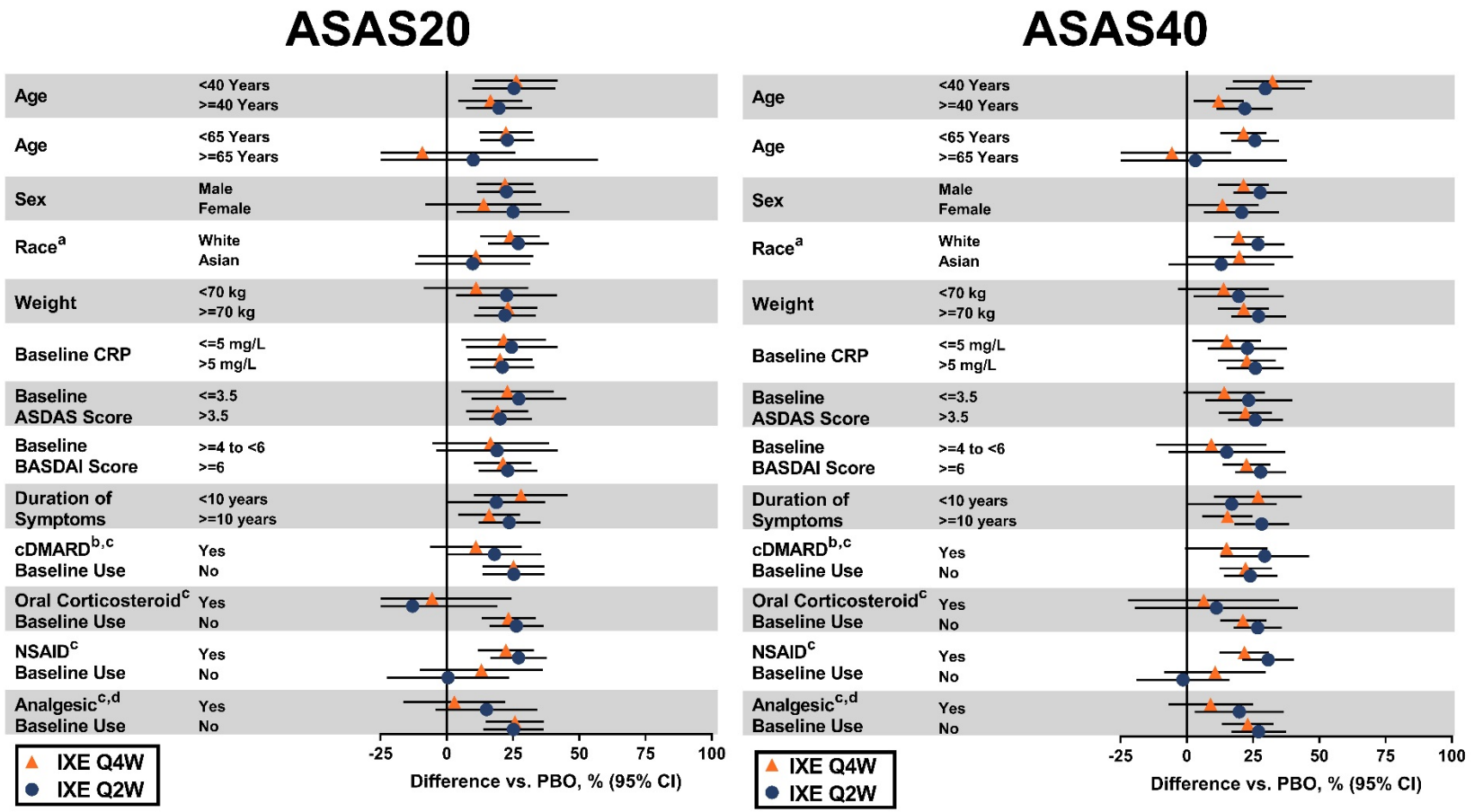
Figure 32. presents the ASAS20 and ASAS40 response rates for selected subgroups in the Primary R-axSpA Analysis Set. The findings from the subgroup analyses were generally consistent with those from the overall population, and the treatment effect of ixekizumab was generally consistent across subgroups.

For the majority of subgroup analyses, both ixekizumab treatment groups demonstrated greater efficacy compared with the placebo group, and there was no difference between ixekizumab treatment groups.

For patients who were 65 years or older (6.0% of the ITT population) or who were receiving oral corticosteroids at baseline (10.4% of the ITT population), interpretation of the data was limited by the small number of patients in each of these subgroups.

In summary, the applicant concludes that subgroup analyses did not identify any demographic or baseline variables with important effects on the efficacy of ixekizumab.

Figure 30. ASAS20 [left panel] and ASAS40 [right panel] response rates (NRI; ITT Population) in selected patient subgroups (Primary R-axSpA Analysis Set).



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; cDMARD = conventional disease-modifying antirheumatic drug; CI = confidence interval; CRP = C-reactive protein; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; NRI = nonresponder imputation; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; Primary R-axSpA Analysis Set = Primary Radiographic Axial Spondyloarthritis Placebo-Controlled Integrated Analysis Set; vs. = versus.

a Additional races included American Indian/Alaska Native (n = 24), Black/African American (n = 5), and Multiple Races (n = 8); however, they are not plotted due to the small number in each subgroup.

b In this subgroup analysis, cDMARDs included hydroxychloroquine, methotrexate, and sulfasalazine.

c Patients were to be on stable doses from baseline visit through Week 16 (double-blind period); therefore, "Baseline Use: Yes" can also be considered concomitant use during the Blinded Treatment Dosing Period.

d In this subgroup analysis, analgesics included systemic opioids and/or short-acting analgesics with no anti-inflammatory effect.

Additional subgroup analysis on number of prior TNFi used was provided during the procedure upon request from the CHMP (**Table 21**).

Table 21: ASAS20 and ASAS40 Response Rates at Week 16 (NRI) By Number of Prior TNFi Used (1 TNFi or 2 TNFi's) Intent to Treat Population Study I1F-MC-RHBW

	Placebo (N = 104)	IXE Q4W (N = 114)	IXE Q2W (N = 98)	All IXE (N = 212)
ASAS20				
1 prior TNFi, n/Ns (%)	19/62 (30.6)	33/70 (47.1)	34/66 (51.5)	67/136 (49.3)
2 prior TNFi's, n/Ns (%)	12/42 (28.6)	22/44 (50.0)	12/31 (38.7)	34/75 (45.3)
ASAS40				
1 prior TNFi, n/Ns (%)	7/62 (11.3)	14/70 (20.0)	24/66 (36.4)	38/136 (27.9)
2 prior TNFi's, n/Ns (%)	6/42 (14.3)	15/44 (34.1)	6/31 (19.4)	21/75 (28.0)

2.4.2.2. Study I1F-MC-RHBW (RHBW)

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

Methods

Study design

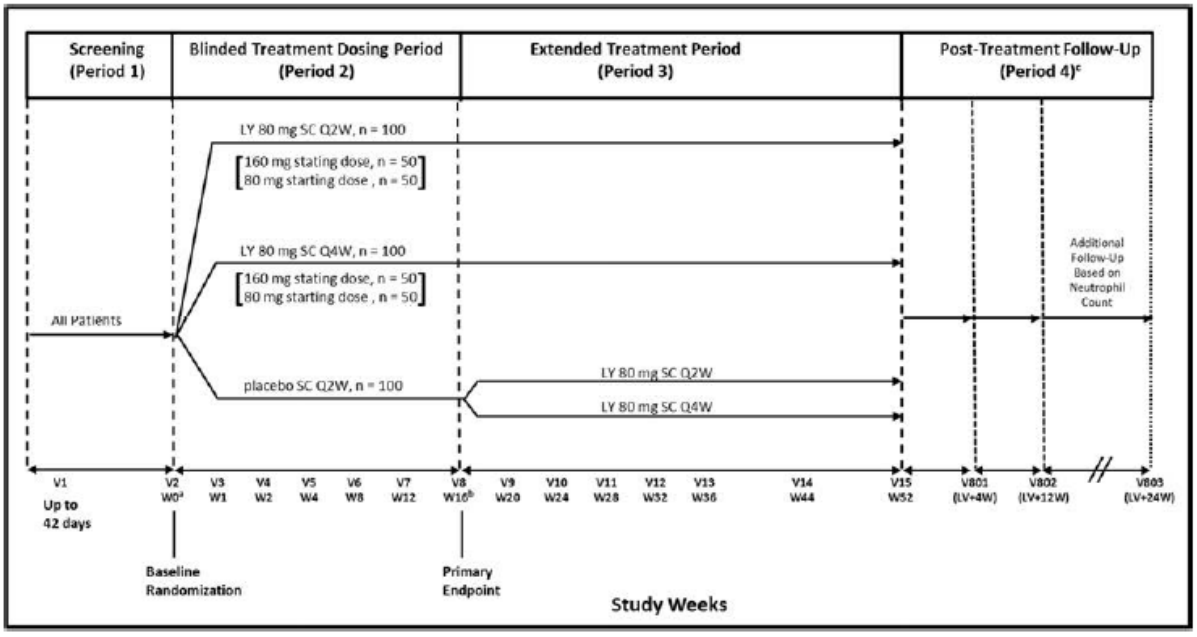
The study design is presented in Figure 31. .

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
- placebo

A starting dose of either 160mg or 80mg was given to patients with ixekizumab.

Figure 31. Study design of study RHBW



Study participants

Key inclusion criteria

The study population included patients aged 18 years or older who met the following criteria:

1. TNFi-experienced (i.e., had prior treatment with 1 to 2 TNFi and discontinued at least 1 TNFi due to intolerance or inadequate response [defined as in the opinion of the investigator, the patient had an inadequate response to at least 12 weeks of treatment with a TNFi])
2. Have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically (based on central reading) according to the modified New York (mNY) criteria and at least 1 SpA feature according to ASAS criteria; had a history of back pain ≥3 months with age at onset <45 years; and had active disease defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and back pain ≥4 on a numeric rating scale (NRS) at screening and baseline.
3. Have an inadequate response to ≥2 NSAIDs or a history of intolerance to NSAIDs and had a history of prior therapy for axSpA of at least 12 weeks prior to screening.

Key exclusion criteria

1. Have total ankylosis of the spine;
2. History of other systemic inflammatory diseases;
3. Have active Crohn's disease or active ulcerative colitis within 6 months prior to baseline
4. Have evidence of active anterior uveitis within 4 weeks prior to baseline

5. current or history of lymphoproliferative disease or malignant disease within 5 years prior to baseline; presence of significant, uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders; recent history of suicide attempt, score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-Self Report 16 items (QIDS-SR16), or at risk for suicide;
6. Serious infection,
7. Presence or history of a known immunodeficiency or of being immunocompromised;
8. herpes zoster or other varicella zoster virus infection within 12 weeks prior to baseline; a known allergy or hypersensitivity to any biologic therapy; major surgery within 8 weeks prior to baseline; surgical treatment to a joint to be assessed in the study within 8 weeks prior to baseline or during the first 16 weeks of the study.
9. Prior/Concurrent Therapy or Clinical Trial Experience: conventional disease-modifying antirheumatic drugs (cDMARDs) and/or any other immunosuppressive agents within 4 weeks prior to baseline (exceptions include methotrexate, sulfasalazine, and hydroxychloroquine);
10. Use of oral corticosteroids >10 mg/day;
11. Concurrent or prior use of biologic or other immunomodulatory agents (Note: previous TNFi therapy was permitted); parenteral glucocorticoid administration within 6 weeks prior to baseline or anticipated administration during Period 2 of the study; a live vaccination or participated in a vaccine clinical study within 12 weeks prior to baseline or intended to have a live vaccination during the course of the study or within 12 weeks of completing treatment in the study; a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline, or intended to have a vaccination of BCG during the course of the study or within 12 months of completing treatment in the study.
12. Diagnostics Assessments: evidence or suspicion of active or latent tuberculosis (TB); positive for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV); electrocardiogram (ECG) abnormalities;, any of the following: neutrophil count <1500 cells/µL, lymphocyte count <800 cells/µL, platelet count <100,000 cells/µL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5xULN), total white blood cell (WBC) count <3000 cells/µL, hemoglobin (HGB) <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients; other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant.

Treatments

The Blinded Treatment Dosing Period (Period 2; Week 0 to Week 16) involved a comparison of 2 dosing regimens of ixekizumab, 80 mg Q2W and 80 mg Q4W, to placebo. Each ixekizumab treatment group included patients receiving an 80-mg or a 160-mg starting dose. All doses were administered via SC injection. During the Extended Treatment Period (Period 3; Week 16 to Week 52), patients originally assigned to either ixekizumab dosing regimen remained on the same dosing regimen through Period 3. At Week 16, patients originally assigned to placebo were re-randomized at a 1:1

ratio to ixekizumab 80 mg Q2W or Q4W with a 160-mg starting dose (as two 80-mg SC injections). To maintain blinding, all patients received 2 injections at baseline (Week 0). During the remainder of Period 2, all patients received 1 injection Q2W. At Week 16, all patients, regardless of treatment group, received 2 SC injections. During the remainder of Period 3, each patient received 1 SC injection Q2W regardless of his or her assigned dosing regimen.

Objectives

The primary objective was to compare ixekizumab 80 mg every 2 weeks (Q2W) and 80 mg every 4 weeks (Q4W) versus placebo in the treatment of patients with active radiographic axial spondyloarthritis (rad-axSpA) at Week 16, as measured by the proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response.

There were also several secondary objectives, see endpoints below.

Outcomes/endpoints

Primary endpoint:

ASAS40 response at week 16.

Key secondary endpoints

- ASAS20 response at Week 16
- ASDAS change from baseline at week 16
- BASDAI change from baseline at week 16
- ASDAS <2.1 response at week 16.
- BASFI change from baseline at week 16
- MRI Spine SPARCC score change from baseline at Week 16
- SF-36 PCS score change from baseline at Week 16
- ASAS HI change from baseline at Week 16

Other endpoints were mostly in line with study RHBV.

Sample size

The total planned sample size of the study was 300 patients. With 100 patients per treatment group and assuming the Week 16 ASAS40 response rates of 7% for the placebo group and 27% for the ixekizumab 80-mg Q2W treatment group, this study was planned to have approximately 96% power to test the superiority of ixekizumab 80 mg Q2W to placebo for ASAS40 at Week 16. A 2-sided Fisher's exact test at an alpha level of 0.05 was assumed.

Randomisation

At Week 0 (Visit 2), patients who met all criteria for enrolment were randomised using a 1:1:1 ratio to receive ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). At randomisation patients were stratified by country, baseline CRP (non-elevated or elevated) and number of prior TNF inhibitors used (1 or 2).

Initially, the study was to enrol approximately 70% of patients with baseline CRP elevated (>5.00 mg/L) and approximately 30% of patients with normal baseline CRP, and approximately 80% of patients with 1 prior TNF inhibitor and approximately 20% of patients with 2 prior TNF inhibitors. Within study protocol amendment (b) (approved 14 Jan 2017) the cohort size of patients having failed 2 prior TNFi was increased from 20% to 35%. Within amendment (c) (approved 01 May 2017) the cohort size of patients having failed 2 prior TNFi was increased from 35% to 40% and the cohort size of patients with non-elevated baseline CRP was increased from 30% to 40%.

Amendment (c) also allowed patients to re-screen for the elevated CRP cohort (once the non-elevated CRP cohort had fully enrolled).

Blinding (masking)

This was a double-blind study. Initial randomisation (study drug administered between Weeks 0 and 16) remained blinded to study site personnel and patients until the final (i.e., end of study) clinical trial database lock has occurred, or patients have entered Study RHBY, whichever occurs first. Study drug assigned during the Extended Treatment Period (Period 3) will be known to the site and patient at entry to Study RHBY. Initial randomisation, as well as study drug assignment during Period 3, remained blinded to the sponsor until the clinical trial database through Week 16 had been locked. The syringes (and contents) containing either ixekizumab or placebo were visibly indistinguishable from each other.

Statistical methods

As pre-planned a database lock and unblinding occurred on 19 Jun 2018 after all patients had completed the Week 16 Visit or discontinued study treatment early, either on or prior to Week 16. The statistical analysis plan (SAP) was originally approved on 07 Apr 2016 (prior to first patient visit) and revised twice on 12 Jun 2018 and 18 Jun 2018 before unblinding of data. There were no changes to the prespecified statistical analysis after the interim database lock and unblinding.

A second (pre-planned) interim database lock (28 February 2019) occurred after all patients had completed the Week 52 Visit or discontinued study drug early, either on or prior to Week 52. Efficacy and safety results from the completed Extended Treatment Period (Weeks 16 to 52; Extended Treatment Period Population), during which study treatment remained blinded to study site personnel and patients, are presented in a separate CSR. Selected analyses were also provided for the combined Blinded Treatment Dosing Period and Extended Treatment Period (Weeks 0 to 52; ITT or Safety Population initially randomised to ixekizumab at Week 0).

At the time of the database lock for the Week 52 CSR, the Post-Treatment Follow-Up Period was still ongoing; results from this period will be presented in a separate report.

Primary analysis
Treatment comparisons of categorical efficacy variables (including the primary endpoint) were performed using a logistic regression analysis model including treatment, geographic region (Europe and non-Europe), number of prior TNFi used, and baseline CRP status (non-elevated or elevated; elevated defined as >5.00 mg/L). The odds ratio and 95% confidence intervals (CIs) were reported; treatment difference and 95% CI were also reported. Secondary analysis was conducted using a Fisher's exact test. For patients who did not meet clinical response criteria or had missing data were considered non-responders (referred to as non-responder imputation [NRI]).

The primary analyses for all continuous efficacy and health outcomes variables (except MRI score) were based on a mixed-effects model of repeated measures (MMRM) analysis method with treatment, geographic region, number of prior TNFi used, baseline CRP status, baseline value (except for the analysis of CRP, in which baseline CRP value was not included in the model), visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors. The primary analyses for MRI endpoints were made using analysis of covariance (ANCOVA) based on observed data.

Secondary/Sensitivity analyses
As a secondary analysis for the primary and major secondary categorical efficacy measures, a categorical MMRM, estimating the percentage of patients achieving response across postbaseline visits, was used. A secondary analysis for continuous efficacy and health outcome variables was conducted using ANCOVA with the modified baseline observation carried forward (mBOCF) method; the last observation carried forward (LOCF) method was also used for major secondary objectives.

The placebo multiple imputation (pMI) method was used for analyses of the efficacy endpoints ASAS40, ASAS20, and ASDAS change from baseline at Week 16.

To evaluate the robustness of statistical analyses of key efficacy data and assumptions, tipping point analyses were performed for the endpoints ASAS40, ASAS20, and mean change from baseline in ASDAS at the primary time point of Week 16.

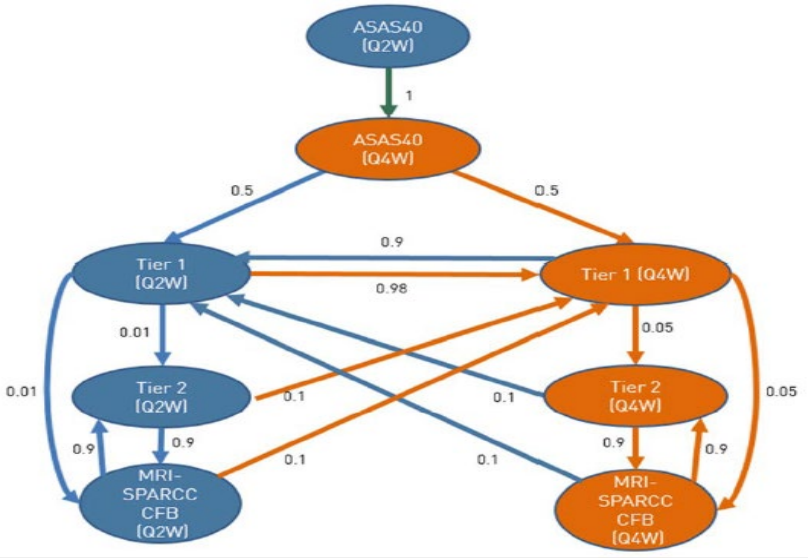
Multiple comparisons/multiplicity
A multiple testing strategy was implemented to control the family-wise type I error rate at a 2-sided α level of 0.05 based on a graphical multiple testing procedure (Bretz et al. 2011). The following primary and major secondary outcomes were to be tested for both ixekizumab 80 mg Q2W and Q4W regimen at Week 16:

Primary - proportion of patients achieving an ASAS40 response [ASAS40]
Secondary 1 - proportion of patients achieving an ASAS20 response [ASAS20]
Secondary 2 - change from baseline in ASDAS score [ASDAS change from baseline (CFB)]
Secondary 3 - change from baseline in BASDAI score [BASDAI CFB]
Secondary 4 - change from baseline in BASFI [BASFI CFB]
Secondary 5 - change from baseline in SF-36 PCS score [SF-36 PCS CFB]
Secondary 6 - proportion of patients achieving ASDAS <2.1 [ASDAS<2.1]
Secondary 7 - change from baseline in ASAS Health Index (ASAS HI) [ASAS HI CFB]
Secondary 8 - change from baseline in MRI of the spine [MRI spine SPARCC score CFB]

With the exception of secondary outcome 8 (MRI spine SPARCC score CFB), the remaining secondary outcomes were grouped into 2 tiers.

The testing steps were as outlined below:

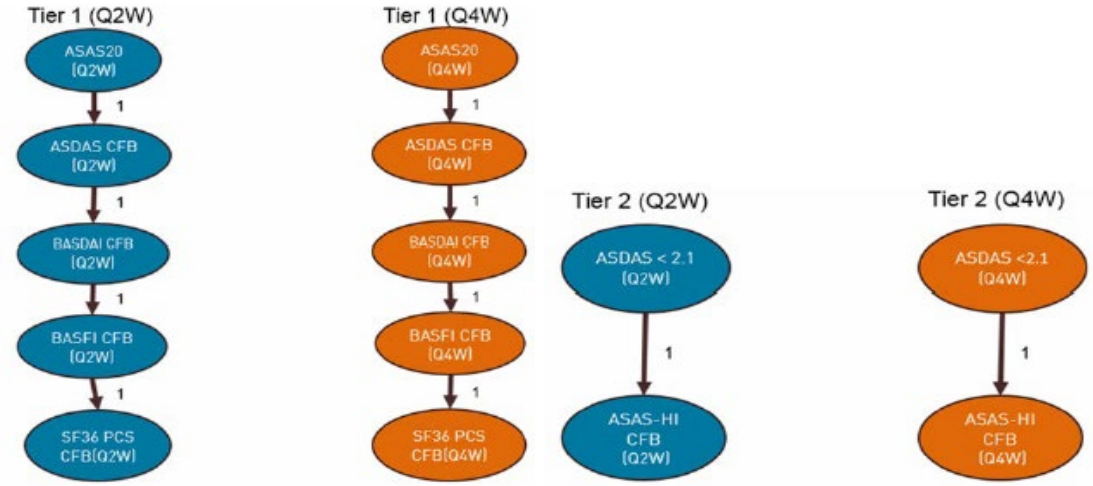
Figure 32. Illustration of graphical multiple testing procedure with initial α = 0.05 allocation and weight



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

Figure 33. Graphical multiple testing scheme used within the Tier 1 group of endpoints (Tier 1 (A); Tier 2 (B))

A **B**



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CFB = change from baseline; Q2W = every 2 weeks; Q4W = every 4 weeks; SF-36 PCS = Short Form 36 physical component score.

Graphical multiple testing scheme used within the Tier 2 group of endpoints

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

Results

Participant flow

A total of 316 patients (98, ixekizumab 80 mg Q2W; 114, ixekizumab 80 mg Q4W; 104, placebo) were randomised and were treated (at least 1 dose) in the Blinded Treatment Dosing Period.

A total of 282 patients (90, ixekizumab 80 mg Q2W; 99, ixekizumab 80 mg Q4W; 93, placebo) completed Week 16 Visit of which 281 (188, ixekizumab/ixekizumab; 93, placebo/ixekizumab) were treated (at least 1 dose) in Extended Treatment Period.

A total of 250 patients (169, ixekizumab/ixekizumab; 81, placebo/ixekizumab) completed Week 52 Visit.

Figure 34. Participant flow in study RHBW from screening until Week 16.

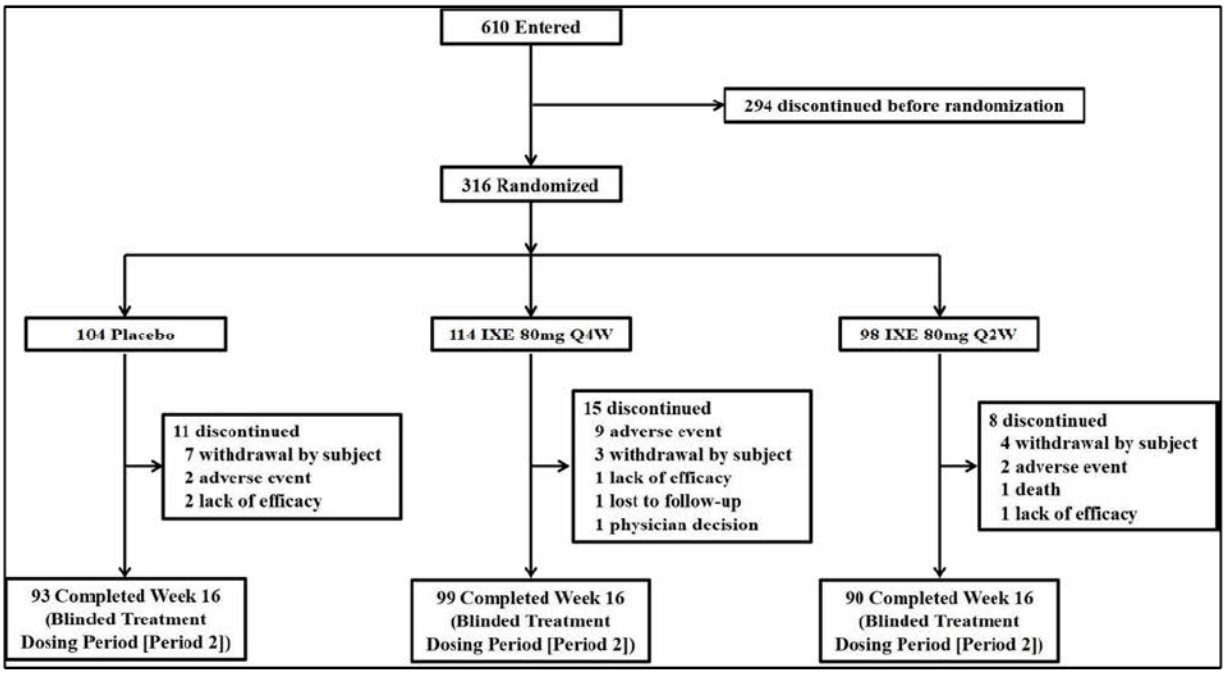
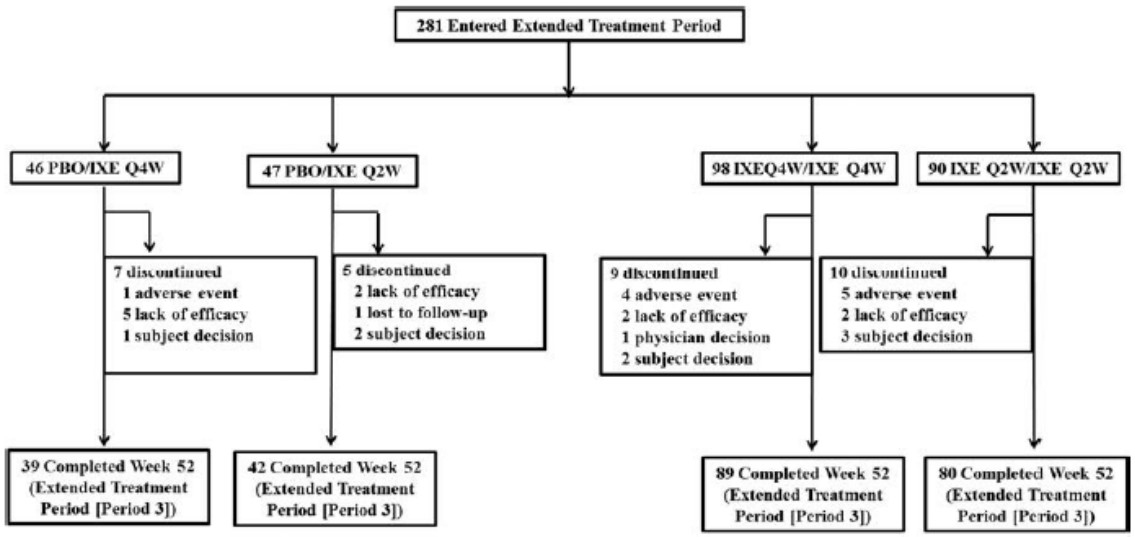


Figure 35. Participant flow in study RHBW during the extended treatment period, week 16 until week 52.



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

In Study RHBW, rates of discontinuations due to AEs through Week 16 were similar for the ixekizumab 80-mg Q2W treatment group relative to placebo, but higher for the ixekizumab 80-mg Q4W treatment group relative to placebo, with no particular AE driving the difference. This observed difference may reflect random variability rather than drug effect, given that the rate of discontinuations due to AEs in the more frequent ixekizumab 80-mg Q2W treatment group is similar as for placebo. In addition, there were no discontinuations due to AEs through Week 16 in the Q4W treatment group in Studies RHBV and RHBX (bDMARD-naive populations)

Recruitment

Date first patient enrolled: 10 May 2016

Date last patient completed Week 52 Visit: 23 January 2019

Date of database lock: 28 February 2019

This study was conducted at 106 study sites in 15 countries.

Conduct of the study

There were 4 protocol amendments:

Protocol amendment (a) - 19 Sep 2016: The main changes implemented with this amendment were related to the conduct of the study and are as follows:

- The SPARCC scoring method for MRI of the spine replaced the ASSpiMRI-Berlin score as a major secondary endpoint. Emerging evidence indicated that the SPARCC may be more discriminative than the Berlin scoring method and may provide higher inter-examiner

reliability. The ASSpiMRI-Berlin scoring method was still included as an endpoint for "other" secondary objectives to allow for comparisons with other studies' data that are based on the Berlin method.

- Adjudication of suspected IBD was added to ensure that all reported events were evaluated uniformly by a single group in an unbiased manner.
- Additional changes were made to enhance clarity of the protocol.

Protocol Amendment (b) - 14 Jan 2017: The main change implemented with this amendment was related to the method of treatment assignment. Specifically, the amendment increased the cohort size of patients having failed 2 prior TNFi (from 20% to 35%) to more accurately reflect the patient population that might be treated in real life and to align with the spontaneous distribution of patients enrolled at the time of the amendment

Protocol Amendment (c) - 01 May 2017: The main changes implemented with this amendment were related to the method of treatment assignment.

The amendment increased the cohort size of patients having failed 2 prior TNFi (from 35% to 40%) and the cohort size of patients with non-elevated baseline CRP (30% to 40%) to more accurately reflect the patient population that might be treated in real life and to align with the spontaneous distribution of patients enrolled at the time of the amendment. The amendment also allowed patients to rescreen for the elevated CRP cohort (once the non-elevated CRP cohort had fully enrolled), which allowed patients to have an additional opportunity to participate in the study and receive study drug.

Protocol Amendment (d) - 02 Jun 2017. The amendment corrected a numbering error in the Exclusion Criteria.

Baseline data

Demographic characteristics, disease history, and baseline characteristics were, according to the applicant, well balanced across treatment groups and consistent with the target population of r-axSpA.

The patient population was predominantly male (80.1%), white (80.6%) and HLA-B27 positive (81.3%). The mean age was 46.1 years. The mean age at onset of axSpA was 28.1 years. The mean duration of axSpA symptoms was 18.4 years. The mean time since axSpA diagnosis was 11.6 years.

Disease activity at baseline was high-to-very high as reflected by mean baseline scores for BASDAI (7.4) and ASDAS (4.1), as well as mean hs-CRP (17.8 mg/L).

At baseline,

- 76.3% of patients were receiving NSAIDs
- 27.2% of patients were receiving conventional DMARDs (sulfasalazine or methotrexate)
- 11.4% of patients were receiving oral corticosteroids
- 30.7% of patients were receiving analgesics
- 62.9% of patients had prior use of 1 TNFi, and
- 37.1% of patients had prior use of 2 TNFi's.

The main reason of discontinuation of TNF-inhibitors was inadequate response (55.7%), loss of response (37.3%) or intolerance (14.2%)

Numbers analysed

Table 22: Population analysed in study RHBW

Period Population and Status	PBO n (%)	IXE80Q4W n (%)	IXE80Q2W n (%)	Total n (%)
Period 2 - Blinded Treatment Dosing Period				
Randomized patients	104	114	98	316
Intent to Treat (ITT)	104	114	98	316
Completed Period 2 (% relative to ITT)	93 (89.4%)	99 (86.8%)	90 (91.8%)	282 (89.2%)
Completed Period 2 and entered Period 4 directly	0	1	0	1
Completed Period 2 and entered Period 3	91	98	90	279
Discontinued from Period 2 (% relative to ITT)	11 (10.6%)	15 (13.2%)	8 (8.2%)	34 (10.8%)
Discontinued from Period 2 and entered Period 4	5	13	4	22
Discontinued from Period 2 but did not enter Period 4	6	2	4	12
Per Protocol Set (PPS) (% relative to ITT)	88 (84.6%)	96 (84.2%)	81 (82.7%)	265 (83.9%)
Completed Period 2 treatment (% relative to PPS)	80 (90.9%)	86 (89.6%)	77 (95.1%)	243 (91.7%)
Safety (% relative to ITT)	104 (100.0%)	114 (100.0%)	98 (100.0%)	316 (100.0%)
Completed Period 2 treatment (% relative to safety)	93 (89.4%)	99 (86.8%)	90 (91.8%)	282 (89.2%)

Abbreviations: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; n = number of patients in the specified category.
SUBJID=30811 and SUBJID=30788 are still on going in the study but have not any EXT dose injection at DBL, so the patients were not counted as "Completed Period 2 and entered Period 3".

Outcomes and estimation

Primary analysis - Blinded Treatment Dosing Period (Week 0 to Week 16)

Table 23 presents nominal and multiplicity-adjusted p-values based on the graphical multiple-testing procedure for the analysis of the primary and major secondary endpoints. Statistically significant differences were observed for the primary and all major secondary endpoints at Week 16 for each ixekizumab treatment group compared to the placebo group, with the exception of ASAS HI change from baseline at Week 16 in the ixekizumab 80 mg Q2W group.

Table 23: Summary of Primary and Major Secondary Analyses at Week 16 (ITT)

	Ixekizumab 80 mg Q4W vs. Placebo		**Ixekizumab 80 mg Q2W vs. Placebo**	
	Unadjusted Nominal p-Value	Multiplicity Adjusted p-Value	Unadjusted Nominal p-Value	Multiplicity Adjusted p-Value
Primary Objective				
ASAS40 response	.017	.017	.003	.003
Major Secondary Objectives				
ASAS20 response	.006	.017	.013	.017
ASDAS change from baseline	<.001	.017	<.001	.017
BASDAI change from baseline	<.001	.017	<.001	.017
BASFI change from baseline	<.001	.017	<.001	.017
SF-36 PCS change from baseline	<.001	.017	<.001	.017
ASDAS <2.1 response	.006	.017	.006	.031
ASAS HI change from baseline	.026	.031	.149	.149
MRI Spine SPARCC change from baseline	.001	.017	<.001	.017

Primary and major secondary endpoints

The primary objective of the study was achieved for both ixekizumab treatment groups. There was a significantly greater percentage of patients who achieved an ASAS40 response at Week 16 for each of the ixekizumab treatment groups compared with the placebo group.

Table 24: Study RHBW: Summary of Primary and Major Secondary Objectives at Week 16

	PBO N = 104	IXE Q4W N = 114	IXE Q2W N = 98
Primary Objective			
ASAS40 Response, n (%)	13 (12.5)	29 (25.4)[a]	30 (30.6)[b]
Difference from PBO, % (95% CI)		12.9 (2.7, 23.2)	18.1 (7.0, 29.2)
Major Secondary Objectives			
ASAS20 Response, n (%)	31 (29.8)	55 (48.2)[a]	46 (46.9)[a]
Difference from PBO, % (95% CI)		18.4 (5.7, 31.1)	17.1 (3.9, 30.4)
ASDAS Change from Baseline, LSM (SE)	-0.11 (0.099)	-1.16 (0.094)[a]	-1.13 (0.103)[a]
BASDAI Change from Baseline, LSM (SE)	-0.92 (0.212)	-2.17 (0.202)[a]	-2.09 (0.221)[a]
BASFI Change from Baseline, LSM (SE)	-0.64 (0.215)	-1.69 (-.205)[a]	-1.92 (0.225)[a]
SF-36 PCS Change from Baseline, LSM (SE)	1.36 (0.815)	6.58 (0.776)[a]	6.12 (0.847)[a]
ASDAS <2.1 Response, n (%)	5 (4.8)	20 (17.5)[a]	16 (16.3)[a]
ASAS HI Change from Baseline, LSM (SE)	-0.89 (0.338)	-1.92 (0.322)[a]	-1.58 (0.352)
MRI Spine SPARCC Change from Baseline, LSM (SE)	3.29 (1.402)	-2.99 (1.384)[a]	-3.97 (1.534)[a]

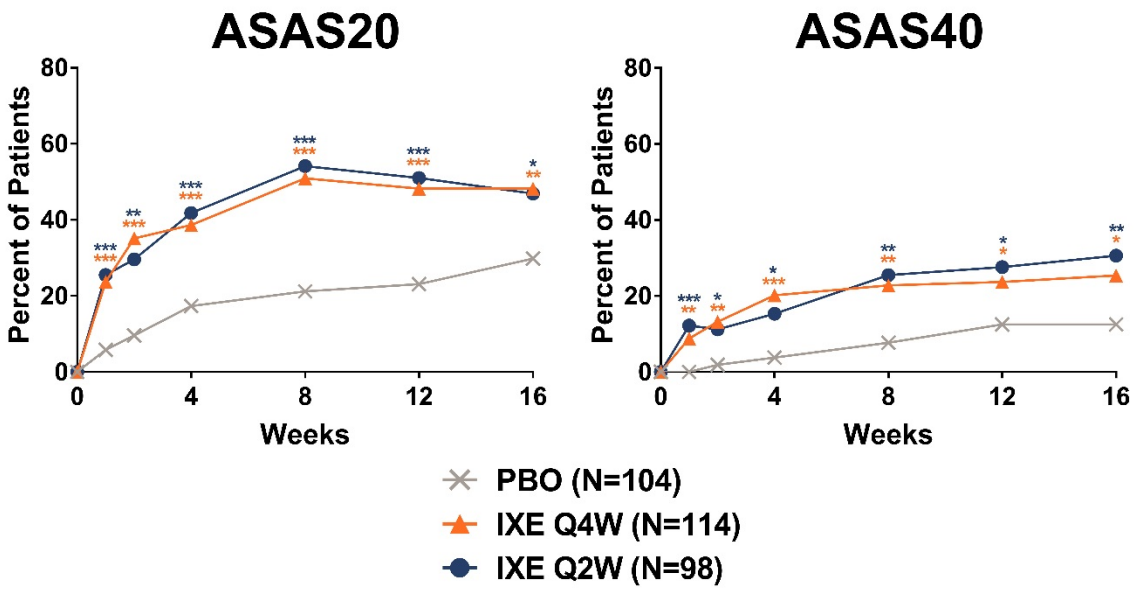
Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; CSR = clinical study report; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; LSM = least squares mean; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; N = number of patients in the ITT population; n = number of patients within each specific category; PBO = placebo; RHBW = Study I1F-MC-RHBW; SE= standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary.

a p<.05 vs. PBO (multiplicity adjusted p-value).

b p<.01 vs. PBO (multiplicity adjusted p-value).

Note: All comparisons of ixekizumab with placebo for the primary and major secondary endpoints were statistically significant, with the exception of change from baseline at Week 16 for ASAS HI for the ixekizumab 80-mg Q2W group, as calculated with the graphical method for multiple testing.

Figure 36. Time course of ASAS20 and ASAS40 response rates (NRI; ITT Population) up to Week 16 for Study RHBW



Other secondary endpoints

Table 25: Study RHBW: Summary of Other Secondary Objectives at Week 16

	PBO N = 104	IXE Q4W N = 114	IXE Q2W N = 98
ASAS Components			
Patient Global Change from Baseline, LSM (SE)	-0.7 (0.23)	-2.4 (0.22)[c]	-2.1 (0.24)[c]
Spinal Pain Change from Baseline, LSM (SE)	-1.0 (0.24)	-2.4 (0.23)[c]	-2.5 (0.25)[c]
BASFI Change from Baseline, LSM (SE)	-0.64 (0.215)	-1.69 (0.205)[c]	-1.92 (0.225)[c]
Inflammation (BASDAI Questions 5 and 6) Change from Baseline, LSM (SE)	-0.70 (0.236)	-2.42 (0.226)[c]	-2.41 (0.246)[c]
BASMI Change from Baseline, LSM (SE)	-0.05 (0.094)	-0.35 (0.090)[a]	-0.22 (0.098)
hs-CRP Change from Baseline, LSM (SE)	9.72 (2.738)	-11.10 (2.619)[c]	-8.12 (2.883)[c]
BASDAI50 Response, n (%)	10 (9.6)	25 (21.9)[a]	23 (23.5)[a]

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; CSR = clinical study report; ITT = intent-to-treat; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; LSM = least squares mean; MRI Spine SPARCC = magnetic resonance imaging of spine Spondyloarthritis Research Consortium of Canada score; N = number of patients in the ITT population; n = number of patients within each specific category; PBO = placebo; RHBW = Study I1F-MC-RHBW; SE= standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary.

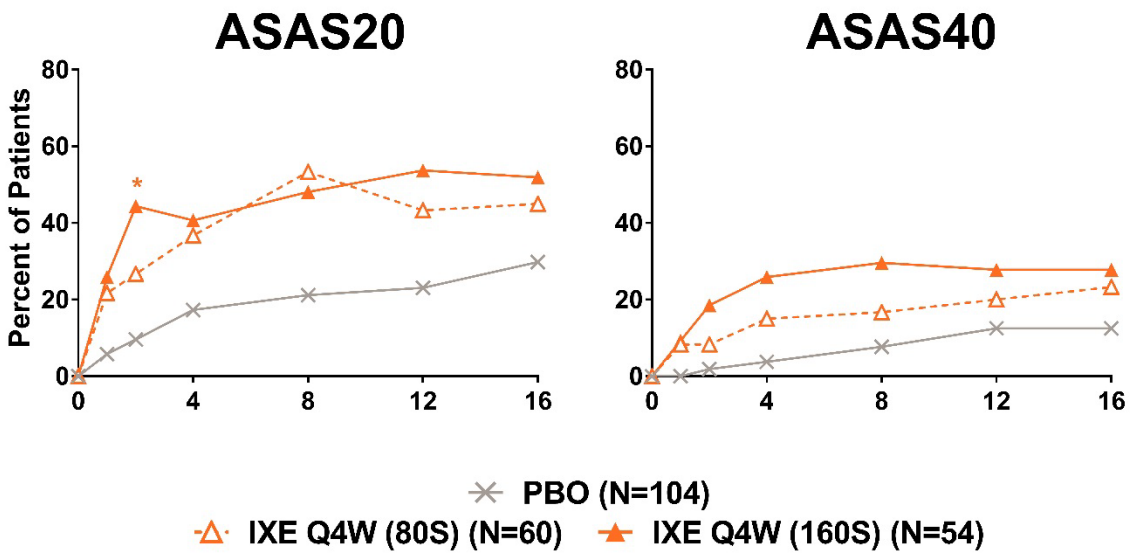
[a]p<.05 vs. PBO (multiplicity adjusted p-value).

[b]p<.01 vs. PBO (multiplicity adjusted p-value).

Note: All comparisons of ixekizumab with placebo for the primary and major secondary endpoints were statistically significant, with the exception of change from baseline at Week 16 for ASAS HI for the ixekizumab 80-mg Q2W group, as calculated with the graphical method for multiple testing.

Efficacy Starting Dose Analyses

Figure 37. Time course of ASAS20 and ASAS40 response rates (NRI; ITT Population) up to Week 16 by starting dose (Study RHBW)



Abbreviations: 80S = 80-mg starting dose at Week 0; 160S = 160-mg starting dose at Week 0; ASAS = Assessment of Spondyloarthritis International Society; ITT = intent-to-treat; IXE Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; NRI = nonresponder imputation; PBO = placebo; RHBW = Study I1F-MC-RHBW; vs. = versus.

* p<.05: IXE Q4W (160S) vs. IXE Q4W (80S).

Extended Treatment Period

Patients from the ITT Population who were initially randomised to ixekizumab at Week 0 had a consistent response across key efficacy and health outcomes endpoints throughout the Extended Treatment Period.

Table 26: Summary of Endpoints at Weeks 16, 36, and 52 ITT Population Initially Randomised to Ixekizumab at Week 0

	Week 16	Week 36	Week 52
ASAS20 response, %			
Ixekizumab 80 mg Q4W	48.2%	53.5%	52.6%
Ixekizumab 80 mg Q2W	46.9%	53.1%	48.0%
ASAS40 response, %			
Ixekizumab 80 mg Q4W	25.4%	34.2%	34.2%
Ixekizumab 80 mg Q2W	30.6%	34.7%	30.6%
ASDAS Mean Change from Baseline			
Ixekizumab 80 mg Q4W	-1.10	-1.19	-1.20
Ixekizumab 80 mg Q2W	-1.17	-1.33	-1.28
BASDAI Mean Change from Baseline			
Ixekizumab 80 mg Q4W	-2.08	-2.44	-2.44
Ixekizumab 80 mg Q2W	-2.05	-2.54	-2.39
BASFI mean Change from Baseline			
Ixekizumab 80 mg Q4W	-1.63	-1.98	-2.08
Ixekizumab 80 mg Q2W	-1.93	-2.25	-2.12
SF-36 PCS Mean Change from Baseline			
Ixekizumab 80 mg Q4W	6.32	7.15	6.52
Ixekizumab 80 mg Q2W	5.98	6.84	7.09
ASDAS <2.1 Response, %			
Ixekizumab 80 mg Q4W	17.5%	25.4%	23.7%
Ixekizumab 80 mg Q2W	16.3%	25.5%	24.5%
ASAS HI Mean Change from Baseline			
Ixekizumab 80 mg Q4W	-2.00	-2.54	-2.34
Ixekizumab 80 mg Q2W	-1.82	-2.31	-2.46

2.4.2.3. Study I1F-MC-RHBX (RHBX)

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

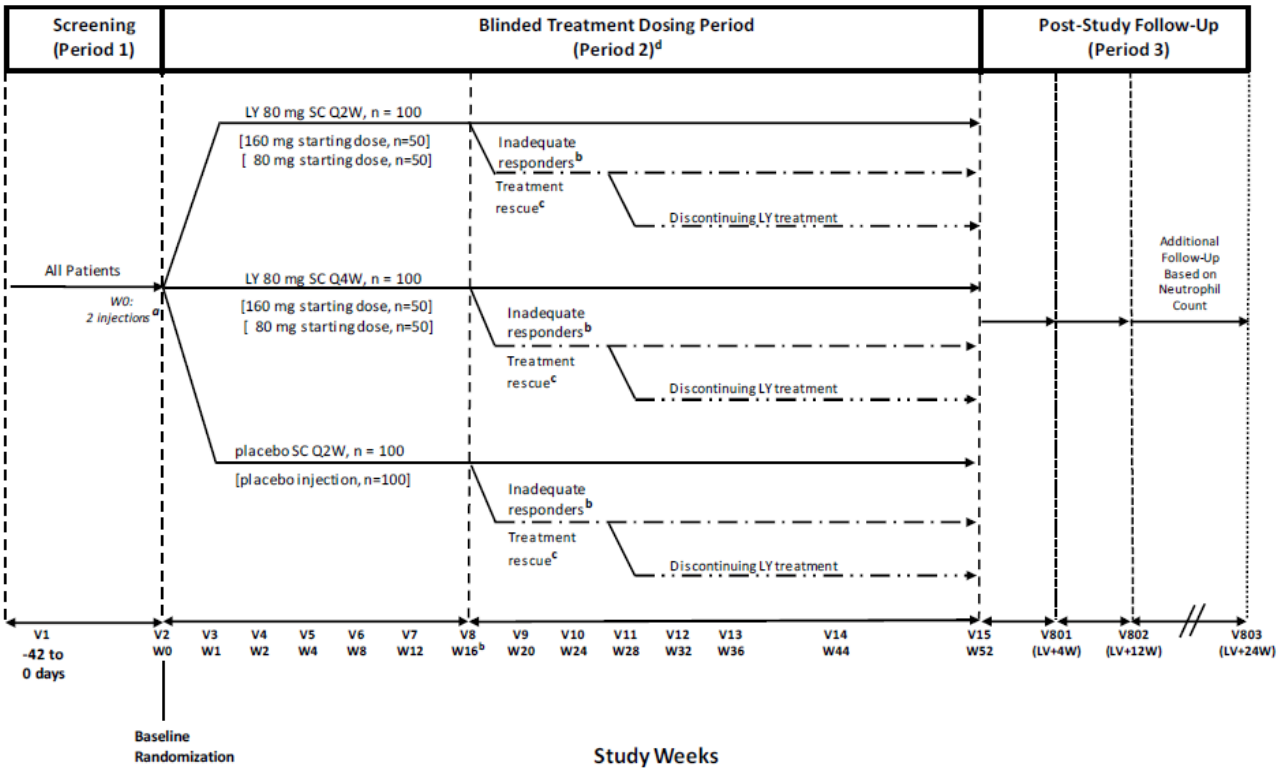
Methods

Study design

Study I1F-MC-RHBX is a Phase 3, multi-centre, randomised, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of 2 ixekizumab treatment regimens (80 mg every 2 weeks [Q2W] and 80 mg every 4 weeks [Q4W] subcutaneous [SC]) as compared to SC

placebo in patients with active nr-axSpA who are biological disease-modifying antirheumatic drug (bDMARD)-naive, during a 52-week treatment period.

Figure 38. Study design of study RHBX



Study participants

Key Inclusion criteria

The study population included patients aged 18 years or older who met the following criteria:

1. Have sacroiliitis present on MRI (according to ASAS/OMERACT criteria and based on central reading) and at least 1 spondyloarthropathy (SpA) feature OR were positive for human leukocyte antigen B27 (HLA-B27) and having at least 2 additional SpA features
2. Have a history of back pain for at least 3 months with age at onset <45 years
3. Have active nr-axSpA, defined as BASDAI ≥4 and total back pain ≥4 on a numeric rating scale (NRS)
4. Have objective signs of inflammation, by sacroiliitis on MRI or elevated C-reactive protein (CRP)
5. Have an inadequate response, as determined by the investigator, to 2 or more NSAIDs for a total duration of at least 4 weeks OR had a history of intolerance to NSAIDs, and
6. Have a history of prior therapy for axSpA of at least 12 weeks

Main Exclusion criteria

Medical conditions:

1. Fulfilment of the modified New York (mNY) criteria (van der Linden et al. 1984) with sacroiliitis defined radiographically, based on central reading: sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally
2. A history of other systemic inflammatory diseases or chronic pain conditions
3. Active Crohn's disease or active ulcerative colitis
4. Active anterior uveitis (an acute episode) within 4 weeks prior to baseline.

Other medical conditions

1. Current or history of lymphoproliferative disease or malignant disease within 5 years prior to baseline
2. A history of fluid overload, myocardial infarction, uncompensated heart failure, or evidence of new-onset ischemic heart disease within 12 weeks prior to baseline
3. Significant, uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders
4. A recent history of suicide attempt, score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16), or at risk for suicide.

Infections

1. A serious infection, hospitalization, or intravenous antibiotics for an infection, within a prespecified period prior to baseline
2. The presence or history of a known immunodeficiency or of being immunocompromised
3. Herpes zoster or other varicella zoster virus infection within 12 weeks prior to baseline
4. Any other active or recent infection within 4 weeks prior to baseline that may pose an unacceptable risk to the patient if enrolled in the study

A known allergy or hypersensitivity to any biologic therapy

1. Surgical treatment to a joint to be assessed in the study within 8 weeks prior to baseline or during the first 16 weeks of the study ☐ Major surgery within 8 weeks prior to baseline

Prior or concurrent therapy or clinical trial experience

1. NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, unless dose is stable for at least 2 weeks prior to baseline
2. csDMARDs or any other immunosuppressive agents within 4 weeks prior to baseline (exceptions include methotrexate, sulfasalazine, and hydroxychloroquine)
3. Oral corticosteroids >10 mg/day

4. Concurrent or prior use of biologic or other immunomodulatory agents, including investigational therapies
5. Current or recent participation in clinical trial involving a study drug Parenteral glucocorticoid administration within 6 weeks prior to baseline or anticipated administration during Period 2 of the study
6. A live vaccination or participated in a vaccine clinical study within 12 weeks prior to baseline or intended to have a live vaccination during the course of the study or within 12 weeks of completing treatment in the study, or
7. A vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline, or intended to have a vaccination of BCG during the course of the study or within 12 months of completing treatment in the study Vaccinations Diagnostic assessments
8. Evidence or suspicion of active or latent TB (note: patients with latent TB may be rescreened after appropriate treatment)
9. Positive for HIV (human immunodeficiency virus), hepatitis B virus (HBV), or hepatitis C virus
10. Electrocardiogram (ECG) abnormalities
11. Any of the following at screening: o neutrophil count <1500 cells/µL, lymphocyte count <800 cells/µL, platelet count <100,000 cells/µL,aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5x upper limit of normal [ULN]), total white blood cell (WBC) count <3000 cells/µL, hemoglobin <8.5 g/dL (85.0 g/L) for male patients or <8.0 g/dL (80 g/L) for female patients, or Other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant.

Treatments

The Blinded Treatment Dosing Period (Period 2) involved a comparison of ixekizumab at 2 treatment regimens (80 mg Q2W and 80 mg Q4W) with placebo. Each ixekizumab treatment group included patients receiving an 80-mg or a 160-mg starting dose at Week 0. All doses were administered via SC injection. To maintain blinding, all patients received 2 injections at baseline (Week 0). During the remainder of Period 2, all patients received 1 injection Q2W.

Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, could be identified by an investigator based on clinical judgment as an inadequate responder. At such time, changes in background therapy, biologic rescue therapy (open-label ixekizumab 80 mg Q2W), or both, could be offered at the discretion of the investigator, while remaining blinded to the original randomization treatment assignment.

Objectives

The primary objective was to compare both ixekizumab regimens (80 mg every 2 weeks [Q2W] or 80 mg every 4 weeks [Q4W]) versus placebo in patients with active non radiographic axial

spondyloarthritis (nr-axSpA), as measured by the proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at

- Week 16 (for regulatory agencies that accept Week 16 as the primary endpoint for approval purposes) or
- Week 52 (for regulatory agencies that require Week 52 as the primary endpoint for approval purposes)

There were also several secondary objectives, see endpoints below

Outcomes/endpoints

Primary endpoint:

ASAS40 response at week 16 and week 52

Key secondary endpoints

- ASDAS change from baseline at week 16 and 52
- BASDAI change from baseline at week 16 and 52
- ASDAS <2.1 response at week 16 and 52
- MRI SIJ SPARCC score change from baseline at Week 16
- SF-36 PCS score change from baseline at Week 16 and 52

Sample size

The planned sample size was 300 patients; 100 per treatment arm (ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo).

Power calculation for Week 16
With 100 patients per treatment group, this study was planned to have approximately 98% power to test the superiority of ixekizumab 80 mg Q2W to placebo for ASAS40 response rate at Week 16. The following assumptions were used for the power calculations for ASAS40 response rate at Week 16 regardless of starting dose:

- 46% for the ixekizumab 80 mg Q2W group, and
- 18% for the placebo group.

A 2-sided Fisher's exact test at an α level of 0.05 was used for the calculation.

Power estimates for Week 52
There was little data from similarly designed 52-week, placebo-controlled trials regarding the ASAS40 response rate for active- and placebo-treated patients to guide power estimation at Week 52. **Table 27** provides power estimates to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 52, assuming various ASAS40 response rates for ixekizumab Q2W and placebo at Week 52. A 2-sided Fisher's exact test at the 0.05 level was assumed.

Table 27: Power Estimates for Week 52

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

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

Randomisation

Patients who met all criteria for enrolment were randomised to double-blind treatment at Week 0 (Visit 2). Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). To achieve between-group comparability, the randomization was stratified by country and screening MRI/CRP status (i- positive MRI and elevated CRP; ii- positive MRI and non-elevated CRP; iii- negative MRI and elevated CRP). Elevated CRP was defined as >5.00 mg/L. The target was to enrol a minimum of approximately 20% for each of the MRI/CRP strata.

Blinding (masking)

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. If an investigator decided to use the treatment modification of ixekizumab Q2W, study site personnel, the patient, and the study team remained blinded to the initial randomisation. Randomisation will remain blinded to study site personnel and patients until the final (that is, end of study) clinical trial database lock has occurred. Randomisation remained blinded to the Sponsor until the interim clinical trial database lock occurred. This interim clinical trial database lock occurred after the last patient completed Visit 15 (Week 52) of the study, or the ETV. Unblinding occurred on 01 Apr 2019. The syringes (and contents) containing either ixekizumab or placebo were visibly indistinguishable from each other. Randomisation codes were generated and emergency unblinding for AEs were allowed to be performed with IWRS, which could have supplemented or taken the place of emergency codes generated by a computer drug-labelling system. This option would have been allowed only if the patient's well-being required knowledge of the patient's treatment assignment.

Statistical methods

Comparisons between each ixekizumab regimen (80 mg Q2W or 80 mg Q4W) and placebo were performed for all analyses planned in Period 2. Period 2 (Blinded Treatment Dosing) started at Week 0 (Visit 2) and ended at Week 52 (Visit 15) or the ETV (between Weeks 0 and 52). An interim database lock and unblinding occur as pre-planned with the Period 2 analysis performed after the last patient had completed Visit 15 (Week 52) or ETV. This interim database lock included all data collected by the

cut-off date including follow-up data from patients who had begun the Post-Study Follow-Up Period (Period 3). The analyses from the Week 52 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

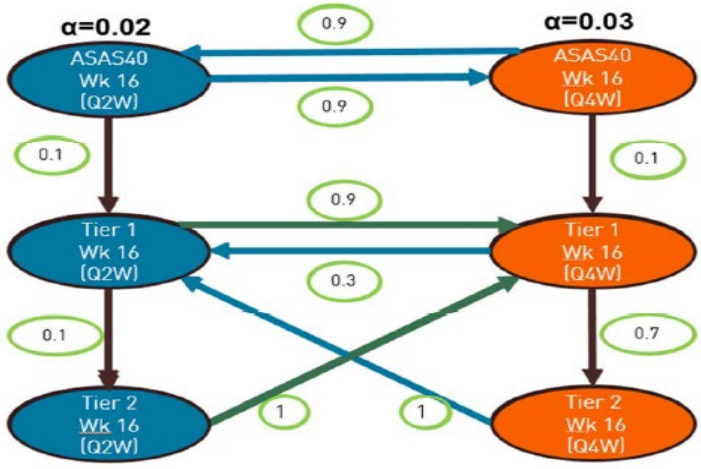
The primary analysis of efficacy and health outcome were conducted on the intent-to-treat (ITT) population including data from all randomised patients. The statistical analysis models were adjusted for geographic region and screening MRI/CRP status and treatment groups of ixekizumab 80 mg Q2W and 80 mg Q4W were analysed without regard to starting dose.

Treatment comparisons of categorical efficacy variables, including the analysis of the primary endpoint, were made using a logistic regression analysis with treatment, geographic region (Europe versus non-Europe), and screening MRI/CRP status in the model. Secondary analysis was conducted using a Fisher's exact test. Patients who did not meet clinical response criteria or had missing data were considered non-responders (referred to as non-responder imputation). Patients deemed inadequate responders by the investigator based on clinical judgement who stopped their originally assigned blinded study treatment and used rescue ixekizumab 80 mg Q2W were also considered non-responders.

Treatment comparisons of continuous efficacy variables were based on the MMRM (mixed-effects models of repeated measures) analysis method with treatment, geographic region, screening MRI/CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors (except for the analysis of CRP, in which baseline CRP value and baseline value-by-visit were not included in the model). The primary analyses for MRI endpoints were made using analysis of covariance (ANCOVA) based on observed data. A secondary analysis for all continuous efficacy and health outcome variables was made using ANCOVA with the modified baseline observation carried forward method.

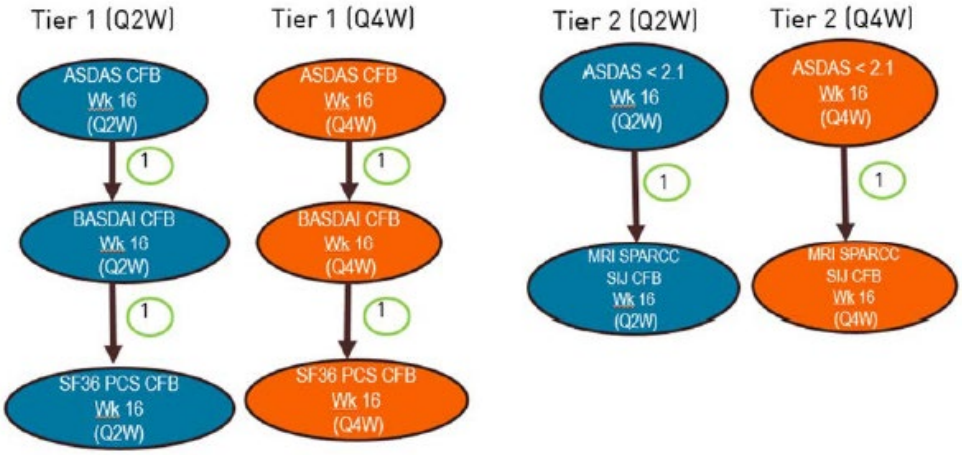
Multiple comparisons/multiplicity

Figure 39. Graphical multiple testing scheme for regulatory authorities that accept 16-week, placebo-controlled data for approval purposes.



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

Figure 40. Graphical multiple testing scheme used within the Tier 1 and Tier 2 group of endpoints.



Results

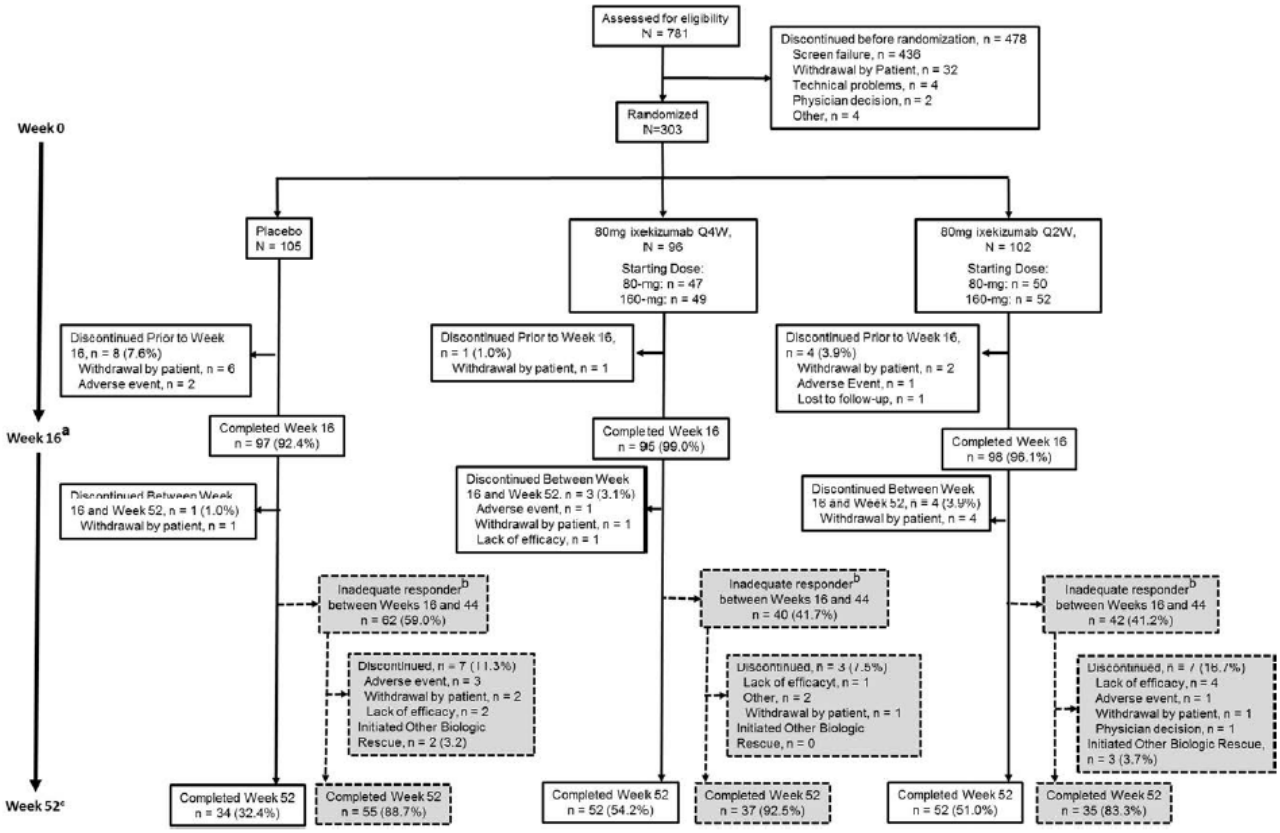
Participant flow

Study RHBX included 303 patients randomised to placebo (105 patients), ixekizumab 80 mg Q4W (96 patients), or ixekizumab 80 mg Q2W (102 patients).

Between Weeks 16 and 44, 144 (47.5%) patients were inadequate responders (62 placebo [59.0%], 40 ixekizumab 80 mg Q4W [41.7%], and 42 ixekizumab 80 mg Q2W [41.2%]), of whom 127 (88.2%) patients completed through Week 52.

A total of 265 (87.5%) patients completed the Blinded Treatment Dosing Period through Week 52, of whom 138 (45.5%) patients were on their originally randomised treatment and 127 (41.9%) patients were on open label ixekizumab 80 mg Q2W rescue treatment.

Figure 41. Patient disposition in Study RHBX.



Of the 303 patients in the ITT population, changes in background therapy while on originally randomised treatment were made by 15 patients (5.0%):

- 7 of 105 patients (6.7%) in the placebo group
- 6 of 96 patients (6.3%) in the ixekizumab 80-mg Q4W group, and
- 2 of 102 patients (2.0%) in the ixekizumab 80-mg Q2W group.

All 15 of the patients who had changes to background therapy also received rescue therapy with open-label ixekizumab 80 mg Q2W at either the same visit or the next visit.

Beginning at Week 16 and up to Week 44, investigators could at their own discretion consider whether or not an individual patient achieved an adequate treatment response and subsequently modify concomitant medications and/or switch to open-label ixekizumab 80 mg Q2W.

A total of 95.7% of patients completed the Blinded Treatment Dosing Period through Week 16, with no difference between the treatment groups.

Recruitment

Date of first patient enrolled: 01 Aug 2016

Date last patient completed Week 52 or discontinued early: 01 Mar 2019.

This study was conducted at 106 study centres in 15 countries.

Conduct of the study

There were 2 protocol amendments.

Protocol amendment (a) - 05 Aug 2016:The main change implemented with this amendment was that adjudication of suspected IBD was added to ensure that all reported events were evaluated uniformly by a single group in an unbiased manner. Additional changes were made to enhance clarity of the protocol.

Protocol amendment (b) - 05 Oct 2018: The main change made with this amendment was to move ASAS40 response at Week 52 from the study's major secondary objectives to its primary objectives. This change was made to accommodate regional regulatory requirements. Additional changes were made to enhance clarity of the protocol.

Baseline data

Patient demographic and other patient characteristics

Demographic characteristics, disease history, and baseline characteristics were generally well balanced across treatment groups, with the exception of baseline MRI SIJ SPARCC score, which was lower in the ixekizumab 80-mg Q4W group than the other groups.

Demographic characteristics, disease history, and baseline characteristics were consistent with a population with nr-axSpA.

The patient population was predominantly white (79.1%) and under 50 years of age (72.8%). The mean age was 40.3 years and there were similar proportions of male and female patients. The mean duration of symptoms since axSpA onset was 10.7 years, and 73.7% of patients were HLA-B27 positive. Disease activity at baseline was high to very high, as reflected by baseline scores for BASDAI (7.0 to 7.3) and ASDAS (3.78 to 3.88) and were similar across the treatment groups.

At baseline,

- 98.0% of patients had previously used a nonbiologic systemic agent
- 9.9% had used a nonbiologic nonsystemic agent
- 38.9% of patients were receiving csDMARDs
- 13.9% of patients were receiving oral corticosteroids
- 89.8% of patients were receiving NSAIDs including cyclooxygenase-2 inhibitors, and
- 19.1% of patients were receiving analgesics.

Numbers analysed

Table 28: Population analysed in study RHBX

Period Population and Status	PBO n (%)	IXE80Q4W n (%)	IXE80Q2W n (%)	Total IXE n (%)	Total n (%)
Period 1 - Screening					
All entered patients					781
Discontinued prior to randomization					478
Physician decision					2
Screen failure					436
Technical problems					4
Withdrawal by subject					32
Other					4
Period 2 - Blinded Treatment Dosing Period					
Randomized patients	105	96	102	198	303
Intent to Treat (ITT)	105	96	102	198	303
Completed 16 Weeks in Period 2 (% relative to ITT)	97 (92.4%)	95 (99.0%)	98 (96.1%)	193 (97.5%)	290 (95.7%)
Discontinued from Period 2 treatment prior to/on Week 16 (% relative to ITT)	8 (7.6%)	1 (1.0%)	4 (3.9%)	5 (2.5%)	13 (4.3%)
Entered Post Treatment Follow-up Period	2	0	2	2	4
Completed 52 Weeks in Period 2 on originally assigned treatment (% relative to ITT)	34 (32.4%)	52 (54.2%)	52 (51.0%)	104 (52.5%)	138 (45.5%)
Entered Post Treatment Follow-up Period	1	3	5	8	9
Discontinued Period 2 on originally assigned treatment after Week 16 (% relative to ITT)	1 (1.0%)	3 (3.1%)	4 (3.9%)	7 (3.5%)	8 (2.6%)
Entered Post Treatment Follow-up Period	0	2	0	2	2
Inadequate Responder (IR) Population (% relative to ITT)	62 (59.0%)	40 (41.7%)	42 (41.2%)	82 (41.4%)	144 (47.5%)
Completed Period 2 on IXE80Q2W rescue treatment (% relative to IR population)	55 (88.7%)	37 (92.5%)	35 (83.3%)	72 (87.8%)	127 (88.2%)
Discontinued Period 2 on IXE80Q2W rescue treatment (% relative to IR population)	7 (11.3%)	3 (7.5%)	7 (16.7%)	10 (12.2%)	17 (11.8%)
Enter Post Treatment Follow-up Period	13	4	9	13	26
Initiated other biologic treatment after IXEQ2W rescue treatment	2 (3.2%)	0	3 (7.1%)	3 (3.7%)	5 (3.5%)
Safety (% relative to ITT)	104 (99.0%)	96 (100.0%)	102 (100.0%)	198 (100.0%)	302 (99.7%)
Completed Period 2 Week 16 (% relative to Safety)	97 (93.3%)	95 (99.0%)	98 (96.1%)	193 (97.5%)	290 (96.0%)
Completed Period 2 Week 52 (% relative to Safety)	89 (85.6%)	89 (92.7%)	87 (85.3%)	176 (88.9%)	265 (87.7%)

Outcomes and estimation

Primary analysis - Blinded Treatment Dosing Period (Week 0 to Week 16)

Table 29 presents the nominal and multiplicity-adjusted p-values based on the graphical multiple-testing procedure for the primary and major secondary endpoints.

Table 29: Summary of Primary and Major Secondary Analyses for the Week 16 analyses (ITT)

	Ixekizumab 80 mg Q4W vs. Placebo		**Ixekizumab 80 mg Q2W vs. Placebo**	
	Unadjusted Nominal p-Value	Multiplicity Adjusted p-Value	Unadjusted Nominal p-Value	Multiplicity Adjusted p-Value
Primary Objective				
ASAS40 response	.009	.010	.002	.004
Major Secondary Objectives				
ASDAS change from baseline	<.001	.010	<.001	.004
BASDAI change from baseline	.031	.031	.001	.010
SF-36 PCS change from baseline	.013	.031	.015	.031
ASDAS <2.1 response	.008	.031	<.001	.031
MRI SIJ SPARCC change from baseline	<.001	.031	<.001	.031

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; MRI = magnetic resonance imaging; Q2W = every 2 weeks; Q4W = every 4 weeks; SF-36 PCS = Medical Outcomes Study 36-Item Short Form-Health Survey Physical Component Summary; SIJ = sacroiliac joints; SPARCC =Spondyloarthritis Research Consortium of Canada; vs. = versus.

Primary and major secondary endpoints

The study achieved its primary and all major secondary objectives. Both ixekizumab treatment groups were superior to placebo with regards to ASAS40 response at Week 16.

Table 30: Study RHBX: Summary of Primary and Major Secondary Objectives at Week 16

	PBO N = 105	IXE Q4W N = 96	IXE Q2W N = 102
Primary Objective			
ASAS40 Response, n (%)	20 (19.0)	34 (35.4)[a]	41 (40.2)[b]
Difference from PBO, % (95% CI)		16.4 (4.2, 28.5)	21.1 (9.0, 33.3)
Major Secondary Objectives			
ASDAS Change from Baseline, LSM (SE)	-0.58 (0.095)	-1.12 (0.097)[a]	-1.26 (0.095)[b]
BASDAI Change from Baseline, LSM (SE)	-1.51 (0.216)	-2.18 (0.220)[a]	-2.52 (0.217)[a]
SF-36 PCS Change from Baseline, LSM (SE)	5.21 (0.800)	8.06 (0.813)[a]	7.96 (0.802)[a]

ASDAS <2.1 Response, n (%)[c]	13 (12.4)	26 (27.7)[a]	33 (32.4)[a]
MRI SIJ SPARCC Change from Baseline, LSM (SE)	-0.31 (0.539)	-3.38 (0.549)[a]	-4.52 (0.530)[a]

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; CSR = clinical study report; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; LSM = least squares mean; PBO = placebo; RHBX = Study I1F-MC-RHBX; SE = standard error; SIJ = sacroiliac joint; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary; SPARCC = Spondyloarthritis Research Consortium of Canada score; vs. = versus.

[a] p<.05 vs. placebo (multiplicity-adjusted p-value).

[b] p<.01 vs. placebo (multiplicity-adjusted p-value).

[c] Analysed in ITT Population with baseline ASDAS ≥2.1 (PBO = 105, IXE Q4W = 94, IXE Q2W = 102).

Note: All comparisons of ixekizumab with placebo for the primary and major secondary endpoints were statistically significant as calculated with the graphical method for multiple testing

Other secondary endpoints

Table 31: Study RHBX: Summary of other secondary endpoints at Week 16

	PBO N = 105	IXE Q4W N = 96	IXE Q2W N = 102
ASAS Components			
Patient Global Change from Baseline, LSM (SE)	-1.30 (0.246)	-2.32 (0.251)[b]	-2.64 (0.247)[c]
Spinal Pain Change from Baseline, LSM (SE)	-1.45 (0.244)	-2.35 (0.248)[a]	-2.59 (0.244)[b]
BASFI Change from Baseline, LSM (SE)	-1.34 (0.228)	-2.01 (0.232)[a]	-2.28 (0.228)[b]
Inflammation (BASDAI Questions 5 and 6) Change from Baseline, LSM (SE)	-1.44 (0.242)	-2.44 (0.246)[b]	-2.89 (0.242)[c]
ASAS20 Response, n (%)	41 (39.0)	52 (54.2)[a]	58 (56.9)[a]
ASAS20 Difference from PBO, % (95% CI)		15.1 (1.5, 28.8)	17.8 (4.4, 31.2)
BASMI Change from Baseline, LSM (SE)	-0.24 (0.079)	-0.43 (0.079)	-0.35 (0.079)
hs-CRP Change from Baseline, LSM (SE)	-4.80 (1.892)	-8.07 (1.933)	-7.80 (1.893)
BASDAI50 Response, n (%)	15 (14.3)	30 (31.3)[b]	34 (33.3)[b]

Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = 50% improvement in BASDAI; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; CSR = clinical study report; hs-CRP = high-sensitivity C-reactive protein; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; LSM = least squares mean; PBO = placebo; RHBX = Study I1F-MC-RHBX; vs. = versus.

[a] p<.05 vs. PBO.

[b] p<.01 vs. PBO.

[c] p<.001 vs. PBO

Additional analyses at Week 52

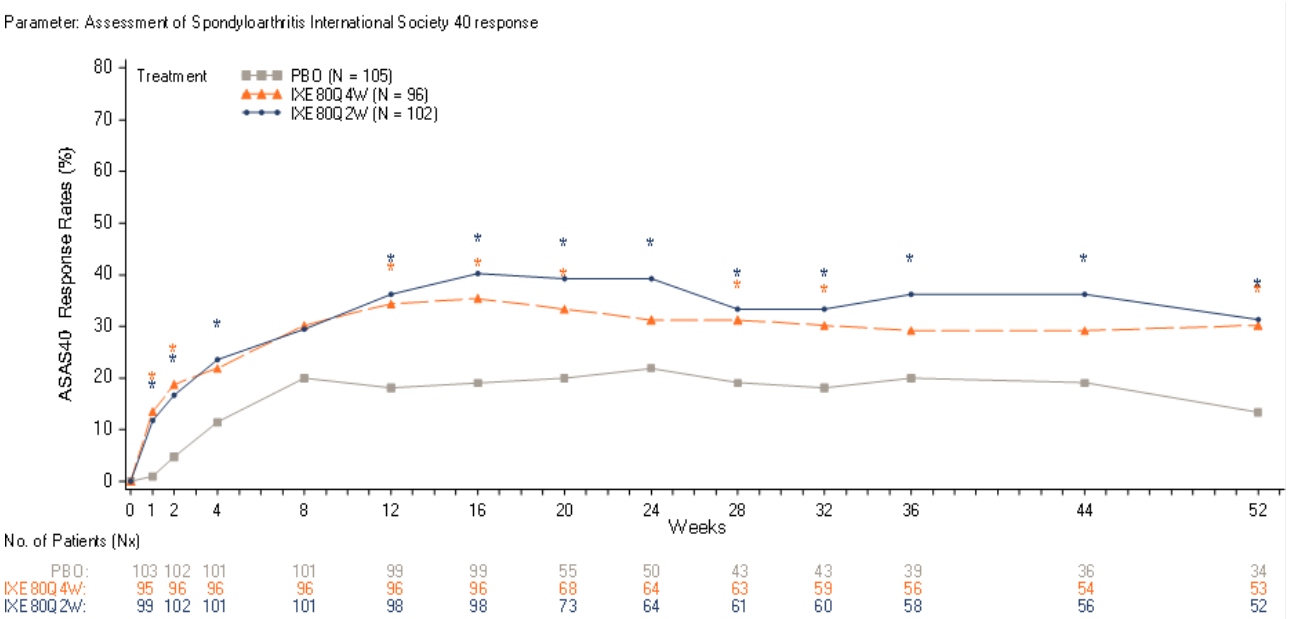
Patients demonstrated a consistent response across key efficacy and health outcomes endpoints through Week 52

ASAS40 at Week 52

Table 32: ASAS40 Response Rates at Week 52

	PBO (N=105)	IXE80Q4W (N=96)	IXE80Q2W (N=102)
Week 52 (Visit 15) (Observed)			
Nx	34	53	52
Response, n (%) *a	14 (41.2%)	29 (54.7%)	32 (61.5%)
95% CI *b	(24.6%, 57.7%)	(41.3%, 68.1%)	(48.3%, 74.8%)
Week 52 (Visit 15) (NRI)			
Response, n (%)	14 (13.3%)	29 (30.2%)	32 (31.4%)
95% CI *b	(6.8%, 19.8%)	(21.0%, 39.4%)	(22.4%, 40.4%)
Difference (95% CI) vs. PBO *b		16.9% (5.6%, 28.1%)	18.0% (6.9%, 29.1%)
Odds Ratio (95% CI) vs. PBO *c		2.82 (1.38, 5.77)	2.85 (1.40, 5.77)

Figure 42. ASAS40 response rates at each postbaseline visit (NRI)Blinded Treatment Dosing Period through Week 52 (ITT)



* p-value <=0.05 versus PBO.

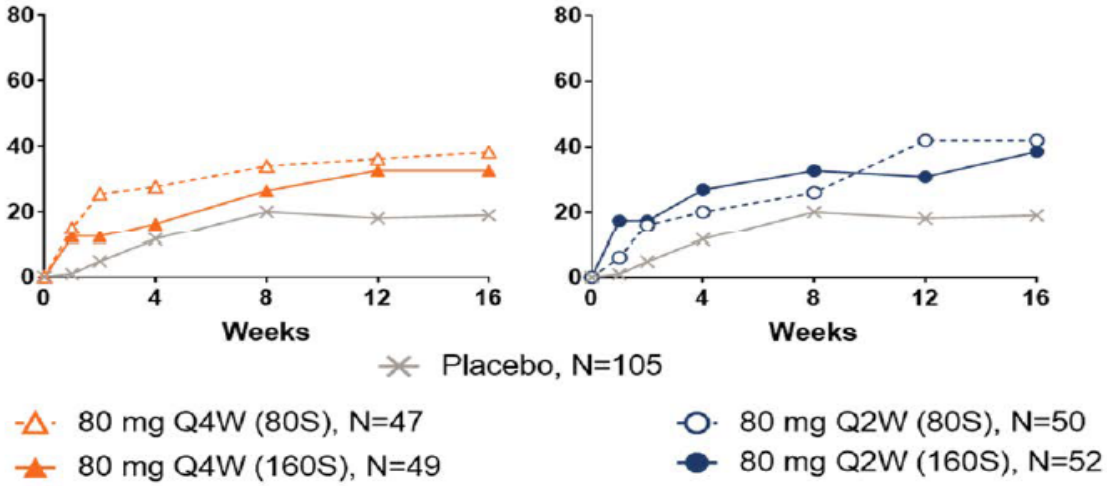
Abbreviations: PBO = Placebo; IXE 80Q 4W = Ixekizumab 80 mg Q 4W; IXE 80Q 2W = Ixekizumab 80 mg Q 2W; N = number of patients in the analysis population; Nx = number of patients with non-missing values; NRI = nonresponder imputation.
Note: Observed data after initiation of biologic rescue of ixekizumab 80 mg Q 2W for inadequate responders is excluded.

Dataset: lillyce/prd/y2439821/t1f_mc_rhbx/intrm1/data/analysis/restricted/adasas.sas7bdat
Program: lillyce/prd/y2439821/t1f_mc_rhbx/intrm1/programs/tfl/original/f_asas2040resp_nri_itt_db.sas
Output: lillyce/prd/y2439821/t1f_mc_rhbx/intrm1/output/restricted/f_asas2040resp_nri_itt_db.rtf

Efficacy Starting Dose Analyses

The impact of ixekizumab starting dose (160 mg vs. 80 mg at Week 0) at Week 16 and Week 52, as assessed by analyses of ASAS20/40 response rates, ASDAS <2.1 response rates and hs-CRP CFB

Figure 43. ASAS40 response rates at each postbaseline visit (NRI) Comparison of starting doses in the ixekizumab 80-mg Q4W and Q2W groups Blinded Treatment Dosing Period prior to biologic rescue, intent-to-treat population



Effect on ASAS40 of patients switching to rescue therapy

All patients in the ITT population who switched to open label ixekizumab 80 mg Q2W rescue therapy were considered as non-responders after the time of switching, from the analysis perspective, regardless of observed response. In addition, despite being judged as IRs by the investigator, many patients in the ixekizumab groups had clinically meaningful levels of response on key outcome measures at the last visit before biologic rescue, more so than patients in the placebo group. At the last visit before biologic rescue, observed ASAS40 response rates were 6.5% in the placebo group, and 25% and 16.7% in the ixekizumab 80-mg Q4W and ixekizumab 80-mg Q2W treatment groups, respectively.

Table 33: Efficacy Endpoints in Patients in the IR Population at the Last Time Point before Switching to Rescue Therapy (Observed Values)

	PBO IR/ IXE80Q2W	IXE80Q4W IR/ IXE80Q2W	IXE80Q2W IR/ IXE80Q2W
ASAS Responses			
ASAS20, n (%)	13 (21.0)	15 (37.5)	15 (35.7)
ASAS40, n (%)	4 (6.5)	10 (25.0)	7 (16.7)
ASDAS Responses			
ASDAS <2.1, low disease activity, n (%)	0	9 (23.1)[a]	6 (14.3)
ASDAS clinically important improvement, n (%)	7 (11.3)	13 (32.5))	15 (35.7
ASDAS major improvement, n (%)	1 (1.6)	7 (17.5)	5 (11.9)
ASDAS change from baseline, mean (SD)	-0.20 (0.831)	-0.75 (1.239)	-0.85 (1.066)
BASDAI			

BASDAI50, 50% improvement, n (%)	1 (1.6)	8 (20.0)	5 (11.9)
BASDAI change from baseline, mean (SD)	-0.63 (1.479)	-1.48 (2.426)	-1.30 (2.087)
CRP (mg/L)			
CRP change from baseline, mean (SD)	-2.64 (18.047)	-6.37 (15.750)	-11.20 (23.417)
BASFI			
BASFI score change from baseline, mean (SD)	-0.60 (1.785)	-1.40 (2.386)	-0.95 (2.070)
MRI SIJ			
MRI SIJ score change from baseline, mean (SD)	0.16 (4.184)	-1.60 (3.547)	-3.70 (10.109)
SF-36 PCS			
SF-36 PCS change from baseline, mean (SD)	3.02 (6.829)	6.40 (9.390)	4.54 (8.574)

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein; IR = inadequate responder; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; MRI = magnetic resonance imaging; PBO = placebo; PCS = Physical Component Summary; SD = standard deviation; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SIJ = sacroiliac joint.
[a] Among patients with ASDAS Score ≥2.1 at baseline (N=39).

Improvements in ASAS40 response rates were observed in all treatment groups following switch to rescue therapy with open label ixekizumab 80 mg Q2W.

Table 34: Efficacy Endpoints in Patients in the IR Population at Time of Rescue and at Week 52 (Observed Values)

	PBO IR/IXE80Q2W		**IXE80Q4W IR/IXE80Q2W**		**IXE80Q4W IR/IXE80Q2W**	
	Time of rescue	**Week 52**	**Time of rescue**	**Week 52**	**Time of rescue**	**Week 52**
ASAS40, n (%)	4 (6.5)	21 (37.5)	10 (25.0)	15 (40.5)	7 (16.7)	15 (41.7)
ASDAS <2.1, n (%)	0	19 (34.5)	9 (23.1)[a]	13 (38.2)[a]	6 (14.3)	13 (36.1)
ASDAS change from baseline, mean (SD)	-0.20 (0.831)	-1.26 (1.301)	-0.75 (1.239)	-1.26 (1.366)	-0.85 (1.066)	-1.33 (1.035)
BASDAI change from baseline, mean (SD)	-0.63 (1.479)	-2.54 (2.493)	-1.48 (2.426)	-2.90 (2.861)	-1.30 (2.087)	-2.43 (2.050)

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; IR = inadequate responder; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; PBO = placebo.
[a] Among patients with ASDAS Score ≥2.1 at baseline (N=39).

Although there was allowance for investigators to change background medication for patients who may have been perceived to be having an inadequate response, this option was rarely used (less than 5% of the ITT population). Patients judged by investigators as IRs were switched to open-label ixekizumab most frequently at the first allowed visit (Week 16).

Ancillary analyses

Efficacy in Subpopulations in Nr-axSpA Studies

Variables analysed

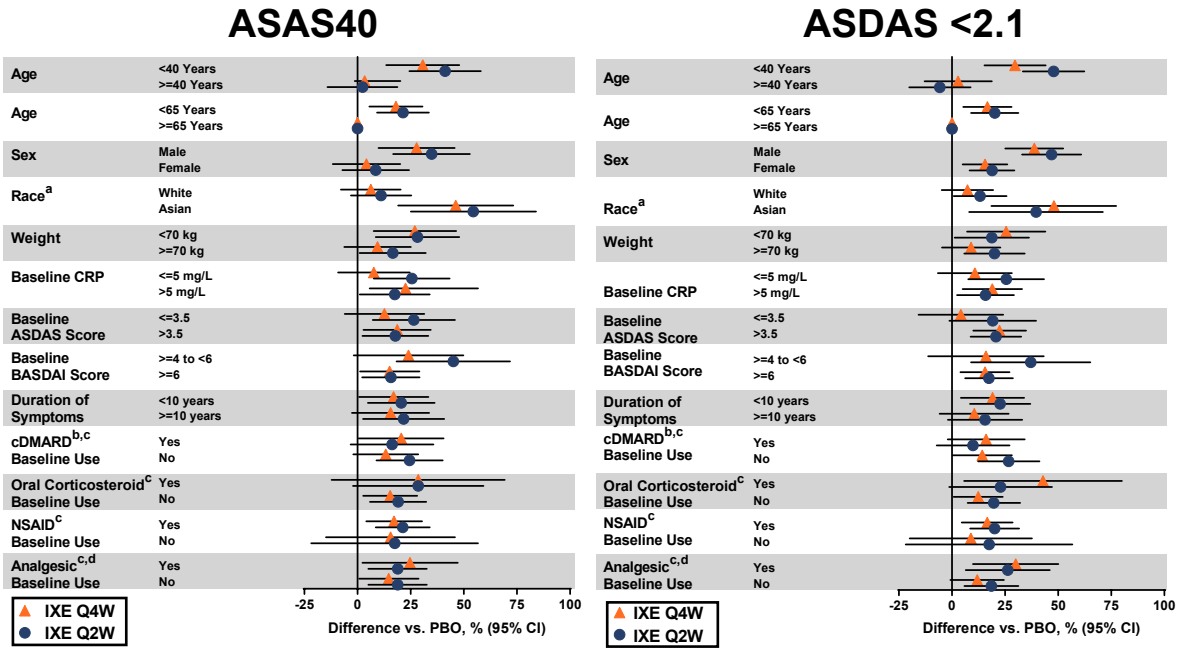
Potential differences in response across patient demographic and baseline disease activity variables were examined for ASAS40 and ASDAS <2.1 response rates at Week 16. The most clinically relevant subgroup variables included

- patient demographics (e.g., sex, age, weight, race)
- disease-related characteristics (e.g., baseline CRP category, baseline ASDAS category, baseline BASDAI category, duration of symptoms since axSpA onset),
- concomitant therapy use at baseline (e.g., cDMARD, oral corticosteroid, NSAIDs, analgesics). Oral corticosteroid and NSAID subgroup evaluations were post hoc analyses.

Results of subgroup analyses

Figure 44. presents the ASAS40 and ASDAS <2.1 response rates for selected subgroups in Study RHBX. The findings from the subgroup analyses were generally consistent with those from the overall population, and the treatment effect of ixekizumab was generally consistent across subgroups.

Figure 44. ASAS40 [left panel] and ASDAS <2.1 [right panel] response rates (NRI; ITT Population) in selected patient subgroups (Study RHBX)



Summary of main studies

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 35: Summary of Efficacy for trial RHBV

Title: A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Radiographic Axial Spondyloarthritis.			
Study identifier	I1F-MC-RHBV		
Design	Phase 3, multicentre, randomized, double-blind, active- and placebo-controlled, parallel-group study		
	Duration of Main phase: Duration of Extension phase:		16 weeks (Double-Blind Treatment Period) 36 weeks (Extension Period)
Hypothesis	Superiority		
Treatment groups	Ixekizumab 80 mg Q2W		Ixekizumab 80 mg Q2W. Duration 16 weeks (Double-Blind Treatment Period), 36 weeks (Extension Period). Number randomized 83.
	Ixekizumab 80 mg Q4W		Ixekizumab 80 mg Q4W. Duration 16 weeks (Double-Blind Treatment Period), 36 weeks (Extension Period). Number randomized 81.
	Placebo		Placebo. Duration 16 weeks (Double-Blind Treatment Period). Number randomized 87.
	Adalimumab (active reference group; comparison to Placebo only)		Adalimumab 40 mg Q2W. Duration 16 weeks (Double-Blind Treatment Period). Number randomized 90.
Endpoints and definitions	Primary endpoint	ASAS40 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the proportion of patients achieving ASAS40 at Week 16.
	Key secondary endpoint	ASAS20 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the proportion of patients achieving ASAS20 at Week 16.
	Key secondary endpoint	ASDAS change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with r-active axSpA as measured by the change from baseline in ASDAS score at Week 16.

	Key secondary endpoint	BASDAI50 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the proportion of patients achieving BASDAI50 response at Week 16.
Endpoints and definitions (continued)	Key secondary endpoint	BASFI change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the change from baseline in BASFI score at Week 16.
	Key secondary endpoint	ASDAS <1.3 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the proportion of patients achieving ASDAS <1.3 response at Week 16.
	Key secondary endpoint	MRI Spine SPARCC score change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the change from baseline in MRI Spine SPARCC score at Week 16.
	Key secondary endpoint	SF-36 PCS score change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the change from baseline in SF-36 PCS score at Week 16.
	Key secondary endpoint	ASAS HI change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with active r-axSpA as measured by the change from baseline in ASAS HI score at Week 16.
Database lock	16-week database lock (Double-Blind Treatment Period): 31 January 2018 (Last patient visit prior to database lock: 08 December 2017). Data from the 16-week database lock is presented within this table. 52-week database lock (Extension Period): 05 October 2018 (Last patient visit prior to database lock: 23 August 2018).		
Results and Analysis			
Analysis Description	Primary Analysis: ASAS40 response at Week 16		

Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of patients	83	81	87	90
	ASAS40	43/83 (51.8%)	39/81 (48.1%)	16/87 (18.4%)	32/90 (35.6%)
Effect estimate per comparison	Primary endpoint: ASAS40 at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo		33.4	
		95% CI		19.9, 46.9	
		p-value		p<.001	
	Primary endpoint: ASAS40 at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo		29.8	
		95% CI		16.2, 43.3	
		p-value		p<.001	
	Primary endpoint: ASAS40 at Week 16	Comparison groups		Adalimumab vs. Placebo	
		% Difference vs. Placebo		17.2	
		95% CI		4.4, 30.0	
		p-value		P=.005	

Results and Analysis					
Analysis Description	Key Secondary Analysis: ASAS20 response at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)				
Descriptive statistics and	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab

estimate variability	Number of patients	83	81	87	90
	ASAS20 response at Week 16	57/83 (68.7%)	52/81 (64.2%)	35/87 (40.2%)	53/90 (58.9%)
Effect estimate per comparison	ASAS20 response at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo		28.4	
		95% CI		14.1, 42.8	
		p-value		p<.001	
	ASAS20 response at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo		24.0	
		95% CI		9.3, 38.6	
		p-value		p=.001	
	ASAS20 response at Week 16	Comparison groups		Adalimumab vs. Placebo	
		% Difference vs. Placebo		18.7	
		95% CI		4.2, 33.1	
		p-value		p=.007	

Results and Analysis					
Analysis Description	Key Secondary Analysis: ASDAS change from baseline at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of patients	83	81	87	90
	ASDAS change from baseline: LSM (SE)	-1.37 (0.101)	-1.43 (0.102)	-0.46 (0.099)	-1.30 (0.096)
Effect estimate per comparison	ASDAS change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)		-0.91 (0.140)	
		95% CI		-1.18, -0.63	

		p-value		p<.001	
	ASDAS change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)		-0.97 (0.141)	
		95% CI		-1.25, -0.70	
		p-value		p<.001	
	ASDAS change from baseline at Week 16	Comparison groups		Adalimumab vs. Placebo	
		LSM Difference (SE)		-0.84 (0.137)	
		95% CI		-1.11, -0.57	
		p-value		p<.001	
Results and Analysis					
Analysis Description	Key Secondary Analysis: BASDAI50 response at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of patients	83	81	87	90
	BASDAI50	36/83 (43.4%)	34/81 (42.0%)	15/87 (17.2%)	29/90 (32.2%)
Effect estimate per comparison	BASDAI50 response at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo		26.1	
		95% CI		12.8, 39.4	
		p-value		p<.001	
	BASDAI50 response at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo		24.7	
		95% CI		11.4, 38.1	
		p-value		p<.001	
		Comparison groups		Adalimumab vs. Placebo	

	BASDAI50 response at Week 16	% Difference vs. Placebo		15.0	
		95% CI		2.5, 27.5	
		p-value		p=.012	
Results and Analysis					
Analysis Description	Key Secondary Analysis: BASFI change from baseline at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of Patients	83	81	87	90
	BASFI change from baseline: LSM (SE)	-2.43 (0.219)	-2.39 (0.222)	-1.16 (0.215)	-2.14 (0.209)
Effect estimate per comparison	BASFI change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)		-1.27 (0.304)	
		95% CI		-1.86, -0.67	
		p-value		p<.001	
	BASFI change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)		-1.22 (0.307)	
		95% CI		-1.83, -0.62	
		p-value		p<.001	
	BASFI change from baseline at Week 16	Comparison groups		Adalimumab vs. Placebo	
		LSM Difference (SE)		-0.97 (0.299)	
		95% CI		-1.56, -0.39	
		p-value		p=.001	
Results and Analysis					
Analysis Description	Key Secondary Analysis: ASDAS <1.3 response at Week 16				

Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of patients	83	81	87	90
	ASDAS <1.3 response	9/83 (10.8%)	13/81 (16.0%)	2/87 (2.3%)	14/90 (15.6%)
Effect estimate per comparison	ASDAS <1.3 response at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo		8.5	
		95% CI		1.2, 15.9	
		p-value		p=0.041	
	ASDAS <1.3 response at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo		13.8	
		95% CI		5.2, 22.3	
		p-value		p=0.007	
	ASDAS <1.3 response at Week 16	Comparison groups		Adalimumab vs. Placebo	
		% Difference vs. Placebo		13.3	
		95% CI		5.1, 21.4	
		p-value		p=0.009	

Results and Analysis					
Analysis Description	**Key Secondary Analysis:** MRI Spine SPARCC score change from baseline at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks ANCOVA for patients with data at both baseline and Week 16				
Descriptive statistics and	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab

estimate variability	Number of Patients with baseline and Week 16 score	76	78	81	82
	MRI Spine SPARCC score change from baseline: LSM (SE)	-9.58 (1.168)	-11.02 (1.160)	-1.51 (1.147)	-11.57 (1.113)
Effect estimate per comparison	MRI Spine SPARCC score change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)		-8.08 (1.603)	
		95% CI		-11.2, -4.9	
		p-value		p<.001	
	MRI Spine SPARCC score change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)		-9.51 (1.591)	
		95% CI		-12.6, -6.4	
		p-value		p<.001	
	MRI Spine SPARCC score change from baseline at Week 16	Comparison groups		Adalimumab vs. Placebo	
		LSM Difference (SE)		-10.07 (1.588)	
		95% CI		-13.2, -6.9	
		p-value		p<.001	

Results and Analysis					
Analysis Description	**Key Secondary Analysis:** SF-36 PCS score change from baseline at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of Patients	83	81	87	90

	SF-36 PCS score change from baseline: LSM (SE)	7.97 (0.767)	7.70 (0.777)	3.64 (0.753)	6.90 (0.731)
Effect estimate per comparison	SF-36 PCS score change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)		4.33 (1.064)	
		95% CI		2.23, 6.42	
		p-value		p<.001	
	SF-36 PCS score change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)		4.05 (1.072)	
		95% CI		1.94, 6.16	
		p-value		p<.001	
	SF-36 PCS score change from baseline at Week 16	Comparison groups		Adalimumab vs. Placebo	
		LSM Difference (SE)		3.26 (1.044)	
		95% CI		1.20, 5.31	
		p-value		p=.002	
Results and Analysis					
Analysis Description	**Key Secondary Analysis:** ASAS HI change from baseline at Week 16				
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM				
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo	Adalimumab
	Number of Patients	83	81	87	90
	ASAS HI score change from baseline: LSM (SE)	-2.74 (0.306)	-2.36 (0.311)	-1.25 (0.300)	-2.30 (0.292)
		Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo	

Effect estimate per comparison	ASAS HI change from baseline at Week 16	LSM Difference (SE)	-1.49 (0.423)
		95% CI	-2.32, -0.66
		p-value	p<.001
	ASAS HI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	-1.11 (0.428)
		95% CI	-1.95, -0.27
		p-value	p=.010
	ASAS HI change from baseline at Week 16	Comparison groups	Adalimumab vs. Placebo
		LSM Difference (SE)	-1.05 (0.416)
		95% CI	-1.87, -0.23
		p-value	p=.012

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS HI = ASAS Health Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; CI = confidence interval; ITT = intent-to-treat; LSM = least squares mean; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; Q2W = every 2 weeks; Q4W = every 4 weeks; r-axSpA = radiographic axial spondyloarthritis; SE = standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey physical component summary; SPARCC = Spondyloarthritis Research Consortium of Canada; vs. = versus.

Table 36: Summary of Efficacy for Pivotal Trial I1F-MC-RHBW

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in TNFi-Experienced Patients with Radiographic Axial Spondyloarthritis		
Study identifier	I1F-MC-RHBW	
Design	Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group study	
	Duration of Main phase: Duration of Extension phase:	16 weeks (Double-Blind Treatment Period) 36 weeks (Extension Period)
Hypothesis	Superiority	
Treatment groups	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q2W. Duration 16 weeks (Double-Blind Treatment Period), 36 weeks (Extension Period). Number randomized 98.
	Ixekizumab 80 mg Q4W	Ixekizumab 80 mg Q2W. Duration 16 weeks (Double-Blind Treatment Period), 36 weeks (Extension Period). Number randomized 114.

	Placebo		Placebo. Duration 16 weeks (Double-Blind Treatment Period). Number randomized 104.
Endpoints and definitions	Primary endpoint	ASAS40 at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the proportion of patients achieving ASAS40 at Week 16.
	Key secondary endpoint	ASAS20 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the proportion of patients achieving ASAS20 at Week 16.
	Key secondary endpoint	ASDAS change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the change from baseline in ASDAS score at Week 16.
	Key secondary endpoint	ASDAS <2.1 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the proportion of patients achieving ASDAS <2.1 response at Week 16
	Key secondary endpoint	BASDAI change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the change from baseline in BASDAI score at Week 16.
	Key secondary endpoint	MRI Spine SPARCC score change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the change from baseline in MRI Spine SPARCC score at Week 16. *This endpoint applies to the MRI addendum only.*
	Key secondary endpoint	SF-36 PCS score change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the change from baseline in SF-36 PCS score at Week 16.

	Key secondary endpoint	BASFI change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the change from baseline in BASFI score at Week 16.
	Key secondary endpoint	ASAS HI change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of TNFi-experienced patients with active r-axSpA as measured by the change from baseline in ASAS HI score at Week 16.
Database lock	16-week database lock (Double-Blind Treatment Period): 19 June 2018 (Last patient visit prior to database lock: 18 May 2018). Data from the 16-week database lock is presented within this table. 52-week database lock (Extension Period): 28 February 2019 (Last patient visit prior to database lock: 23 January 2019).		

Results and Analysis				
Analysis Description	**Primary Analysis:** ASAS40 response at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	ASAS40	30/98 (30.6%)	29/114 (25.4%)	13/104 (12.5%)
Effect estimate per comparison	Primary endpoint: ASAS40 at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo	18.1	
		95% CI	7.0, 29.2	
		p-value	p=.003	
	Primary endpoint: ASAS40 at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo	12.9	
		95% CI	2.7, 23.2	

		p-value		p=.017
Results and Analysis				
Analysis Description	**Key Secondary Analysis:** ASAS20 response at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	ASAS20	46/98 (46.9%)	55/114 (48.2%)	31/104 (29.8%)
Effect estimate per comparison	ASAS20 at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo
		% Difference vs. Placebo		17.1
		95% CI		3.9, 30.4
		p-value		p=.013
	ASAS20 at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo
		% Difference vs. Placebo		18.4
		95% CI		5.7, 31.1
		p-value		p=.006

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** ASDAS change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104

estimate variability	ASDAS score change from baseline: LSM (SE)	-1.13 (0.103)	-1.16 (0.094)	-0.11 (0.099)
Effect estimate per comparison	ASDAS change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-1.03 (0.140)	
		95% CI	-1.30, -0.75	
		p-value	p<.001	
	ASDAS change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-1.05 (0.135)	
		95% CI	-1.32, -0.79	
		p-value	p<.001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** ASDAS <2.1 response at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	ASDAS <2.1 response	16/98 (16.3%)	20/114 (17.5%)	5/104 (4.8%)
Effect estimate per comparison	ASDAS <2.1 response at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo	11.5	
		95% CI	3.1, 19.9	
		p-value	p=.006	
	ASDAS <2.1 response at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo	12.7	
		95% CI	4.6, 20.8	

		p-value	p=.006

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** BASDAI change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	BASDAI score change from baseline: LSM (SE)	-2.09 (0.221)	-2.17 (0.202)	-0.92 (0.212)
Effect estimate per comparison	BASDAI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-1.16 (0.301)	
		95% CI	-1.76, -0.57	
		p-value	p<.001	
	BASDAI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-1.24 (0.291)	
		95% CI	-1.81, -0.67	
		p-value	p<.001	

Results and Analysis	
Analysis Description	**Key Secondary Analysis:** MRI Spine SPARCC score change from baseline at Week 16
Analysis population, time point description, and statistical model	ITT Population Who Participated in the MRI Addendum 16 weeks ANCOVA for patients with data at both baseline and Week 16

Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients with baseline and Week 16 scores	45	49	46
	MRI Spine SPARCC score change from baseline: LSM (SE)	-3.97 (1.534)	-2.99 (1.384)	3.29 (1.402)
Effect estimate per comparison	MRI Spine SPARCC score change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo
		LSM Difference (SE)		-7.27 (1.978)
		95% CI		-11.2, -3.4
		p-value		p<.001
	MRI Spine SPARCC score change from baseline at Week 16	Comparison groups		Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)		-6.29 (1.896)
		95% CI		-10.0, -2.5
		p-value		p=.001

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** SF-36 PCS score change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	SF-36 PCS score change from baseline: LSM (SE)	6.12 (0.847)	6.58 (0.776)	1.36 (0.815)
Effect estimate	SF-36 PCS score change from	Comparison groups		Ixekizumab 80 mg Q2W vs. Placebo
		LSM Difference (SE)		4.76 (1.151)

per comparison	baseline at Week 16	95% CI	2.49, 7.02
		p-value	p<.001
	SF-36 PCS score change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	5.21 (1.115)
		95% CI	3.02, 7.41
		p-value	p<.001

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** BASFI change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	BASFI score change from baseline: LSM (SE)	-1.92 (0.225)	-1.69 (0.205)	-0.64 (0.215)

Effect estimate per comparison	BASFI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		LSM Difference (SE)	-1.28 (0.307)
		95% CI	-1.89, -0.68
		p-value	p<.001
	BASFI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	-1.05 (0.295)
		95% CI	-1.63, -0.47
		p-value	p<.001

Results and Analysis	
Analysis Description	**Key Secondary Analysis:** ASAS HI change from baseline at Week 16

Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	98	114	104
	ASAS HI score change from baseline: LSM (SE)	-1.58 (0.352)	-1.92 (0.322)	-0.89 (0.338)
Effect estimate per comparison	ASAS HI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-0.69 (0.477)	
		95% CI	-1.63, 0.25	
		p-value	p=.149	
	ASAS HI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-1.03 (0.460)	
		95% CI	-1.94, -0.13	
		p-value	p=.026	

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS HI = ASAS Health Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; ITT = intent-to-treat; LSM = least squares mean; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; Q2W = every 2 weeks; Q4W = every 4 weeks; r-axSpA = radiographic axial spondyloarthritis; SE = standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey physical component summary; SPARCC = Spondyloarthritis Research Consortium of Canada; TNFi = tumor necrosis factor inhibitor; vs. = versus.

Table 37: Summary of Efficacy for Pivotal Trial I1F-MC-RHBX

Title: A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic Axial Spondyloarthritis			
Study identifier	I1F-MC-RHBX		
Design	Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group study		
	Duration of Main phase: Duration of Extension phase:		52 weeks (Double-Blind Treatment Period) N/A
Hypothesis	Superiority		
Treatment groups [a]	Ixekizumab 80 mg Q2W		Ixekizumab 80 mg Q2W. Duration 52 weeks (Double-Blind Treatment Period). Number randomized 102.
	Ixekizumab 80 mg Q4W		Ixekizumab 80 mg Q4W. Duration 52 weeks (Double-Blind Treatment Period). Number randomized 96.
	Placebo		Placebo. Duration 52 weeks (Double-Blind Treatment Period). Number randomized 105.
Endpoints [b] **and definitions**	Primary endpoint	ASAS40 at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with nr-axSpA as measured by the proportion of patients achieving ASAS40 at Week 16.
	Key secondary endpoint	ASDAS change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with nr-axSpA as measured by the change from baseline in ASDAS score at Week 16.
	Key secondary endpoint	BASDAI change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with nr-axSpA as measured by the change from baseline in BASDAI score at Week 16.
	Key secondary endpoint	SF-36 PCS score change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with nr-axSpA as measured by the change from baseline in SF-36 PCS score at Week 16.
	Key secondary endpoint	ASDAS <2.1 response at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with nr-axSpA as measured by the proportion of patients achieving ASDAS <2.1 response at Week 16

	Key secondary endpoint	MRI SIJ SPARCC score change from baseline at Week 16	To assess whether ixekizumab is superior to placebo in the treatment of bDMARD-naive patients with nr-axSpA as measured by the change from baseline in MRI SIJ SPARCC score at Week 16.
Database lock	52-week database lock (Double-Blind Treatment Period): 01 April 2019 (Last patient visit prior to database lock: 01 March 2019). Data from the 52-week database lock is presented within this table.		

Results and Analysis				
Analysis Description	**Primary Analysis:** ASAS40 response at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks Logistic Regression Model (NRI)			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	102	96	105
	ASAS40	41/102 (40.2%)	34/96 (35.4%)	20/105 (19.0%)
Effect estimate per comparison	Primary endpoint: ASAS40 at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo	21.1	
		95% CI	9.0, 33.3	
		p-value	p=.002	
	Primary endpoint: ASAS40 at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo	16.4	
		95% CI	4.2, 28.5	
		p-value	p=.009	

Results and Analysis	
Analysis Description	**Key Secondary Analysis:** ASDAS change from baseline at Week 16

Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	102	96	105
	ASDAS change from baseline: LSM (SE)	-1.26 (0.095)	-1.12 (0.097)	-0.58 (0.095)
Effect estimate per comparison	ASDAS change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-0.68 (0.134)	
		95% CI	-0.94, -0.41	
		p-value	p<.001	
	ASDAS change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-0.54 (0.136)	
		95% CI	-0.81, -0.28	
		p-value	p<.001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** BASDAI change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	102	96	105
	BASDAI change from baseline: LSM (SE)	-2.52 (0.217)	-2.18 (0.220)	-1.51 (0.216)

Effect estimate per comparison	BASDAI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		LSM Difference (SE)	-1.01 (0.305)
		95% CI	-1.61, -0.41
		p-value	p=.001
	BASDAI change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	-0.67 (0.308)
		95% CI	-1.28, -0.06
		p-value	p=.031

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** SF-36 PCS score change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks MMRM			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	102	96	105
	SF-36 PCS score change from baseline: LSM (SE)	7.96 (0.802)	8.06 (0.813)	5.21 (0.800)

Effect estimate per comparison	SF-36 PCS score change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		LSM Difference (SE)	2.75 (1.128)
		95% CI	0.53, 4.97
		p-value	p=.015
	SF-36 PCS score change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	2.85 (1.139)
		95% CI	0.61, 5.09
		p-value	p=.013

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** ASDAS <2.1 response at Week 16			
Analysis population, time point description, and statistical model	ITT Population with Baseline ASDAS ≥2.1 16 weeks Logistic Regression Model (NRI)			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients	102	94	105
	ASDAS <2.1 response	33/102 (32.4%)	26/94 (27.7%)	13/99 (12.4%)
Effect estimate per comparison	ASDAS <2.1 response at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		% Difference vs. Placebo	20.0	
		95% CI	8.9, 31.0	
		p-value	p<.001	
	ASDAS <2.1 response at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		% Difference vs. Placebo	15.3	
		95% CI	4.3, 26.3	
		p-value	p=.008	

Results and Analysis				
Analysis Description	**Key Secondary Analysis:** MRI SIJ SPARCC score change from baseline at Week 16			
Analysis population, time point description, and statistical model	ITT Population 16 weeks ANCOVA for patients with data at both baseline and Week 16			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of patients with baseline and Week 16 scores	92	85	90

	MRI SIJ SPARCC score change from baseline: LSM (SE)	-4.52 (0.530)	-3.38 (0.549)	-0.31 (0.539)
Effect estimate per comparison	MRI SIJ SPARCC score change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-4.20 (0.751)	
		95% CI	-5.68, -2.72	
		p-value	p<.001	
	MRI SIJ SPARCC score change from baseline at Week 16	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-3.07 (0.764)	
		95% CI	-4.58, -1.57	
		p-value	p<.001	

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS HI = ASAS Health Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; CI = confidence interval; ITT = intent-to-treat; LSM = least squares mean; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; Q2W = every 2 weeks; Q4W = every 4 weeks; r-axSpA = radiographic axial spondyloarthritis; SE = standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey physical component summary; SIJ = sacroiliac joint; SPARCC = Spondyloarthritis Research Consortium of Canada; vs. = versus.

Analysis performed across trials (pooled analyses and meta-analysis)

Data from the pivotal Phase 3 studies are presented side-by-side within this section as summarized in the Clinical Overview. According to the applicant, the side-by-side presentation illustrates reproducibility and comparability of outcomes.

Subgroup, immunogenicity, and starting dose data from the 2 pivotal Phase 3 r-axSpA studies (RHBV and RHBW) has been integrated into the **Primary R-axSpA Analysis Set**.

In addition, immunogenicity data from the 2 pivotal Phase 3 r-axSpA studies (RHBV and RHBW) have also been summarised for patients who were initially randomised to ixekizumab at Week 0 and who had ixekizumab exposure up to Week 52 during the combined Blinded Dosing and Extended Treatment Periods.

Study Populations

Disposition

Completion of the Blinded Treatment Dosing Period through Week 16 for ixekizumab-treated patients in the pivotal studies ranged

- from 95.2% to 96.3% in Study RHBV
- from 86.8% to 91.8% in Study RHBW, and
- from 96.1% to 99.0% in Study RHBX.

Discontinuation rates through Week 16 were somewhat higher across all treatment groups including placebo in Study RHBW (TNFi-experienced patients) relative to Studies RHBV and RHBX (bDMARD-naive patients). Across studies, the most frequent reasons for discontinuation were AEs and subject decision.

Patient Demographics and Other Patient Characteristics

Patient demographics, baseline characteristics, and disease severity were reflective of the intended patient population (r-axSpA or nr-axSpA) and are summarised in the table below.

Table 38: Patient Demographics and Baseline Characteristics by Pivotal Study

	RHBV N = 341	**RHBW N = 316**	**RHBX N = 303**
Age (years), mean (SD)	41.7 (11.66)	46.1 (12.43)	40.3 (12.92)
Sex, n (%)			
Male	276 (81.2)	253 (80.1)	143 (47.2)
Weight (kg), mean (SD)	78.09 (15.804)	83.20 (18.705)	77.49 (17.213)
BMI (kg/m^2), mean (SD)	26.49 (4.925)	28.67 (6.239)	27.31 (5.624)
Race, n (%)			
American Indian or Alaska Native	14 (4.1)	12 (3.8)	13 (4.3)
Asian	107 (31.5)	40 (12.7)	41 (13.6)
Black or African American	0	5 (1.6)	0
Native Hawaiian/Other Pacific Islander	0	0	0
White	213 (62.6)	254 (80.6)	239 (79.1)
Multiple	6 (1.8)	4 (1.3)	9 (3.0)
Geographic Region, n (%)			
America	54 (15.9)	138 (43.7)	102 (33.7)
Asia	105 (30.9)	34 (10.8)	38 (12.5)
Europe	181 (53.2)	128 (40.5)	163 (53.8)
Age of onset of axSpA (years), mean (SD)	26.1 (8.20)	28.1 (9.46)	30 (9.63)
Duration of symptoms since axSpA onset (years), mean (SD)	15.95 (10.250)	18.44 (11.070)	10.66 (9.692)
Prior TNFi's, n (%)			
Used 1 TNFi	–	198 (62.9)	–
Used 2 TNFi's	–	117 (37.1)[a]	–
Inadequate Response	–	283 (89.9)[a]	–
Intolerance	–	32 (10.2)[a]	–
HLA-B27 positive, n (%)	308 (90.9)	257 (81.3)	221 (73.7)

Abbreviations: axSpA = axial spondyloarthritis; BMI = body mass index; CRP = C-reactive protein; CSR = clinical study report; HLA-B27 = Human Leukocyte Antigen B27; ITT = intent-to-treat; N = number of patients in the ITT population; n = number of patients within each specific category; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; RHBX = I1F-MC-RHBX; SD = standard deviation; TNFi = tumour necrosis factor inhibitors.

[a] One patient did not take prior TNFi's, and hence the denominator for percentage calculation is 315.

Table 39: Patient Baseline Disease Severity by Pivotal Study

	RHBV N = 341	RHBW N = 316	RHBX N = 303
Patient global assessment of disease activity (NRS), mean (SD)	7.0 (1.63)	7.9 (1.69)	7.4 (1.63)
Spinal Pain, mean (SD)			
Spinal pain due to axSpA	7.2 (1.47)	7.9 (1.46)	7.4 (1.65)
Spinal pain at night due to axSpA	7.0 (1.64)	7.7 (1.71)	7.3 (1.80)
ASDAS, mean (SD)	3.76 (0.782)	4.13 (0.815)	3.83 (0.848)
BASFI score, mean (SD)	6.18 (1.961)	7.26 (1.662)	6.52 (1.963)
BASDAI score, mean (SD)	6.72 (1.398)	7.44 (1.298)	7.16 (1.440)
BASDAI inflammation score (mean of Questions 5 and 6), mean (SD)	6.66 (1.695)	7.29 (1.734)	6.97 (1.807)
CRP concentration (mg/L), mean (SD)	13.512 (17.1034)	17.801 (26.6486)	12.940 (20.3748)
CRP category >5.00 mg/L, n (%)	219 (64.4)	207 (65.5)	191 (63.0)
BASMI linear score, mean (SD)	4.16 (1.497)	4.77 (1.553)	3.16 (1.194)
MRI SPARCC score, mean (SD)			
MRI of spine	16.76 (23.745)	8.62 (16.109)	–
MRI of SIJ	5.15 (10.201)	–	6.35 (9.461)
Health Outcomes, mean (SD)			
SF-36 PCS score	33.38 (7.957)	28.61 (7.898)	32.61 (7.728)
ASAS HI score	8.05 (3.558)	9.70 (3.625)	9.09 (3.558)
Concomitant medication			
Sulfasalazine dosage (g/day), mean (SD)	1.60 (0.557)	1.85 (0.684)	1.68 (0.616)
Methotrexate dosage (mg/week), mean (SD)	15.31 (4.515)	15.79 (4.823)	16.65 (4.886)
NSAID/COX-2 inhibitor use, n (%)	312 (91.8)	241 (76.3)	272 (89.8)
Oral corticosteroid use, n (%)	32 (9.4)	36 (11.4)	42 (13.9)
Analgesic use, n (%)	45 (13.2)	97 (30.7)	58 (19.1)

Abbreviations: ASAS HI = ASAS Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; axSpA = axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; COX-2 = cyclooxygenase-2; CRP = C-reactive protein; CSR = clinical study report; ITT = intent-to-treat; MRI = magnetic resonance imaging; N = number of patients in the ITT population; n = number of patients within each specific category; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; RHBX = I1F-MC-RHBX; SD = standard deviation; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Summary; SIJ = sacroiliac joint; SPARCC = Spondyloarthritis Research Consortium of Canada.

Comparison of Efficacy Results of All Studies

The table below summarises the significance testing of the primary and major secondary endpoints of the pivotal studies, in accordance with each study's multiple testing procedure.

The primary endpoint (ASAS40 at Week 16) was the same across the 3 pivotal studies. The major secondary objectives of ASDAS and SF-36 PCS score are also common across the 3 pivotal studies.

The major secondary objectives of ASAS20, ASDAS, BASFI, MRI Spine SPARCC, SF-36 PCS, and ASAS HI scores at Week 16 are common across the 2 r-axSpA studies.

Table 40: Pivotal Studies: Summary of Primary and Major Secondary Objectives at Week 16 with Multiple Testing Procedure ITTT Population Blinded Treatment Dosing Period

	RHBV				RHBW				RHBX			
	IXE Q4W vs. PBO		IXE Q2W vs. PBO		IXE Q4W vs. PBO		IXE Q2W vs. PBO		IXE Q4W vs. PBO		IXE Q2W vs. PBO	
	Adjusted p-Value[a]	Sig?	Adjusted p-Value[a]	Sig?	Adjusted p-Value[a]	Sig?	Adjusted p-Value[a]	Sig?	Adjusted p-Value[a]	Sig?	Adjusted p-Value[a]	Sig?
Primary Objective												
ASAS40 Response	<.001	Yes	<.001	Yes	.017	Yes	.003	Yes	.010	Yes	.004	Yes
Major Secondary Objectives												
ASAS20 Response	.001	Yes	<.001	Yes	.017	Yes	.017	Yes	N/A			
ASDAS Change from Baseline	.001	Yes	<.001	Yes	.017	Yes	.017	Yes	.010	Yes	.004	Yes
ASDAS ID Response	.008	Yes	.041	Yes	N/A				N/A			
ASDAS <2.1 Response	N/A				.017	Yes	.031	Yes	.031	Yes	.031	Yes
BASDAI50 Response	.001	Yes	<.001	Yes	N/A				N/A			
BASDAI Change from Baseline	N/A				.017	Yes	.017	Yes	.031	Yes	.010	Yes
BASFI Change from Baseline	.001	Yes	<.001	Yes	.017	Yes	.017	Yes	N/A			
MRI Spine SPARCC Change from Baseline	.001	Yes	<.001	Yes	.017	Yes	.017	Yes	N/A			
MRI SIJ SPARCC change from baseline	N/A				N/A				.031	Yes	.031	Yes
SF-36 PCS Change from Baseline	.001	Yes	<.001	Yes	.017	Yes	.017	Yes	.031	Yes	.031	Yes
ASAS HI Change from Baseline	.011	Yes	.041	Yes	.031	Yes	.149	No	N/A			

Footnotes overleaf

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASDAS ID = ASDAS inactive disease; ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CSR = clinical study report; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; ITT = intent-to-treat; MRI = magnetic resonance imaging; NA = not applicable; PBO = placebo; Sig = significant; SF-36 PCS = Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Summary; SIJ = sacroiliac joint; SPARCC = Spondyloarthritis Research Consortium of Canada score; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; RHBX = Study I1F-MC-RHBX; vs. = versus.

[a] Multiplicity-adjusted p-value.

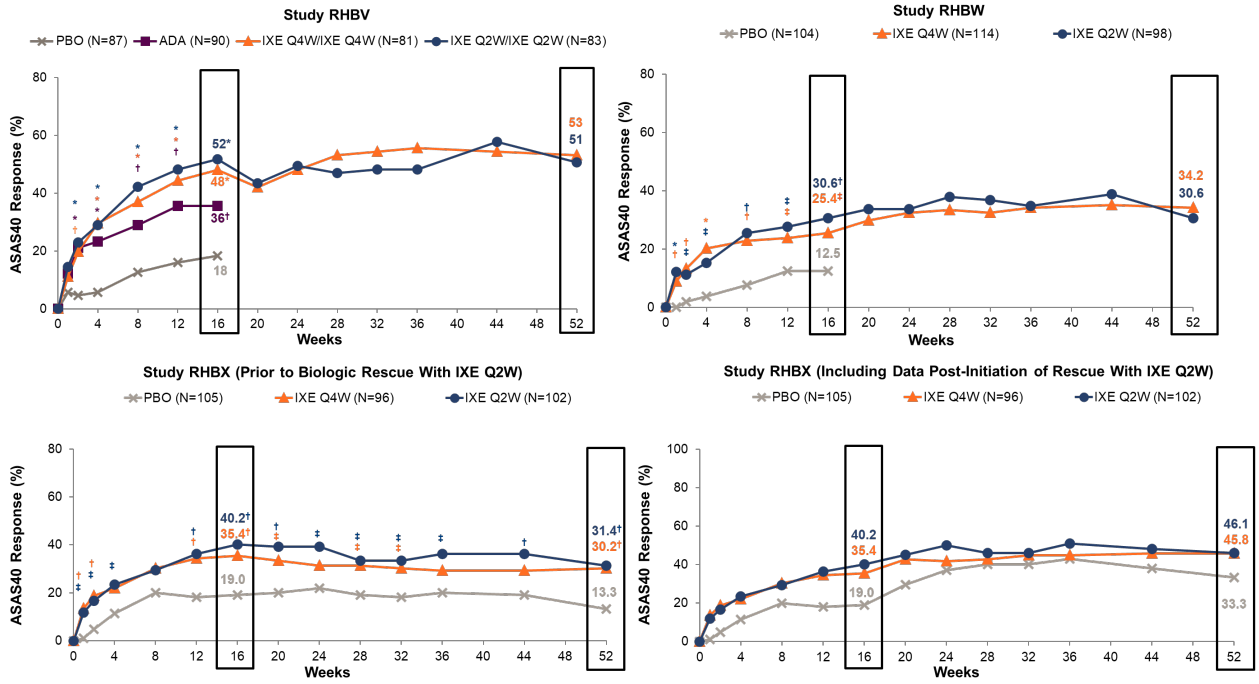
Note: All comparisons of ixekizumab with placebo for the primary and major secondary endpoints were statistically significant, with the exception of change from baseline at Week 16 for ASAS HI for the ixekizumab 80-mg Q2W group in Study RHBW, as calculated with the graphical method for multiple testing, with the family-wise type I error rate strongly controlled at a 2-sided α level of 0.05 for multiple comparisons.

Speed of Onset of Efficacy

In Studies RHBW and RHBX, greater percentages of patients in both ixekizumab groups versus placebo achieved ASAS20 and ASAS40 as early as Week 1. In Study RHBV, the ASAS40 responses in the ixekizumab groups were different from the placebo group at Week 2.

During the procedure, the MAH provided the time course of ASAS40 response, which indicates that the response reaches plateau by Week 16 to 20 (Figure 45.).

Figure 45. ASAS40 response rates through Week 52 (NRI) Studies RHBV, RHBW, and RHBX



Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; IXE Q2W = 80 mg of ixekizumab every 2 weeks; IXE Q4W = 80 mg of ixekizumab every 4 weeks; NRI = nonresponder imputation; PBO = placebo.
*p≤.001 vs. PBO; †p<.01 vs. PBO; ‡p<.05 vs. PBO.

Supportive study

Study RHBY is a long-term extension study with a double-blind, placebo-controlled, randomised withdrawal–retreatment period, enrolling patients who completed any of the 3 pivotal Phase 3 studies and met eligibility criteria. At the time of this Type II variation, Study RHBY was ongoing, and the periods where patients participated in the double-blind, placebo-controlled, randomised withdrawal–retreatment were still blinded.

2.4.3. Discussion on clinical efficacy

Ixekizumab, a IL-17A-inhibitor, is approved for plaque psoriasis and PsA. This application aims to extend the indication to treatment of active axial spondyloarthritis (axSpA); including both radiographic (r-axSpA) and non-radiographic disease (nr-axSpA). According to the proposed SmPC, the recommended posology is a bolus dose of 160 mg, followed by 80 mg by subcutaneous injection every 4 weeks.

Design and conduct of main clinical studies

The MAH has conducted 3 pivotal studies in 930 adult patients with axSpA axial: 2 studies in patients with r-axSpA (**RHBV** and **RHBW**) and 1 study in patients with nr-axSpA (RHBX). All three studies have a randomized, double blind, parallel group design with a screening period of up to 42 days followed by randomisation, testing two different dose regimens of Ixekizumab (80mg Q2W or 80mg Q4W) with or without a bolus dose of 160 mg. One study (RHBV) also included an active comparator, adalimumab 40mg Q2W. The placebo-controlled period was 16 weeks in the two r-axSpA studies (RHBV, RHBW) and 52 weeks in the nr-axSpA study (**RHBX**). In all three studies, the primary endpoint, ASAS 40, was measured at week 16.

The MAH has essentially followed the recommendation of the EMA clinical guidance for AS (Guideline on clinical investigation for the treatment of ankylosing spondylitis, CPMP/EWP/4891/03) in the clinical development programme. In addition to using ASAS 40 as a primary endpoint, the MAH has examined several secondary endpoints which explores structural damage, mobility and patient reported Health outcomes, all in line with the guideline. The scales used in the studies are acceptable, as were the cut of values used for ASDAS.

The MAH has received a central scientific advice (EMA/CHMP/SAWP/339078/2011) and the advice has overall been adhered to.

The MAH provided accurate details that the Clinical trials were performed in accordance with GCP.

The study populations in all phase 3 studies consisted of adults with active axSpA with a history of prior therapy for axSpA of at least 12 weeks and an inadequate response or intolerance to NSAID. This was not clearly expressed in the initial indication text, but upon CHMP's request, the MAH has changed the indication text to better align with the intended population (cf discussion below).

Disease activity was based on measurements of BASDAI (>=4) and spinal pain (>=4) which are in line with guideline. The ASAS criteria for spondylarthritis was the main inclusion criteria in all three studies with the specification that in the two studies examining patient with R-axSpA (RHBV and RHBW), all patients also fulfilled the *radiological* criteria of the modified New York criteria for AS (i.e. evidence of sacroiliitis on plain X-ray). The modified New York criteria have been used in previous studies examining patient with radiographic axSpA and are also the criteria recommended in the EMA guideline for this group.

In study **RHBX**, examining patients with nR-axSpA, eligible subjects were requested to have objective signs of inflammation, specified as sacroiliitis on MRI or elevated C-reactive protein (CRP). Please see discussion in relation to the proposed indication below.

Overall, the proportion of screening failures were high in the main clinical studies; between 40-55%. The MAH provided clarifications on the reasons for screening failures mainly due to not meeting the x-ray eligibility criteria or having insufficient disease activity in r-AxSpA studies. In the nr-axSpA study, the main reason for screening failure was not meeting the ASAS criteria for axSpA, absence of objective signs of inflammation and presence of definite radiographic sacroiliitis by central reading. The CHMP considered that this doesn't have significant impact on the representativeness of the studied population for the proposed indication.

Statistical considerations with regards to the phase III studies

Study RHBV and study RHBW (r-axSpA)

Studies **RHBV** and **RHBW** shared a number of features based on similarities in design and definition of endpoints. In both studies, there were two interim database locks planned for analyses based on data collected up to week 16 and up to week 52, respectively. Two separate CSRs have been submitted

referring in turn to two versions of the statistical analysis plan. The primary analysis was performed based on week 16 data. Though described as an interim analysis, the submitted dossiers contain full information on the primary efficacy endpoints (which were evaluated at week 16 for EU registration) for each study, so there is no need for a statistical adjustment to account for the 'interim' analysis. Each trial is currently in the open-label long-term extension phase. The primary objective and major secondary objectives comprised comparisons between ixekizumab 80 mg Q2W and 80 mg Q4W respectively, and placebo. The primary analysis was based on the ITT population including all randomised patients. The analyses further reflected the restrictions at randomisation in adjusting for the stratification factors. In study **RHBV,** the last secondary efficacy objective was to test assay sensitivity by comparing adalimumab 40 mg Q2W with placebo. No statistical comparisons were planned between ixekizumab and adalimumab; the lack of head-to-head comparisons between the two active treatments is acceptable.

In both studies RHBV and RHBW, the primary endpoint was the proportion of patients achieving treatment success, defined as achieving ASAS40 at Week 16 while still on randomised treatment. For responder analyses, a non-responder imputation was used which is non-controversial. An analysis using all available data irrespective of whether a patient discontinued randomised treatment or not have been presented supporting the primary endpoint analysis. For continuous endpoints, the primary analyses as based on MMRM and relying on the missing at random assumption (MAR) could be criticised, depending however on the missing data pattern. Here, the proportions of subjects who did not complete the blinded treatment period through week 16 were non-substantial and similar between treatment arms although higher in study **RHBW** than in study **RHBV**. A number of additional analyses using alternative approaches were planned. While the underlying assumptions and statistical properties of the LOCF and mBOCF analyses could be questioned, the MAH provided also sensitivity analyses using placebo-based imputation and tipping point analyses which are acceptable by CHMP.

A graphical multiple-testing procedure was implemented for the primary objective and major secondary objectives to control the family-wise type I error rate at a 2-sided alpha level of 0.05. A similar approach was used for all three studies albeit with some differences in number of major secondary endpoints and their definition; there were also differences in weights (i.e. how alpha was allocated within the multiple testing procedure). As described graphically, the multiple testing procedure, irrespective of study (**RHBV, RHBW and RHBX**) is acceptable. There was no multiplicity adjustment for the other secondary endpoints. The latter implies that no formal claims can be made regarding e.g. long-term efficacy (week 52 analyses). For e.g. the primary endpoint, uncontrolled ASAS40 response rates for weeks 16, 36 and 52 for each ixekizumab arm have been presented based on the ITT population with patients with missing observations imputed as non-responders. This approach is agreed. The proportion of patients who lacked ASAS40 observations at week 52 was approximately 10% in study **RHBV** and 20% in study **RHBW** and similar in the ixekizumab Q2W and Q4W arm, respectively.

In both studies, the primary analysis was performed ignoring the two different ixekizumab starting doses. Separate, non-powered, not multiplicity adjusted analyses were planned in order to assess the impact of ixekizumab starting dose of 160 mg versus 80 mg on treatment response at Week 16 and time to onset of action. Based on these analyses, no firm conclusions can be drawn.

Study RHBX (nr-axSpA)

The analyses planned as described in the study RHBX protocol were similar to those planned for both Studies **RHBV** and **RHBW** and seem appropriate. The SAP had not been submitted initially and was therefore requested. The SAP has then been provided and confirmed that all details concerning the graphical multiple testing scheme had been pre-defined.

Analogous to studies **RHBV** and study **RHBW**, a secondary objective was to explore the effect of starting dose (160 mg compared to 80 mg) on onset of action and treatment response. However, with a limited

sample size since not powered and without being otherwise formally planned, no firm conclusions can be drawn.

Contrary to studies **RHBV** and **RHBW**, study **RHBX** had a double-blind, placebo-controlled treatment period of 52 weeks. To meet different regulatory requirements, there were two separate primary endpoints that were tested independently: proportion of patients achieving an ASAS40 response at either Week 16, which is in line with the relevant EMA guideline, or Week 52 implying two separate lists of primary and major secondary endpoints with multiplicity adjustment within each of the lists using the graphical multiple testing procedure. For the week 16 analysis, the multiple testing procedure included the primary endpoint and five major secondary endpoints with all comparisons planned and performed at Week 16. Analyses based on comparisons week 52 were not multiplicity adjusted and formal claims regarding long-term efficacy is not appropriate albeit this study offered comparisons versus placebo.

Exclusively for study **RHBX** and as a consequence of the one-year placebo-controlled treatment period, subjects identified by investigators as showing inadequate response based on clinical judgment could initiate rescue treatment with ixekizumab 80 mg Q2W starting from week 16. Therefore, an Inadequate Responder (IR) population was defined and used for selected safety and efficacy summaries. This population included a total of 47.5% (144/303) of randomised subjects. In the placebo group, this concerned 59.0% (62/105), in the ixekizumab Q4W arm 41.7% (40/96) and in the ixekizumab Q2W arm 41.2% (42/102). Outcomes presented based on the IR population were summarized by originally assigned treatment group without inferential statistics. This is supported since these were not randomised comparisons. Given the high proportion of subjects classified as inadequate responders also in the two ixekizumab arms, the MAH was requested to present time to inadequate response and/or treatment discontinuation. The provided Kaplan-Meier plot for time to open-label treatment of ixekizumab 80 mg Q2W by originally assigned treatment group confirmed that most of the patients who switched to open-label ixekizumab 80 mg Q2W did so at Week 16, the earliest time point that a switch to open-label ixekizumab Q2W or an adjustment of non-biologic background medication was allowed.

Due to the design of study **RHBX**, there was a dramatic drop in the number of subjects after Week 16 which may impact on the robustness of the week 52 data. The MAH considered that the approach to detect treatment differences was robust and reliable because of the lack of bias toward any treatment group. This was, according to the MAH, due to the blinded nature of the study, the conservative approach to qualifying patients as "non-responder" and conservative non-responder imputation (NRI) method for missing data imputation, together with the inclusion of all randomised patients in the analyses at visits after Week 16. It is acceptable by CHMP that this is conservative for the estimation of efficacy within a treatment group but is not necessarily true for between group comparisons.

Concerning all three studies, **RHBV, RHBW and RHBX**, the MAH was requested to revise the presentation of outcomes in section 5.1 in the SmPC to better align with the primary analysis of each of the study and hence the multiplicity protected outcomes of the primary and major secondary outcomes. Other secondary analyses not multiplicity adjusted including a *post-hoc* analysis performed in study RHBV had been included and there was much focus on p-values and confidence intervals were lacking. The section 5.1 is in line with the primary analysis of each study including also 95% CIs.

Efficacy data and additional analyses

Main data from the three pivotal clinical studies

In Study **RHBV,** 341 **TNF-inhibitor naive r-axSpA** patients were randomized to 1 of 4 treatment groups (Ixekizumab 80mg Q2W, Ixekizumab 80mg Q4W, placebo or Adalimumab 40 mg Q2W). In addition, the patient in the two Ixekizumab group were randomized 1:1 to receive a bolus dose of 160 mg Ixekizumab.

Demographic and baseline disease characteristics were generally comparable between the 4 groups. After 16 weeks, patients in the placebo and Adalimumab group were randomized to receive Ixekizumab 80mg Q2W or 80mg Q4W, with or without a bolus dose of 160 mg.

The study met the primary and all major secondary endpoints. The difference in clinical response vs placebo was for both tested doses of the drug both statistically and clinically relevant. The outcomes of the secondary endpoints were in line with the outcome of the primary endpoint. A bolus dose of 160mg did not seem to result in earlier or better response.

The primary endpoint, ASAS 40 response at week 16, was reached for 48% of the patient treated with Ixekizumab 80mg Q4W and for 52% of the patient treated with Ixekizumab 80 mg Q2W. Among the patients treated with placebo, 18% reached ASAS 40 at week 16. In the Adalimumab 40mg Q2W group, 36% reached ASAS 40 response. The study was not designed to test non-inferiority of Ixekizumab compared to Adalimumab.

Numerically higher response rate compared to placebo was observed already after one week and for the patients initially randomized to ixekizumab, the effect appeared to be sustained during the extended study period, 52 weeks.

In study **RHBW**, 316 **TNF-inhibitor experienced r-axSpA** patients were randomized to 1 of 3 treatments group (Ixekizumab 80mg Q2W, Ixekizumab 80mg Q4W or placebo). In addition, patients in the two Ixekizumab groups were randomized 1:1 to receive a bolus dose of 160 mg Ixekizumab. Demographics and disease characteristics were generally the same between groups. 62.9% of the patients had received one previous TNF-inhibitor and 37.1% of the patients had received 2 TNF inhibitors. As in the RHBV study, patients in the placebo arm were randomised at week 16 to receive Ixekizumab 80mg Q2W or 80mg Q4W, with or without a bolus dose of 160 mg.

The inclusion criteria in study **RHBW** lists patients who have had *an inadequate response* following at least 12 weeks of treatment. The term "inadequate response" relative to prior TNFi exposure includes both patients who never achieved an adequate response, as well as patients who had initially responded and then lost response.–

Statistically significant differences were observed for the primary endpoint and most major secondary endpoints at Week 16 for each ixekizumab treatment group compared to the placebo group. Not only statistically significant but also clinically relevant differences vs placebo was noted for both tested doses of ixekizumab vs placebo with regards to the primary endpoint. For the primary endpoint, the difference between the two doses of ixekizumab was relatively small. In both dose groups, the clinical response seemed to be maintained up to 1 year.

The primary efficacy endpoint of ASAS 40 response at week 16 was achieved for 30.6% in the Ixekizumab 80mg Q2W group, 25.4% Ixekixumab 80mg Q4W and 12.5% Placebo. The lower response rate in TNF-inhibitor experienced patients compared to naïve patients is expected.

In this patient group, a bolus dose of 160 mg was associated with a numerically improved efficacy at earlier timepoint across several parameters, including spinal pain, disease activity, function and HR-QoL. For example, ASAS20 response at week 2 for the 80mg Q4W group was 44.4% in the 160 mg starting dose group vs 26.7% in the 80 mg starting dose group.

Numerically greater ASAS20 and ASAS40 responses were observed in each ixekizumab treatment group, compared to the placebo group, regardless of the number of prior TNFi used. Additional analyses clarified that the response rates were consistently numerically higher for each ixekizumab regimen versus placebo in the subgroup of patients with 1 prior TNFi, as well as in the subgroup of patients with 2 prior TNFi's.

In study **RHBX,** 303 patients with **non-radiographic axial spondyloarthritis** were randomized to 1 of 3 treatments group (Ixekizumab 80mg Q2W, Ixekizumab 80mg Q4W or placebo). After week 16, non-

responders (as determined by the treating physician) in all three groups were offered rescue therapy with open-label Ixekizumab 80mg Q2W.

Statistically significant improvements in efficacy were observed for each of the ixekizumab treatment groups vs placebo across the primary and all major secondary objectives. The magnitude of improvement vs placebo with regards to the primary endpoint ASAS40 at week 16 is considered clinically relevant for both tested doses of Ixekizumab. The numerical difference between the two dose groups was relatively small and not considered clinically relevant. There seem to be no beneficial effect of giving a bolus dose of 160 mg.

The primary efficacy endpoint of ASAS 40 response at week 16 was achieved for by 40.2% in the Ixekizumab 80mg Q2W, 35.4% Ixekixumab in the 80mg Q4W and in the 19.0% Placebo group. The effect was seen as early as week 1 and seem to be maintained up to week 52.

The placebo-controlled period in study **RHBX** was 52 weeks, but between week 16 and 44, patients could be offered rescue treatment if their treating physician classified the patient as a non-responder irrespectively of whether the study endpoints were achieved or no. Of the 265 patients (87,5%) who completed 52 weeks, 45,5% were still on their originally randomized treatment and 127 patients (41,9%) were on open label ixekizumab Q2W rescue treatment. Of the patients classified as inadequate responders between week 16 and 44, 52% was originally randomized to placebo, 41.2 % to ixekizumab 2QW and 41.7 % to ixekizumab Q4W. The proportion of patients originally randomized to ixekizumab receiving rescue-treatment with open label ixekizumab was surprisingly high. The MAH argued that despite being classified as an inadequate responder by the physician at week 16 (last visit before rescue), 16.5% patients in the 2QW group, 25% patients in the Q4W group and 6.5% of the placebo group had indeed reached the endpoint of ASAS40 at that timepoint. The MAH clarified that the decision to "rescue" a patient was solely based on the treating physicians' judgement and not based on any specific predefined outcome measure. The CRP values were blinded beyond baseline through week 52 and the lack of access to CRP values may have led treating physicians to take a rather conservative approach to rescue in the best interest of the patient. The MAH clarification is considered acceptable by CHMP.**-**

A few statistically significant treatment-by-subgroup interactions were identified in each of the pivotal studies. The applicant has adequately discussed these, and it has been concluded that there are no clinical meaningful implications of these findings mainly due to the small sample size in the subgroup analyses.

Data to support proposed indication

The three successful main studies include adult patients with active axSpA (r-axSpA and nr-axSpA) with a history of prior axSpA-therapy of at least 12 weeks and an inadequate response or intolerance to NSAID. Thus, the studied population is essentially restricted to subjects with prior experience of conventional treatment. At the CHMP's request, the MAH has revised the wording of the indication both in patients with radiographic and non-radiographic axSpA to better reflect the intended population.

In study **RHBX**, examining patients with nR-axSpA eligible subjects were requested to have objective signs of inflammation, specified as sacroiliitis on MRI or elevated C-reactive protein (CRP). At the CHMP's request, the MAH added *"as indicated by elevated CRP and / or MRI",* to the indication wording for patients with nR-axSpA for clarification**.**

Data to support proposed posology

In all three main studies, an early effect response was seen already after 1-2 weeks. The response was still increasing during the first months but some of the patients did not receive any beneficial effect of ixekizumab. Upon request, the MAH provided time-course information reporting a plateau of ASAS40 response by week 16. This information is now included in the SmPC.

Based on the more rapid response after induction observed in study RHBW that included a AS TNF-ir population, the MAH initially proposed an induction dose of 160mg in this sub-group, but not in the TNF-naïve or nr-AxSpA population. However, upon request, the MAH provided a discussion of pros and cons for recommending the bolus dose to all patients. The conclusion was since both psoriatic arthritis and axSpA are part of the same disease spectrum (spondyloarthritis) and there were no impact on the safety profile (except for a numerically higher number of hepatic event, described as transient asymptomatic laboratory changes in aminotransferases), harmonizing the dose regimen between the spondyloarthritis and recommending a 160 mg bolus dose in all these patients is appropriate. This is acceptable by CHMP.

In study **RHBX**, at week 16, and up to week 44, it was possible to switch patients that were considered to be non-responders to the ixekizumab 80 mg Q2W treatment, and the MAH was asked to discuss whether a dose escalation would benefit these patients not responding to the lower dose. Descriptive data on ASAS40, ASDAS and BASDAI indicated a slight trend in favour of a dose escalation. However, it is acknowledged by CHMP that study RHBX was not designed for testing the effect of switching treatment and that the provided information is thus not considered sufficient to support a dose escalation.

In nr-axSpA in particular, it is not established whether treatment in a well responding patient should be continued on a chronic basis, or whether dose tapering or even treatment discontinuation can be considered at some point. The MAH indicated to currently collect randomised withdrawal data in the ongoing study RHBY. The MAH has committed, based on CHMP's recommendation, to submit the results post-approval, in line with the EU Guideline on axSpA.

2.4.4. Conclusions on the clinical efficacy

All three phase III studies met the primary endpoint of superiority over placebo in ASAS 40 response rate at week 16. In addition, most major secondary endpoints (evaluating disease activity, objective signs of inflammation, function and patient reported quality of life) were achieved.

The initially proposed indication targeted all subjects with active axSpA, although the studied populations were restricted to subjects with prior experience of conventional treatment. At the CHMP's request, the MAH has revised the indication for both the r-axSpA and nr-axSpA populations to reflect the intended population.

In study **RHBX**, examining patients with nR-axSpA eligible subjects were requested to have objective signs of inflammation, specified as sacroiliitis on MRI or elevated C-reactive protein (CRP). At the CHMP's request, the MAH added "as indicated by elevated CRP and / or MRI", to the indication wording for patients with nR-axSpA for clarification.

The wording of the final indication is as follows:

<u>Axial spondyloarthritis</u>

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis

Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

The proposed posology, 80 mg 4QW with a bolus dose of 160 mg to all patients, was considered

acceptable to the CHMP as it is supported by the data provided.

2.5. Clinical safety

Introduction

For this submission, the applicant summarized safety data from 2 integrated analysis sets: The **Placebo-Controlled axSpA Integrated Analysis Set** and the **All axSpA Ixekizumab Exposures Integrated Analysis Set**, as described below:

- The **Placebo-Controlled axSpA Integrated Analysis Set** included patient data from the 2 randomised, Phase 3, r-axSpA placebo-controlled studies (Studies RHBV and RHBW) and from the randomised, Phase 3, nr-axSpA placebo-controlled study (Study RHBX) from screening up through Week 16. The term "Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16)" to this period of interest. For Study RHBX, the Blinded Treatment Dosing Period included a 52-week, blinded, placebo-controlled period, but only Weeks 0 to 16 were integrated in this data set to be consistent with the design, patient management, and data collection of the other 2 studies. Adalimumab treatment group was not included in this integrated analysis set as this treatment group was included only in Study RHBV and not in Studies RHBW and RHBX.
- The **All axSpA Ixekizumab Exposures Integrated Analysis Set** (termed the **"All axSpA Analysis Set"**) included all available ixekizumab data from Studies RHBV, RHBW, and RHBX, as well as data from patients receiving open-label ixekizumab in Study RHBY.

The safety population, defined as all randomised patients who received at least 1 dose of study treatment, was used in each of the integrated analysis sets.

Table 41: Overview of Studies of Ixekizumab for this Type II Variation

Type, Phase	Identifier	Study Description	Population	Treatments by Study Period	Number of Patients in Treatment Group	Status[a]
Pivotal, Phase 3	I1F-MC-RHBV	Multicentre, randomised, double-blind, placebo- and active-controlled, parallel-group study followed by an extended treatment period. Primary endpoint at Week 16.	Adult bDMARD-naive patients with active r-axSpA (ASAS criteria: sacroiliitis defined radiographically [mNY criteria] and ≥1 SpA feature).	Blinded Treatment Dosing Period (Weeks 0[b] to 16): IXE Q2W IXE Q4W ADA Q2W[c] Placebo Extended Treatment Period (Weeks 16 to 52): IXE Q2W IXE Q4W	Blinded Treatment Dosing Period: 340 patients exposed (at least 1 dose): 83 to IXE Q2W 81 to IXE Q4W 90 to ADA Q2W 86 to placebo Extended Treatment Period:329 patients: 165 to IXE Q2W 164 to IXE Q4W	Completed

Type, Phase	Identifier	Study Description	Population	Treatments by Study Period	Number of Patients in Treatment Group	Status[a]
Pivotal, Phase 3	I1F-MC-RHBW	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study followed by an extended treatment period. Primary endpoint at Week 16.	Adult TNFi-experienced[d] patients with active r-axSpA (ASAS criteria: sacroiliitis defined radiographically [mNY criteria] and ≥1 SpA feature).	Blinded Treatment Dosing Period (Weeks 0[b] to 16): IXE Q2W IXE Q4W Placebo Extended Treatment Period (Weeks 16 to 52): IXE Q2W IXE Q4W	Blinded Treatment Dosing Period: 316 patients exposed (at least 1 dose): 98 to IXE Q2W 114 to IXE Q4W; 104 to placebo Extended Treatment Period: 281 patients: 137 to IXE Q2W 144 to IXE Q4W	Ongoing; Blinded Treatment Dosing Period: interim DBL completed (19 Jun 2018); Extended Treatment Period: interim DBL completed (28 Feb 2019);
Pivotal, Phase 3	I1F-MC-RHBX	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study.	Adult bDMARD-naive patients with active nr-axSpA (sacroiliitis on MRI [ASAS/OMERACT criteria] and ≥1 SpA feature [ASAS criteria] *or* HLA-B27 positive and ≥2 additional SpA features [ASAS criteria]).	Blinded Treatment Dosing Period (Weeks 0[b] to 52)[e]: IXE Q2W IXE Q4W Placebo	Blinded Treatment Dosing Period: 302 patients exposed (at least 1 dose): 102 to IXE Q2W 96 to IXE Q4W 104 to placebo	Ongoing; Blinded Treatment Dosing Period: interim DBL completed (01 Apr 2019)

Type, Phase	Identifier	Study Description	Population	Treatments by Study Period	Number of Patients in Treatment Group	Status[a]
Supportive, Phase 3	I1F-MC-RHBY	Multicentre study with an initial lead-in period, followed by a double-blind, placebo-controlled, randomised withdrawal-retreatment period and then a long-term extension period.	Adult patients who completed any of the originating studies (RHBV, RHBW, or RHBX): Patients will have r-axSpA or nr-axSpA. Patients may have experience with TNFi[d].	Lead-In Period (Weeks 0 to 24): IXE Q2W IXE Q4W Extension Period (Weeks 24 to 64) and Long-Term Extension Period (Weeks 64 to104): *Patients eligible for the randomised withdrawal-retreatment period:* IXE Q2W IXE Q4W Placebo *Patients ineligible for the randomised withdrawal-retreatment period:* IXE Q2W IXE Q4W	Lead-In Period: 754 patients exposed (at least 1 dose): 415 to IXE Q2W 339 to IXE Q4W Extension Period and Long-Term Extension Period: *Patients eligible for the randomised withdrawal-retreatment period:* 131 patients (double blind, placebo-controlled: number of patients in each dosing regimen unavailable) *Patients ineligible for the randomised withdrawal-retreatment period:* 459 patients: 257 to IXE Q2W 202 to IXE Q4W	Ongoing; No DBL completed; In the Extension Period and Long-Term Extension Period: *Patients eligible for the randomised withdrawal-retreatment period:* double-blind placebo-controlled. *Patients ineligible for the randomised withdrawal retreatment period:* open-label.

Patient exposure

There were 868 patients in the Safety Population of the Placebo-Controlled axSpA Integrated Analysis Set (**Table 42**).

Table 42: Exposure to Ixekizumab, Placebo-Controlled axSpA Integrated Analysis Set, Weeks 0 to 16

Analysis Set	**Placebo-Controlled axSpA Integrated Analysis Set**			
Studies Included	**RHBV, RHBW, RHBX**			
Treatment Group	**PBO (N = 294)**	**IXE Q4W (N = 291)**	**IXE Q2W (N = 283)**	**Total IXE (N = 574)**
Days of Exposure, n (%)				
>0	294 (100.0)	291 (100.0)	283 (100.0)	574 (100.0)
≥7	294 (100.0)	291 (100.0)	283 (100.0)	574 (100.0)
≥14	291 (99.0)	291 (100.0)	283 (100.0)	574 (100.0)
≥30	290 (98.6)	286 (98.3)	283 (100.0)	569 (99.1)
≥60	286 (97.3)	283 (97.3)	275 (97.2)	558 (97.2)
≥90	283 (96.3)	276 (94.8)	274 (96.8)	550 (95.8)
≥112	255 (86.7)	237 (81.4)	254 (89.8)	491 (85.5)
Mean days exposure	111.7	110.8	112.9	111.8
Total Patient-Years	89.9	88.3	87.5	175.8

A total of 929 patients have been exposed to any dose of ixekizumab in the All axSpA Analysis Set (total exposure of 1336.2 patient-years). This includes 323 patients (total exposure of 542.7 patient-years) who were treated for at least 1 year with ixekizumab 80 mg Q4W (**Table 43**).

Table 43: Exposure to Ixekizumab by Integrated Analysis Set, All axSpA Analysis Set, All Treatment Periods

Analysis Set	**All axSpA Analysis Set**
Studies Included	**RHBV, RHBW, RHBX, RHBY**
Treatment Group	**Pooled axSpA IXE (N = 929)**
Days of Exposure, n (%)	
>0	929 (100.0)
≥7	929 (100.0)
≥14	929 (100.0)
≥30	924 (99.5)
≥60	904 (97.3)
≥90	890 (95.8)
≥120	879 (94.6)
≥183	842 (90.6)
≥365	738 (79.4)
≥548	409 (44.0)
≥730	193 (20.8)

≥1095	0
Total Patient-Years	1336.2

Patient Disposition

Placebo-Controlled axSpA Integrated Analysis Set

Of the 868 patients in the safety population of the Placebo-Controlled axSpA Integrated Analysis Set During Weeks 0 to 16, 35 (6.1%) ixekizumab-treated patients and 18 (6.1%) placebo-treated patients discontinued study drug. The most common reasons for discontinuation were subject decision and AEs.

Demographic and Other Characteristics of Study Population

The patients were predominantly male (total IXE, 69.2%, placebo, 68.4%), White (total IXE, 76.1%; placebo, 72.4%), and human leucocyte antigen B27 (HLA-B27)-positive (total IXE, 81.3%; placebo, 81.5%). Between the Total Ixekizumab (total IXE) and placebo groups, baseline characteristics were similar with respect to mean age at baseline (total IXE, 42.7 years; placebo, 43.1 years), age of onset (total IXE, 28.2 years; placebo, 28 years) duration of axSpA symptoms total IXE,(14.84 years; placebo, 15.45 years), and mean body weight. At baseline, percentage of nonsteroidal anti-inflammatory drug (NSAID) (including cyclooxygenase-2 [COX-2] inhibitors), conventional disease-modifying antirheumatic drug (cDMARDs; methotrexate, sulfasalazine, or hydroxychloroquine), oral corticosteroid, and analgesic (systemic opioids and/or short-acting analgesics with no anti-inflammatory effect) use was similar between the 2 groups:

Use of NSAIDs (total IXE, 84.5%; placebo, 87.4%), cDMARDs (total IXE, 34.5%; placebo, 33.7%), conventional oral corticosteroids (total IXE, 12.0%; placebo, 11.6%) and analgesics (total IXE, 23.9%; placebo, 22.4%) was similar between the two groups.

Prespecified medical history of interest included colitis ulcerative (total IXE, 1.6%; placebo, 1.4%), Crohn's disease (total IXE 0.2% placebo 0.7%), Iridocyclitis (total IXE 18.6%; placebo, 18.0%) and Psoriasis (total IXE 8.9%; placebo 9.5%).

Historical illnesses of interest included colitis ulcerative (total IXE, 0.7%; placebo, 0%), Crohn's disease: (total IXE, 0.2%; placebo, 0.3%), Iridocyclitis (total IXE, 16.7%; placebo, 16.0%) and Psoriasis (total IXE, 0.9%; placebo, 1.0%).

Pre-existing conditions and AEs occurring prior to the first dose of treatment included Colitis ulcerative (total IXE, 0.9%; placebo, 1.4%), Crohn's disease(total IXE, 0.2%; placebo, 0.7%), Iridocyclitis (total IXE, 1.9%; placebo, 2.0%) and Psoriasis (total IXE, 8.5%; placebo, 9.5).

Adverse events

Overview of Adverse Events in Individual Studies

The tables below (**00**) show the AEs reported during the Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16) of the r-axSpA studies (RHBV and RHBW) and the nr-axSpA study (RHBX) in side-by-side displays.

The safety findings from the axSpA clinical programme were considered by the applicant consistent with respect to TEAEs, SAEs, AE of special interests with the known safety profile of the ixekizumab clinical programme in Ps and PsA.

Within the axSpA programme, the safety profile was considered consistent between the individual studies in r-axSpA and nr-axSpA with the exception of more frequent reports of Injection Site Reactions (HLT) in the nr-axSpA study when comparing by specific ixekizumab regimens as well as by total IXE group.

However, no difference was noted in the severity or type of Injection Site Reactions (HLT) in the nr-axSpA study relative to the r-axSpA studies nor relative to the ixekizumab clinical programme (that is, Ps, PsA, and axSpA). Higher frequencies of TEAEs, SAEs, and treatment discontinuation due to AEs were, according to the applicant, noted in the TNFi-experienced patients in the r-axSpA Study RHBW. The prior use of anti-TNF-treatment were considered to have potentially contributed to this. The frequencies for the total IXE group in the nr-axSpA study (18.7% for Weeks 0 to 16) were considered within the range of Injection Site Reactions reported across the entire ixekizumab clinical programme although they were higher than the frequency reported for the total IXE group in the r-axSpA studies (8.5% [Study RHBV] and 11.8% [Study RHBW] for Weeks 0 to 16). In particular, the percentage of patients who reported Injection Site Reaction TEAEs in the ixekizumab 80 mg Q4W group (15.6%) and ixekizumab 80 mg Q2W group (21.6%) at Weeks 0 to 16 in the nr-axSpA study was higher compared with the corresponding groups in the r-axSpA studies (Q4W: 3.7% Q2W: 13.3%% [RHBV]; Q4W: 7.9%; Q2W: 16.3% [RHBW]).

The summary of adverse events for the All axSpA Ixekizumab Exposures Integrated Analysis Set updated with available since the time of database lock for Studies RHBW and RHBX data was provided upon request from CHMP (**Table 44**). The safety profile remained consistent with safety profile of ixekizumab axSpA Safety Population presented in the original application.

Table 44: Individual Studies: Overview of Adverse Events, Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16), Safety Population, Studies RHBV, RHBW, and RHBX

	Study I1F-MC-RHBV (r-axSpA)					Study I1F-MC-RHBW (r-axSpA)				Study I1F-MC-RHBX (nr-axSpA)			
Treatment Group	PBO N = 86	ADA Q2W N = 90	IXE Q4W N = 81	IXE Q2W N = 83	Total IXE N = 164	PBO N = 104	IXE Q4W N = 114	IXE Q2W N = 98	Total IXE N = 212	PBO N = 104	IXE Q4W N = 96	IXE Q2W N = 102	Total IXE N = 198
Category, n (%)													
Patients with ≥1 TEAE	34 (39.5)	44 (48.9)	37 (45.7)	38 (45.8)	75 (45.7)	52 (50.0)	73 (64.0)	60 (61.2)	133 (62.7)	52 (50.0)	52 (54.2)	65 (63.7)	117 (59.1)
Mild	22 (25.6)	28 (31.1)	24 (29.6)	30 (36.1)	54 (32.9)	19 (18.3)	34 (29.8)	23 (23.5)	57 (26.9)	36 (34.6)	30 (31.3)	44 (43.1)	74 (37.4)
Moderate	11 (12.8)	14 (15.6)	13 (16.0)	6 (7.2)	19 (11.6)	24 (23.1)	36 (31.6)	33 (33.7)	69 (32.5)	12 (11.5)	22 (22.9)	17 (16.7)	39 (19.7)
Severe	1 (1.2)	2 (2.2)	0	2 (2.4)	2 (1.2)	9 (8.7)	3 (2.6)	4 (4.1)	7 (3.3)	4 (3.8)	0	4 (3.9)	4 (2.0)
Death	0	0	0	0	0	0	0	1 (1.0)	1 (0.5)	0	0	0	0
Patient with ≥1 SAE	0	3 (3.3)	1 (1.2)	1 (1.2)	2 (1.2)	5 (4.8)	4 (3.5)	3 (3.1)	7 (3.3)	1 (1.0)	0	1 (1.0)	1 (0.5)
Discontinuation due to AE	0	1 (1.1)	0	3 (3.6)	3 (1.8)	2 (1.9)	10 (8.8)	3 (3.1)	13 (6.1)	2 (1.9)	0	1 (1.0)	1 (0.5)

Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; AE = adverse event; CSR = clinical study report; IXE = ixekizumab; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; nr-axSpA = non-radiographic axial spondyloarthritis; PBO = placebo; r-axSpA = radiographic axial spondyloarthritis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 45: Individual Studies: TEAEs Occurring in ≥2% of Patients in the Total Ixekizumab Group of Either Study, MedDRA Preferred Terms, Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16), Safety Population, Studies RHBV, RHBW, and RHBX

	Study I1F-MC-RHBV (r-axSpA)					Study I1F-MC-RHBW (r-axSpA)				Study I1F-MC-RHBX (nr-axSpA)			
Treatment Group	PBO N = 86	ADA Q2W N = 90	IXE Q4W N = 81	IXE Q2W N = 83	Total IXE N = 164	PBO N = 104	IXE Q4W N = 114	IXE Q2W N = 98	Total IXE N = 212	PBO N = 104	IXE Q4W N = 96	IXE Q2W N = 102	Total IXE N = 198
MedDRA Preferred Term, n (%)													
Nasopharyngitis	6 (7.0)	6 (6.7)	6 (7.4)	5 (6.0)	11 (6.7)	2 (1.9)	5 (4.4)	4 (4.1)	9 (4.2)	7 (6.7)	13 (13.5)	8 (7.8)	21 (10.6)
Upper respiratory tract infection	4 (4.7)	2 (2.2)	7 (8.6)	4 (4.8)	11 (6.7)	3 (2.9)	9 (7.9)	4 (4.1)	13 (6.1)	2 (1.9)	3 (3.1)	4 (3.9)	7 (3.5)
Injection site reaction	2 (2.3)	3 (3.3)	0	7 (8.4)	7 (4.3)	1 (1.0)	3 (2.6)	8 (8.2)	11 (5.2)	4 (3.8)	10 (10.4)	13 (12.7)	23 (11.6)
Injection site erythema	0	1 (1.1)	2 (2.5)	2 (2.4)	4 (2.4)	1 (1.0)	1 (0.9)	2 (2.0)	3 (1.4)	1 (1.0)	3 (3.1)	4 (3.9)	7 (3.5)
Rhinorrhoea	1 (1.2)	1 (1.1)	1 (1.2)	3 (3.6)	4 (2.4)	0	0	0	0	0	1 (1.0)	0	1 (0.5)
Diarrhoea	2 (2.3)	4 (4.4)	0	2 (2.4)	2 (1.2)	0	6 (5.3)	4 (4.1)	10 (4.7)	2 (1.9)	2 (2.1)	0	2 (1.0)
Arthralgia	0	0	2 (2.5)	0	2 (1.2)	4 (3.8)	7 (6.1)	3 (3.1)	10 (4.7)	0	1 (1.0)	1 (1.0)	2 (1.0)
Headache	0	3 (3.3)	0	1 (1.2)	1 (0.6)	1 (1.0)	3 (2.6)	3 (3.1)	6 (2.8)	2 (1.9)	4 (4.2)	4 (3.9)	8 (4.0)
Injection site pain	2 (2.3)	3 (3.3)	0	1 (1.2)	1 (0.6)	2 (1.9)	4 (3.5)	4 (4.1)	8 (3.8)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)
Iridocyclitis	0	0	1 (1.2)	0	1 (0.6)	0	2 (1.8)	3 (3.1)	5 (2.4)	2 (1.9)	1 (1.0)	1 (1.0)	2 (1.0)
Pharyngitis	2 (2.3)	2 (2.2)	2 (2.5)	2 (2.4)	4 (2.4)	0	2 (1.8)	3 (3.1)	5 (2.4)	2 (1.9)	2 (2.1)	1 (1.0)	3 (1.5)
Musculoskeletal pain	0	1 (1.1)	0	0	0	2 (1.9)	4 (3.5)	1 (1.0)	5 (2.4)	0	0	1 (1.0)	1 (0.5)
Oropharyngeal pain	0	0	0	0	0	0	5 (4.4)	0	5 (2.4)	0	0	2 (2.0)	2 (1.0)
Hypertension	1 (1.2)	0	1 (1.2)	1 (1.2)	2 (1.2)	4 (3.8)	1 (0.9)	2 (2.0)	3 (1.4)	3 (2.9)	4 (4.2)	3 (2.9)	7 (3.5)
Blood creatine phosphokinase increased	0	0	0	0	0	2 (1.9)	0	2 (2.0)	2 (0.9)	0	3 (3.1)	3 (2.9)	6 (3.0)
Oral herpes	0	2 (2.2)	0	1 (1.2)	1 (0.6)	1 (1.0)	0	1 (1.0)	1 (0.5)	3 (2.9)	4 (4.2)	0	4 (2.0)

Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; CSR = clinical study report; IXE = ixekizumab; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients in the specified category; nr-axSpA = non-radiographic axial spondyloarthritis; PBO = placebo; r-axSpA = radiographic axial spondyloarthritis; TEAE = treatment-emergent

adverse event. Note: In the individual studies, the Total IXE was not compared with PBO. Data cutoff dates: Study RHBX 01 Apr 2019, Study RHBV 06 Dec 2018, Study RHBW 28 Feb 2019.

Table 46: Individual Studies: Overview of Adverse Events of Special Interest, Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16), Safety Population, Studies RHBV, RHBW, and RHBX

	Study I1F-MC-RHBV (r-axSpA)					Study I1F-MC-RHBW (r-axSpA)				Study I1F-MC-RHBX (nr-axSpA)			
Treatment Group	PBO N = 86	ADA Q2W N = 90	IXE Q4W N = 81	IXE Q2W N = 83	Total IXE N = 164	PBO N = 104	IXE Q4W N = 114	IXE Q2W N = 98	Total IXE N = 212	PBO N = 104	IXE Q4W N = 96	IXE Q2W N = 102	Total IXE N = 198
AESI, n (%)													
Infections	13 (15.1)	19 (21.1)	17 (21.0)	17 (20.5)	34 (20.7)	10 (9.6)	34 (29.8)	23 (23.5)	57 (26.9)	23 (22.1)	26 (27.1)	26 (25.5)	52 (26.3)
Cytopaenias[a]	1 (1.2)	2 (2.2)	1 (1.2)	0	1 (0.6)	0	0	2 (2.0)	2 (0.9)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)
Allergic reactions/ hypersensitivities	1 (1.2)	4 (4.4)	3 (3.7)	3 (3.6)	6 (3.7)	1 (1.0)	3 (2.6)	6 (6.1)	9 (4.2)	3 (2.9)	1 (1.0)	3 (2.9)	4 (2.0)
Potential anaphylaxis	0	0	0	0	0	0	0	0	0	1 (1.0)	0	0	0
Non-anaphylaxis	1 (1.2)	4 (4.4)	3 (3.7)	3 (3.6)	6 (3.7)	1 (1.0)	3 (2.6)	6 (6.1)	9 (4.2)	2 (1.9)	1 (1.0)	3 (2.9)	4 (2.0)
Injection Site Reactions (HLT)	4 (4.7)	7 (7.8)	3 (3.7)	11 (13.3)	14 (8.5)	6 (5.8)	9 (7.9)	16 (16.3)	25 (11.8)	7 (6.7)	15 (15.6)	22 (21.6)	37 (18.7)
Cerebro-cardiovascular events	0	0	1 (1.2)	0	1 (0.6)	1 (1.0)	0	2 (2.0)	2 (0.9)	0	0	0	0
MACE	0	0	0	0	0	0	0	0	0	0	0	0	0
Malignancies	0	0	0	0	0	0	1 (0.9)	0	1 (0.5)	0	0	0	0
Hepatic events (narrow terms)	1 (1.2)	2 (2.2)	2 (2.5)	2 (2.4)	4 (2.4)	2 (1.9)	5 (4.4)	1 (1.0)	6 (2.8)	5 (4.8)	1 (1.0)	3 (2.9)	4 (2.0)
Depression	0	1 (1.1)	0	0	0	5 (4.8)	0	2 (2.0)	2 (0.9)	0	0	3 (2.9)	3 (1.5)
Suicide	0	0	0	0	0	0	0	1 (1.0)	1 (0.5)	0	0	0	0
IBD	0	0	0	1 (1.2)	1 (0.6)	1 (1.0)	3 (2.6)	0	3 (1.4)	1 (1.0)	1 (1.0)	0	1 (0.5)
Adjudicated	0	0	0	1 (1.2)	1 (0.6)	1 (1.0)	3 (2.6)	0	3 (1.4)	0	1[e](1.0)	0	1 (0.5)
Specific IBD (narrow terms)[b]	0	0	0	1 (1.2)	1 (0.6)	1 (1.0)	2 (1.8)	0	2 (0.9)	1 (1.0)[d]	0[e]	0	0

Non-specific IBD (broad terms)[c]	0	0	0	0	0	1 (1.0)	1 (0.9)	0	1 (0.5)	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: ADA Q2W = adalimumab 40 mg every 2 weeks; AESI = adverse event of special interest; CSR = clinical study report; HLT = High Level Term; IBD = inflammatory bowel disease; IXE = ixekizumab; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; MACE = major adverse cerebro-cardiovascular event; N = number of patients in the analysis population; n = number of patients in the specified category; nr-axSpA = non-radiographic axial spondyloarthritis; PBO = placebo; r-axSpA = radiographic axial spondyloarthritis.

a Cytopaenias include Neutropaenia (Studies RHBV, RHBW, and RHBX), Leucopenia (Studies RHBW and RHBX), and Monocyte count decreased (Study RHBX).

b The following IBD-specific terms (narrow terms) were reported: Colitis ulcerative, Crohn's disease, Inflammatory bowel disease, and Proctitis ulcerative.

c The following IBD-non-specific term (broad terms) was reported: Colitis.

d Adjudicated as insufficient information.

e One case of diarrhoea was adjudicated as definitive Crohn's disease.

Table 47: TEAEs Occurring in ≥1% of Patients in the Total Ixekizumab Group MedDRA Preferred Term by Decreasing Frequency, Placebo-Controlled axSpA Integrated Analysis Set, Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16)

Treatment Group	PBO N = 294	IXE Q4W N = 291	IXE Q2W N = 283	Total IXE N = 574
Category, n (%)				
Patients with ≥1 TEAE	138 (46.9)	162 (55.7)[a]	163 (57.6)[a]	325 (56.6)[a]
Injection site reaction[b]	7 (2.4)	13 (4.5)	28 (9.9)[a,c]	41 (7.1)[a]
Nasopharyngitis[b]	15 (5.1)	24 (8.2)	17 (6.0)	41 (7.1)
Upper respiratory tract infection[b]	9 (3.1)	19 (6.5)	12 (4.2)	31 (5.4)
Headache	3 (1.0)	7 (2.4)	8 (2.8)	15 (2.6)
Injection site erythema[b]	2 (0.7)	6 (2.1)	8 (2.8)[a]	14 (2.4)
Diarrhoea	4 (1.4)	8 (2.7)	6 (2.1)	14 (2.4)
Arthralgia	4 (1.4)	10 (3.4)	4 (1.4)	14 (2.4)
Hypertension	8 (2.7)	6 (2.1)	6 (2.1)	12 (2.1)
Pharyngitis	4 (1.4)	6 (2.1)	6 (2.1)	12 (2.1)
Injection site pain[b]	5 (1.7)	5 (1.7)	6 (2.1)	11 (1.9)
Back pain	5 (1.7)	3 (1.0)	5 (1.8)	8 (1.4)
Blood creatine phosphokinase increased	2 (0.7)	3 (1.0)	5 (1.8)	8 (1.4)
Pruritus	0	3 (1.0)	5 (1.8)[a]	8 (1.4)[a]
Iridocyclitis	2 (0.7)	4 (1.4)	4 (1.4)	8 (1.4)
Bronchitis	3 (1.0)	4 (1.4)	3 (1.1)	7 (1.2)
Oropharyngeal pain[b]	0	5 (1.7)[a]	2 (0.7)	7 (1.2)
Dry eye	1 (0.3)	1 (0.3)	5 (1.8)	6 (1.0)
Diarrhoea infectious	0	1 (0.3)	5 (1.8)[a]	6 (1.0)
Oral herpes	4 (1.4)	4 (1.4)	2 (0.7)	6 (1.0)
Musculoskeletal pain	2 (0.7)	4 (1.4)	2 (0.7)	6 (1.0)

Abbreviations: ADR = adverse drug reaction; IXE = ixekizumab; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; SCS = Summary of Clinical Safety; TEAE = treatment-emergent adverse event.

a p<.05 vs. PBO.

b Upper respiratory tract infection, Nasopharyngitis, Injection site reaction, Injection site pain, Injection site erythema, and Oropharyngeal pain have been previously identified as ADRs for ixekizumab.

c p<.05 vs. IXE Q4W.

Table 48: Summary of Adverse Events, Percentage and Patient-Time-Adjusted Incidence Rate axSpA Safety Population All AxSpA Ixekizumab Exposures Integrated Analysis Set – All Treatment Period

	Pooled AxSpA IXE			
	Frequency (N=932)		Incidence Rate Total Patient-Years = 1571	
Category	n (%)	95% CI	IR	95% CI
Treatment-Emergent Adverse Event (TEAE)	764 (82.0%)	(79.5, 84.4)	48.6	(45.3, 52.2)
TEAE by Severity*a				
Mild	304 (32.6%)	(29.6, 35.6)	19.4	(17.3, 21.7)
Moderate	372 (39.9%)	(36.8, 43.1)	23.7	(21.4, 26.2)
Severe	87 (9.3%)	(7.5, 11.2)	5.5	(4.5, 6.8)
Missing	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Death	3 (0.3%)	(0.0, 0.7)	0.2	(0.1, 0.6)
Serious Adverse Event*b	82 (8.8%)	(7.0, 10.6)	5.2	(4.2, 6.5)
Treatment-Emergent Adverse Event Possibly Related to Study Drug	365 (39.2%)	(36.0, 42.3)	23.2	(21.0, 25.7)
Discontinuation from Study Drug due to Adverse Event (Including Death)	56 (6.0%)	(4.5, 7.5)	3.6	(2.7, 4.6)

Abbreviations: IXE = Ixekizumab; IR = incidence rate per 100 patient-years; N = number of patients in the analysis population; n = number of patients with at least one treatment-emergent adverse event (TEAE) in the specified category; TEAE = treatment-emergent adverse event; Total Patient-Years = total time patients were in the treatment period; MACE = major adverse cerebro-cardiovascular events; CI = confidence interval.

The AE profile for the nr-axSpA study up to Week 52 and prior to biologic rescue is considered to remain consistent with that of Weeks 0 to 16.

Up to Week 52 and prior to biologic rescue, Injection Site Reactions were reported more in the ixekizumab-treated patients than in placebo-treated patients. According to the applicant, there were no clinically meaningful findings between the treatment groups with regard to cytopaenia, cerebro-cardiovascular events, including MACE and malignancies, or interstitial lung disease (ILD). The applicant concluded that with the exception of more frequent reports of Injection Site Reactions, the results from the r-axSpA and nr-axSpA studies were consistent; these findings are also consistent with the known safety profile of the ixekizumab clinical programme.

Serious adverse event/deaths/other significant events

In the Placebo-controlled axSpA integrated analysis set, 10 (1.7%) ixekizumab-treated patients and 6 (2.0%) placebo-treated patients had at least 1 SAE. The reported events were:

- Ixekizumab 80mg Q2W (n=5): Crohn´s disease, dyspepsia, Erythema multiforme, Gastroenteritis, Depression, Atrial tachycardia, Blood creatine phosphokinase increased, Completed suicide, Major depression.
- Ixekizumab 80mg Q4W (n=5): Urinary tract infection, Pharyngitis, Crohn´s disease, Peritonitis, Fracture pain
- Placebo (n=6): Colitis ulcerative, Femur fracture, Inguinal hernia, Vasculitis, Arthritis, Anaphylactoid reaction

In the All axSpA Analysis Set, 74 (8.0%) patients had at least 1 SAE (**Table 49**). The Preferred Term of the SAEs reported for >2 patients were as follows:

- Osteoarthritis: n = 6 (0.6%)
- Crohn's disease: n = 3 (0.3%)
- Colitis ulcerative: n = 3 (0.3%).

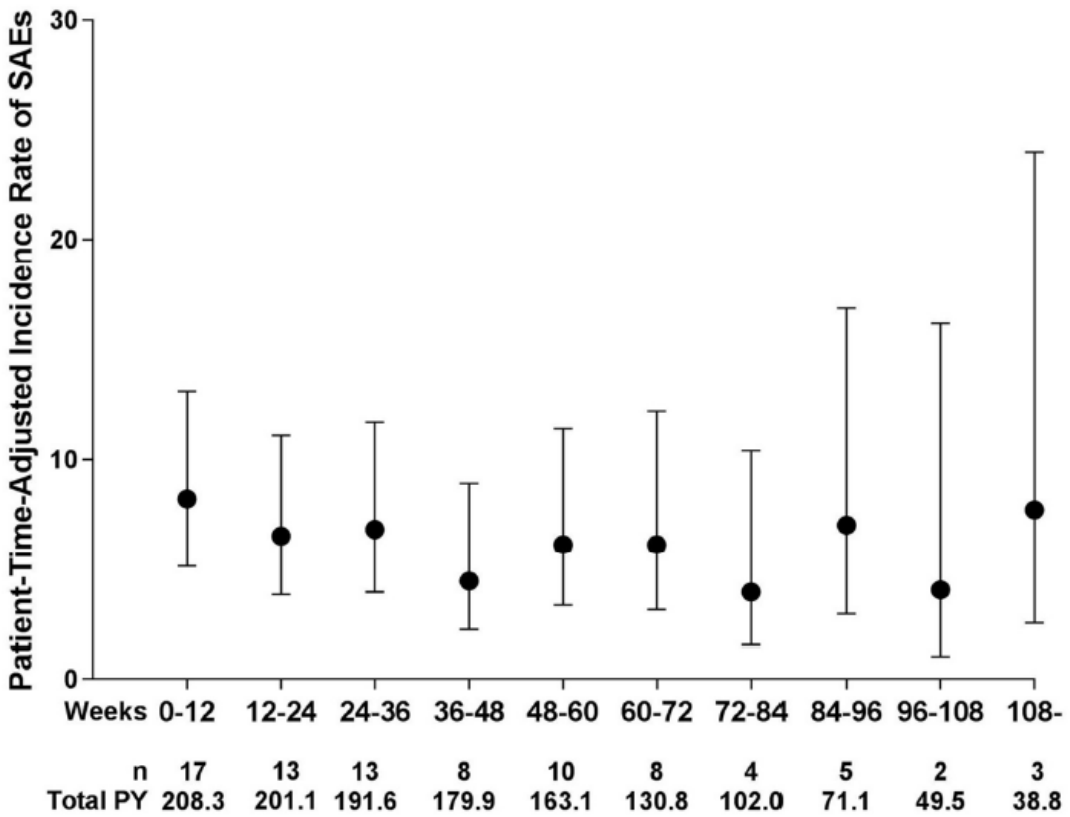
Table 49: Serious adverse events, MedDRA Preferred Term by Decreasing Frequency Percentage and Patient-Time-Adjusted Incidence Rate axSpA Safety Population All axSpA Ixekizumab Exposures Integrated Analysis Set - All Treatment Period

	Pooled AxSpA IXE			
	Frequency (N=929)		Incidence Rate Total Patient-Years = 1336.2	
Preferred term	n (%)	95% CI	IR	95% CI
Patients with >=1 SAE	74 (8.0%)	(6.2, 9.7)	5.5	(4.4, 7.0)
Osteoarthritis	6 (0.6%)	(0.1, 1.2)	0.4	(0.2, 1.0)
Ovarian cancer	1 (0.4%)	(0.0, 1.1)	0.3	(0.0, 1.9)
Colitis ulcerative	3 (0.3%)	(0.0, 0.7)	0.2	(0.1, 0.7)
Crohn's disease	3 (0.3%)	(0.0, 0.7)	0.2	(0.1, 0.7)
Blood creatine phosphokinase increased	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Bradycardia	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Cellulitis	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Depression	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)

Gastroenteritis	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Hyperkalaemia	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Inguinal hernia	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Sinusitis	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Urinary tract infection	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Orchitis	1 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.7)
Abdominal pain	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Acute kidney injury	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Acute myocardial infarction	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)

Abbreviations: IXE = Ixekizumab; N = number of patients in the analysis population; SAE = serious adverse event; n = number of patients with at least one adverse event at the specified category; CI = confidence interval; IR = incidence rate per 100 patient years; Total Patient-Years = total time at risk in years.

Figure 46. Incidence rate of serious adverse events by 12-week intervals with 95% confidence intervals, All axSpA Ixekizumab Exposures Integrated Analysis Set - All Treatment Period.



Abbreviations: axSpA = axial spondyloarthritis; n = number of patients with ≥1 event; PY = patient-years; SAEs = serious adverse events.
Note: Incidence rate is for patients with ≥1 event in the category per 100 PY.

Two deaths were reported as of the data cut off of 01 Apr 2019.

One death was reported in Study RHBW during the Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16). The patient, a 36-year old male, committed suicide 54 days after the first dose of

ixekizumab and 26 days after the last dose of ixekizumab (80 mg at Weeks 0, 2, and 4). The patient was intoxicated and committed suicide via gunshot. The patient was diagnosed by his primary care physician with mild depression approximately 11 months before starting study drug and had been medicated with duloxetine since the diagnosis. The patient had no personal history of substance abuse, aggressive behaviour toward self or others, victim of abuse or neglect, preceding psychomotor restlessness, or major life changes, nor did the patient have a family history of mental illness. No signs or symptoms of suicidal ideation, suicidal thoughts, or suicidal behaviors were identified during the study. The blinded investigator assessed the event as not related to study drug.

The second death was reported in a 30-year-old, male patient who participated in Study RHBY (after completing Study RHBX) about 9 months after starting study treatment. It was believed that the patient was murdered because of drug trafficking issues. This information was obtained by third parties (unable to confirm). The site had no documentary evidence of the death of the patient or the circumstances in which it occurred. The investigator stated that for security reasons, they would not try to obtain, by any means, more information about what happened in this case. The investigator considered the event of death (believed murdered due to drug trafficking issues) unrelated to study drugs or to protocol procedure.

One further death was reporter after data cut-off date for this submission in a 77-year-old, white, male patient who completed Study RHBW and enrolled in Study RHBY. The patient was hospitalised with a diagnosis of sepsis, which was considered life-threatening, approximately 1 year and 1 month (21 May 2019) after beginning open-label study drug in Period 1 of Study RHBY. Head, thorax, and abdominal and pelvic scans were negative; abdominal x-ray revealed dilation of the gastrointestinal loops, possibly the small intestine, testifying to picture of possible subocclusion. Treatment included unspecified intravenous antibiotics in the intensive care unit for supportive care (as family refused respiratory support). Two days later, the patient died due to the SAE of sepsis (*Streptococcus* group C on haemocultures) based on probable pneumonia with multiorgan failure (acute renal failure, increase troponin, and respiratory distress). No change was made with the open-label study drug in response to the event prior to death. An autopsy was not performed. In the opinion of the investigator, the sepsis was not related to open-label study drug in Period 1 of Study RHBY or protocol procedures; however the sepsis was considered to be related to open-label study drug in Period 2 of Study RHBY because biologic drugs could increase the risk of infection and the patient had symptoms following injection of study drugs.

Adverse Events of Special Interest

Infections

Placebo-Controlled axSpA Integrated Analysis Set

TEAEs: A higher percentage of ixekizumab-treated patients (n = 143 [24.9%]) reported at least 1 infection-related TEAE compared with placebo-treated patients (n = 46 [15.6%]). Both ixekizumab treatment groups had a higher percentage of patients with these TEAEs compared with the placebo group, and according to the applicant, no meaningful difference was observed between the ixekizumab treatment groups in the frequency of infection-related TEAEs.

- 66 patients (23.3%), ixekizumab 80 mg Q2W;
- 77 patients (26.5%), ixekizumab 80 mg Q4W;
- 46 patients (15.6%), placebo.

Most of the infections were mild or moderate in severity; there was 1 patient in each of the ixekizumab treatment groups who reported at least 1 severe infection-related TEAE. Nasopharyngitis and Upper respiratory tract infection were the most often reported infections in the total IXE treatment group. No

cases of active TB were reported. There were 2 (0.7%) patients in the ixekizumab 80 mg Q4W with Herpes zoster infection (1 mild and 1 moderate) and 1 (0.3%) patient in the placebo group with mild Herpes zoster; there were no ophthalmic or disseminated cases identified. There was 1 (0.4%) patient in the ixekizumab 80 mg Q2W group with mild Oesophageal candidiasis.

SAEs: Infection-related SAEs were reported for 4 (0.7%) ixekizumab-treated patients (Q2W, Gastroenteritis; Q4W, Peritonitis, Pharyngitis, and Urinary tract infection).

Discontinuations due to AE: Three (0.5%) ixekizumab-treated patients discontinued study treatment due to an infection-related AE (Q2W, Diarrhoea infectious; Q4W, Diverticulitis and Peritonitis

Candida infections: Mild *Candida* infections were reported by 3 (0.5%) ixekizumab-treated patients (Q4W, Vulvovaginal candidiasis; Q2W, Genital candidiasis and Oesophageal candidiasis) and 2 (0.7%) placebo-treated patients (Vulvovaginal candidiasis and Oral candidiasis). There were no reports of deep organ or bloodstream infections

Opportunistic infections: Opportunistic infections (narrow terms) were reported by 3 (0.5%) ixekizumab-treated patients (Q2W, Oesophageal candidiasis; Q4W, 2 patients with Herpes zoster). In the placebo group, 1 patient reported an OI of Herpes zoster.

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: In the All axSpA Analysis Set, 478 (51.5%) patients had an infection-related TEAE. The majority of these patients had mild or moderate infections; 18 (1.9%) patients had at least 1 severe infection (3 patients with Gastroenteritis; 2 patients with Pneumonia; and 1 patient for each of the following: Bronchitis, Pharyngitis, Tonsillitis, Respiratory tract infection, Tinea pedis, Subcutaneous abscess, Pyelonephritis, Pyelonephritis acute, Orchitis, *Clostridium difficile* colitis, Erysipelas, Pericoronitis, and Peritonitis). The most frequent infection Preferred Terms were Nasopharyngitis, Upper respiratory tract infection, and Pharyngitis. No cases of active TB were reported. There were 11 (1.2%) patients with Herpes zoster infection (7 mild; 4 moderate) and 1 patient with moderate Ophthalmic herpes simplex

SAEs: Infection-related SAEs were reported for 17 (1.8%) patients (Table 45.). Cellulitis, Gastroenteritis, Sinusitis and Urinary tract infection were reported by 2 patients; the other SAEs were reported by 1 patient.

Discontinuations due to AE: Ten (1.1%) patients discontinued study drug due to an infection-related AE, including:

- Cellulitis
- *Clostridium difficile* infection
- Conjunctivitis
- Diarrhoea infectious
- Diverticulitis
- Eczema infected
- Oesophageal candidiasis
- Ophthalmic herpes simplex
- Peritonitis, and
- Rash pustular.

Candida infections: *Candida* infections of mild or moderate severity were reported in 22 (2.4%) patients; the cases which were reported as OIs are described below. There were no reports of deep organ or bloodstream infections.

Opportunistic infections: There were 15 (1.6%) patients who reported an OI

Of the 15 patients with OIs (narrow terms):

4 patients reported Candidiasis:

- 3 patients reported Oesophageal candidiasis (2 mild, 1 moderate) and 1 patient reported moderate Fungal oesophagitis, and

11 patients reported Herpes zoster infection; all events were mild or moderate in severity. Of these patients, 1 patient (RHBW-454-30365) reported multidermatomal involvement (T11-T12 dermatome).

There were 15 (45.5%) patients with treatment-emergent Neutropaenia Grade 2 or worse who reported an infection; none of these cases were an SAE.

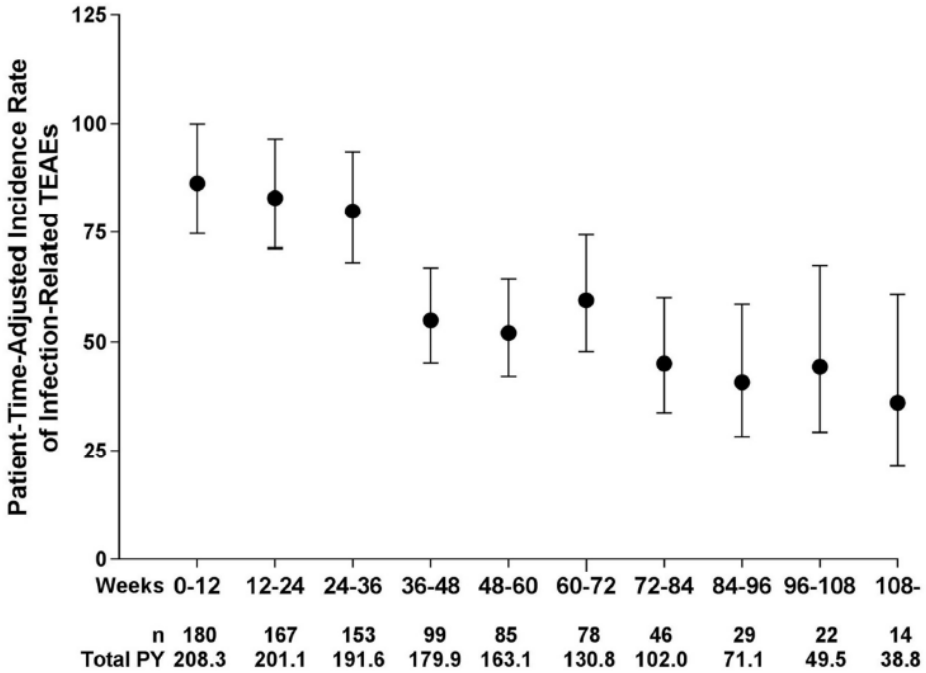
There was no trend for an increase in the incidence rate of infection-related TEAEs over longer durations of exposure to ixekizumab (Figure 47.).

Table 50: Serious Adverse Events, MedDRA Preferred Term by Decreasing Frequency within System Organ Class, Percentage and Patient-Time-Adjusted Incidence Rate axSpA Safety Population All axSpA Ixekizumab Exposures Integrated Analysis Set - All Treatment Period

	Pooled AxSpA IXE			
System organ class Preferred term	Frequency (N=929)	95% CI	IR	95% CI
Patients with >=1 SAE	74 (8.0%)	(6.2, 9.7)	5.5	(4.4, 7.0)
Infections and infestations	17 (1.8%)	(1.0, 2.7)	1.3	(0.8, 2.0)
Cellulitis	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Gastroenteritis	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Sinusitis	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Urinary tract infection	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Orchitis	1 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.7)
Clostridium difficile colitis	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Erysipelas	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Peritonitis	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Pharyngitis	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Pneumonia	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Pneumonia haemophilus	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Respiratory tract infection	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Tonsillitis	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)

Abbreviations: IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients with at least one serious adverse event at the specified category; SAE = serious adverse event; CI = confidence interval; IR = incidence rate per 100 patientyears; PY = patient years; Total Patient-Years = total time patients were in the treatment period.

Figure 47. Incidence rate of infection-related treatment-emergent adverse events by 12-week intervals with 95% confidence intervals, All axSpA Ixekizumab Exposures Integrated Analysis Set - All Treatment Period.



Abbreviations: axSpA = axial spondyloarthritis; n = number of patients with ≥1 event; PY = patient-years; TEAEs = treatment emergent adverse events.
Note: Incidence rate is for patients with ≥1 event in the category per 100 PY.

Cytopaenias

Placebo-Controlled axSpA Integrated Analysis Set

In the ixekizumab 80 mg Q2W group, 3 patients reported Neutropenia, and 1 of them also reported Leucopenia. In the ixekizumab 80 mg Q4W group, 2 patients in the ixekizumab 80 mg Q4W group reported Neutropaenia. In the placebo group, 1 patient reported Neutropaenia and another patient reported Neutropaenia, Leucopenia, and Monocyte count decreased. All of the reported TEAEs were narrow terms. At the time neutropaenia was reported, there was no infection reported for any of these 7 patients.

No cytopaenia-related SAEs were reported and

No patients discontinued study drug due to a cytopaenia-related AE

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: In the All axSpA Analysis Set, 23 (2.5%) patients reported at least 1 cytopaenia-related TEAE within the Haematopoietic leucopenia SMQ. The most frequently reported TEAE was Neutropaenia, followed by Leucopenia.

No cytopaenia-related SAEs were reported.One (0.1%) patient discontinued study drug due to Neutropaenia

There was no trend for an increase in the rate of cytopaenia-related TEAEs over longer durations of exposure to ixekizumab.

Neutropaenia and Thrombocytopaenia are included as ADRs in the currently approved SmPC.

Allergic Reactions/Hypersensitivities

Placebo-Controlled axSpA Integrated Analysis Set

TEAEs: There were 19 (3.3%) ixekizumab-treated patients and 5 (1.7%) placebo-treated patients with at least 1 allergic reactions/hypersensitivity-related TEAE (immediate [anaphylaxis or nonanaphylaxis] or nonimmediate). All the reported allergic reactions/hypersensitivity TEAEs, except 1 case of anaphylaxis in the placebo group, were non-anaphylactic in nature

- 12 patients (4.2%), ixekizumab 80 mg Q2W;
- 7 patients (2.4%), ixekizumab 80 mg Q4W;
- 5 patients (1.7%), placebo.

Rash and eczema were the most reported allergic reactions/hypersensitivity Preferred Terms and were each reported by 4 (0.7%) ixekizumab-treated patients. The majority(22) of allergic reactions/hypersensitivity TEAEs were mild or moderate in severity.

Five (0.9%) ixekizumab-treated patients and 2 (0.7%) placebo-treated patients reported immediate allergic reactions/hypersensitivity events:

- 4 (1.4%) patients ixekizumab 80 mg Q2W;
- 1 (0.3%) patient, ixekizumab 80 mg Q4W;
- 2 (0.7%) patients, placebo.

Fourteen (2.4%) ixekizumab-treated patients and 3 (1.0%) placebo-treated patients reported nonimmediate allergic reactions/hypersensitivity events.

- 8 (2.8%) patients, ixekizumab 80 mg Q2W;
- 6 (2.1%) patients, ixekizumab 80 mg Q4W;
- 3 (1.0%) patients, placebo

SAEs: There was 1 (0.2%) ixekizumab-treated patient with a nonimmediate allergic reactions/hypersensitivity SAE (Q2W, Erythema multiforme) and 1 (0.3%) placebo-treated patient who reported an SAE of Anaphylactoid reaction

Discontinuations due to AE: There was 1 (0.2%) ixekizumab-treated patient who discontinued study drug due to a nonserious allergic reactions/hypersensitivity AE (Q2W, Rash generalised) and 1 (0.3%) placebo-treated patient who discontinued study drug due to a severe SAE (Anaphylactoid reaction)

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: In the All axSpA Analysis Set, 74 (8.0%) patients had an allergic reaction/hypersensitivity TEAE

The majority of allergic reaction/hypersensitivity TEAEs were mild or moderate in severity. There was 1 (0.1%) patient with a severe allergic reaction/hypersensitivity TEAE (Q2W, Erythema multiforme)

Eighteen (1.9%) patients reported immediate allergic reactions/hypersensitivity TEAE, while 59 (6.4%) patients reported nonimmediate allergic reactions/hypersensitivity TEAE.

SAEs: There was 1 (0.1%) patient with a nonimmediate allergic reactions/hypersensitivity SAE (Erythema multiforme)

Discontinuations due to AE: There were 4 (0.4%) patients who discontinued study drug due to an allergic reaction/hypersensitivity TEAE (Dermatitis allergic, Rash generalised, Rash pustular, and Rash)

Allergic Reaction/Hypersensitivity TEAEs by 12-Week Intervals: According to the applicant, there was no trend for an increase in the rate of allergic reactions/hypersensitivity TEAEs over longer durations of

exposure to ixekizumab, consistent with the known safety profile of ixekizumab.

Hypersensitivity is included in the Special Warnings and Precautions for Use section in the currently approved SmPC; no update to the label is proposed.

Injection Site Reactions

Placebo-Controlled axSpA Integrated Analysis Set

TEAEs: There was a higher percentage of ixekizumab-treated patients (n = 76 [13.2%]) with at least 1 Injection Site Reactions HLT compared with placebo-treated patients (n = 17 [5.8%]). The ixekizumab 80 mg Q2W group had a higher percentage of patients with these TEAEs compared with the ixekizumab 80 mg Q4W group and placebo group.

Injection site reaction, Injection site erythema, and Injection site pain were the most frequently reported Preferred Terms related to injection sites. Most patients reported Injection Site Reactions that were mild or moderate in severity. There were 2 patients with a severe Injection site reaction in the ixekizumab 80 mg Q2W group; no other patient had a severe TEAE under Injection Site Reactions HLT

A total of 213 events were reported by the 76 ixekizumab-treated patients who had Injection Site Reactions (HLT) (Q2W, 155 events, 49 patients; Q4W, 58 events, 27 patients) and a total of 58 events were reported by the 17 placebo-treated patients who had Injection Site Reactions

SAEs: No Injection Site Reactions were SAEs.

Discontinuations due to AE: Three patients in the ixekizumab 80 mg Q2W group (1.1%, Injection site reaction for all 3 patients) and 1 patient in the ixekizumab 80 mg Q4W group (0.3%, Injection site pain) discontinued study drug due to Injection Site Reactions.

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: In the All axSpA Analysis Set, 154 (16.6%) patients had at least 1 TE Injection Site Reaction (number of events = 175). Among these, 5.9% had 1 event, 4.8% had 2 or 3 events, and 5.8% had ≥4 events.

Injection site reaction and Injection site erythema Preferred Terms were the most frequently reported TEAEs related to injection sites. Most patients reported Injection Site Reactions that were mild or moderate in severity; 6 (0.6%) patients had a severe Injection site reaction

SAEs: No Injection Site Reactions were reported as SAEs.

Discontinuations due to AE: Seven (0.8%) patients discontinued study drug due to Injection Site Reactions.

Cerebro-Cardiovascular Events

Placebo-Controlled axSpA Integrated Analysis Set

TEAEs: There were 3 (0.5%) ixekizumab-treated patients (whereof to in the Q2W group), and 2 (0.7%) placebo-treated patients with at least 1 cerebro-cardiovascular-related TEAE.

In the ixekizumab 80 mg Q2W, 1 patient reported atrial fibrillation and another reported atrial tachycardia. In the ixekizumab 80 mg Q4W group, 1 patient reported a TEAE of aphasia, which was adjudicated as a Transient ischaemic attack. In the placebo group, 1 patient reported Stent placement which was adjudicated as an event.

SAE: One ixekizumab-treated patient reported an SAE (Q2W, Atrial tachycardia)

Discontinuations due to AE: No patients discontinued study drug due to a cerebro-cardiovascular event

No MACE was reported.

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: In the All axSpA Analysis Set, 14 (1.5%) patients reported a cerebro-cardiovascular TEAE. The TEAEs of 12 of these patients were adjudicated as an event as follows: myocardial infarction (2), transient ischaemic attack (1), atrial arrhythmia and ventricular arrhythmia (1), atrial arrhythmia (4), ventricular arrhythmia (3) and heart block.

SAEs: Cerebro-cardiovascular SAEs were reported for 6 (0.7%) patients. The events were myocardial infarction (2), atrial tachycardia, atrioventricular block complete, bradycardia and cerebral haemorrhage.

Discontinuations due to AE: No patients discontinued study drug due to a cerebro-cardiovascular event

Cerebro-Cardiovascular TEAEs and MACE by 12-Week Intervals: There was no trend for an increase in the rate of cerebro-cardiovascular TEAEs or MACE over longer durations of exposure to ixekizumab, consistent with the known safety profile of ixekizumab.

Malignancies

Placebo-Controlled axSpA Integrated Analysis Set

One (0.2%) ixekizumab-treated patient reported a malignancy-related TEAE. This patient, in the ixekizumab 80 mg Q4W treatment group, reported a TEAE of Acute promyelocytic leukaemia which led to study drug discontinuation and resulted in hospitalisation during the post treatment follow-up period (reported at that time as an SAE).

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: In the All axSpA Analysis Set, 6 (0.6%) patients reported a malignancy-related TEAE. The reported TEAEs were Ovarian cancer, Acute promyelocytic leukaemia, Anal cancer, Bladder cancer, Breast cancer, and Chronic lymphocytic leukaemia

SAEs: All the TEAEs were reported as SAEs;

Discontinuations due to AE: All 6 patients discontinued study drug due to malignancy-related AEs.

Malignancy-Related TEAEs by 12-Week Intervals: There was no trend for an increase in the rate of malignancy-related TEAEs over longer durations of exposure to ixekizumab, consistent with the known safety profile of ixekizumab.

Hepatic Events

Placebo-Controlled axSpA Integrated Analysis Set

TEAEs: There were 14 (2.4%) ixekizumab-treated patients (whereof 6 in the Q2W dosing group) and 8 (2.7%) placebo-treated patients with at least 1 hepatic-related TEAE.

The most commonly reported hepatic-related TEAEs were Aspartate aminotransferase increased and Alanine aminotransferase increased. One patient (RHBW-554-30035) in the ixekizumab 80 mg Q4W group had Alanine aminotransferase increased and Aspartate aminotransferase increased (both ≥5x upper limit of normal [ULN]).

SAEs: No hepatic-related SAEs were reported

Discontinuations due to AE: One placebo-treated patient discontinued study drug due to a hepatic-related AE (Alanine aminotransferase increased)

All axSpA Ixekizumab Exposures Integrated Analysis Set

TEAEs: 67 (7.2%) patients reported at least 1 hepatic-related TEAE; the most commonly reported hepatic-related TEAEs were Alanine aminotransferase increased and Aspartate aminotransferase increased

SAEs: No hepatic-related SAEs were reported

Discontinuations due to AE: One (0.1%) patient discontinued study drug due to a hepatic-related AE (Transaminases increased)

Hepatic-Related TEAEs by 12-Week Intervals: According to the applicant, there was no trend for an increase in the rate of hepatic-related TEAEs over longer durations of exposure to ixekizumab, consistent with the known safety profile of ixekizumab.

Depression and Suicide/Self-Injury

Placebo-Controlled axSpA Integrated Analysis Set

There were 5 (0.9%) ixekizumab-treated patients (all in the Q2W dosing group) and 5 (1.7%) placebo-treated patients who reported at least 1 depression-related or suicide/self-injury-related TEAE.

Deaths: One completed suicide was reported in the ixekizumab 80 mg Q2W group, as presented above.

SAEs: Three (1.1%) patients in the ixekizumab 80 mg Q2W group reported a depression-related or a suicide-related SAE (Depression, Completed suicide, and Major depression)

Discontinuations due to AE: One (0.4%) patient in the ixekizumab 80 mg Q2W group discontinued study treatment (Completed suicide)

All axSpA Ixekizumab Exposures Integrated Analysis Set

In the All axSpA Analysis Set, 13 (1.4%) patients reported a depression-related or a suicide-related TEAE Of these, 12 (1.3%) patients reported narrow terms TEAEs: Depression (n = 9), Completed suicide, Major depression, and Suicidal ideation; there was 1 patient who reported a broad term TEAE (Mood altered).

Deaths: One completed suicide was reported in the ixekizumab 80 mg Q2W

SAEs: Four (0.4%) patients reported a depression-related (Depression [n = 2] and Major depression) or a suicide-related (Completed suicide) SAE

Discontinuations due to AE: Two (0.2%) patients discontinued from study drug (Completed suicide, Suicidal ideation)

Depression-Related or Suicide-Related TEAEs by 12-Week Intervals: There was no trend for an increase in the rate of depression-related or suicide-related TEAEs over longer durations of exposure to ixekizumab.

Inflammatory Bowel Disease

Placebo-Controlled axSpA Integrated Analysis Set

There were 4 (0.7%) ixekizumab-treated patients, whereof 1 (0.4%) in the Q2W dosing group, and 3 (1.0%) in the Q4W dosing group and 2 (0.7%) placebo-treated patients who reported at least 1 IBD-related specific (narrow terms) or non-specific (broad terms) TEAE:

SAEs: The 2 TEAEs of Crohn's disease in the ixekizumab treatment groups (1 in each ixekizumab treatment group) and the 1 TEAE of Colitis ulcerative in the placebo group were SAEs

Discontinuations due to AE: All 3 patients in the ixekizumab 80 mg Q4W group discontinued due to IBD-related TEAEs; none of these TEAEs were serious

All axSpA Ixekizumab Exposures Integrated Analysis Set

In the All axSpA Analysis Set, 16 (1.7%) patients reported at least 1 IBD-related specific or non-specific TEAE

SAEs: There were 6 (0.6%) patients with IBD-related SAEs (3 patients with Crohn's disease and 3 patients with Colitis ulcerative)

Discontinuations due to AE: Seven (0.8%) patients discontinued study drug due to an IBD-related TEAE (2 patients with Crohn's disease, 3 patients with Colitis ulcerative, 1 patient with Proctitis ulcerative, and 1 patient with Colitis)

Inflammatory Bowel Disease TEAEs by 12-Week Intervals: According to the applicant, there was no trend for an increase in the rate of IBD-related specific TEAEs over longer durations of exposure to ixekizumab, consistent with the known safety profile of ixekizumab.

Inflammatory bowel disease is included in the Special Warnings and Precautions for Use section of the currently approved SmPC; no update to the label is proposed by the applicant.

Interstitial Lung Disease

No TEAEs of ILD were reported.

Upon request from the CHMP, the MAH has presented the incidence rates of the AEs of special interest in the Placebo-Controlled axSpA Integrated Analysis Set (**Table 51**) and the All axSpA Ixekizumab Exposures Integrated Analysis Set (**Table 52**).

Table 51: Summary of Adverse Events of Special Interest, Patient-Time-Adjusted Incidence Rate axSpA Safety Population Placebo-Controlled axSpA Integrated Analysis Set – Blinded Treatment Dosing Period Weeks 0-16 (RHBV, RHBW, RHBX)

Category	PBO (N=294) n (IR)	IXE80Q4W (N=291) n (IR)	IXE80Q2W (N=283) n (IR)	Total IXE (N=574) n (IR)	Total (N=868) n (IR)
Treatment-Emergent Adverse Event of Special Interest (TEAE)	76 (84.5)	105 (119.0)	110 (125.7)	215 (122.3)	291 (109.5)
Cytopenias - based on SMQ	2 (2.2)	2 (2.3)	3 (3.4)	5 (2.8)	7 (2.6)
Hepatic	8 (8.9)	8 (9.1)	6 (6.9)	14 (8.0)	22 (8.3)
Infection	46 (51.2)	77 (87.2)	66 (75.4)	143 (81.4)	189 (71.1)
Injection-site reactions	17 (18.9)	27 (30.6)	49 (56.0)	76 (43.2)	93 (35.0)
Allergic reactions/hypersensitivities	5 (5.6)	7 (7.9)	12 (13.7)	19 (10.8)	24 (9.0)
Anaphylaxis	1 (1.1)	0	0	0	1 (0.4)
Criterion 1	1 (1.1)	0	0	0	1 (0.4)
Criterion 2	0	0	0	0	0
Non-Anaphylaxis	4 (4.4)	7 (7.9)	12 (13.7)	19 (10.8)	23 (8.7)
Confirmed Cerebro-cardiovascular events	1 (1.1)	1 (1.1)	2 (2.3)	3 (1.7)	4 (1.5)
MACE confirmed events	0	0	0	0	0
Malignancies	0	1 (1.1)	0	1 (0.6)	1 (0.4)
Depression	5 (5.6)	0	5 (5.7)	5 (2.8)	10 (3.8)
Interstitial lung disease	0	0	0	0	0
Specific Inflammatory bowel disease (IBD)	2 (2.2)	2 (2.3)	1 (1.1)	3 (1.7)	5 (1.9)
Inflammatory Bowel Disease (IBD) - PT	1 (1.1)	0	0	0	1 (0.4)
Crohn's Disease	0	1 (1.1)	1 (1.1)	2 (1.1)	2 (0.8)
Ulcerative Colitis	1 (1.1)	1 (1.1)	0	1 (0.6)	2 (0.8)
IBD Confirmed by Adjudication	1 (1.1)	4 (4.5)	1 (1.1)	5 (2.8)	6 (2.3)
Crohn's Disease Confirmed by Adjudication	1 (1.1)	3 (3.4)	1 (1.1)	4 (2.3)	5 (1.9)
Ulcerative Colitis Confirmed by Adjudication	0	1 (1.1)	0	1 (0.6)	1 (0.4)

Abbreviations: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; TEAE = treatment-emergent adverse event; n = number of patients with at least one treatment-emergent adverse event (TEAE) in the specified category; Total Patient-Years = total time patients were in the treatment period; IR = incidence rate per 100 patient-years; MACE = Major Adverse Cerebro-Cardiovascular Events.

Table 52: Summary of Adverse Events, Percentage and Patient-Time-Adjusted Incidence Rate axSpA Safety Population All axSpA Ixekizumab Exposures Integrated Analysis Set – All Treatment Period

	Pooled AxSpA IXE			
	Frequency (N=929)		Incidence Rate Total Patient-Years = 1336.2	
Category	n (%)	95% CI	IR	95% CI
Treatment-Emergent Adverse Event of Special Interest (TEAE)	591 (63.6%)	(60.5, 66.7)	44.2	(40.8, 47.9)
Cytopenias - based on SMQ	23 (2.5%)	(1.5, 3.5)	1.7	(1.1, 2.6)
Hepatic	67 (7.2%)	(5.5, 8.9)	5.0	(3.9, 6.4)
Infection	478 (51.5%)	(48.2, 54.7)	35.8	(32.7, 39.1)
Injection-site reactions	154 (16.6%)	(14.2, 19.0)	11.5	(9.8, 13.5)
Allergic reactions/hypersensitivities	74 (8.0%)	(6.2, 9.7)	5.5	(4.4, 7.0)
Anaphylaxis	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Criterion 1	0	(0.0, 0.3)	0.0	(0.0, 0.6)
Criterion 2	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Non-Anaphylaxis	73 (7.9%)	(6.1, 9.6)	5.5	(4.3, 6.9)
Confirmed Cerebro-cardiovascular events	12 (1.3%)	(0.6, 2.0)	0.9	(0.5, 1.6)
MACE confirmed events	2 (0.2%)	(0.0, 0.5)	0.1	(0.0, 0.6)
Malignancies	6 (0.6%)	(0.1, 1.2)	0.4	(0.2, 1.0)
Depression	13 (1.4%)	(0.6, 2.2)	1.0	(0.6, 1.7)
Interstitial lung disease	0	(0.0, 0.3)	0.0	(0.0, 0.6)
Specific Inflammatory bowel disease (IBD)	11 (1.2%)	(0.5, 1.9)	0.8	(0.5, 1.5)
Inflammatory Bowel Disease (IBD) - PT	1 (0.1%)	(0.0, 0.3)	0.1	(0.0, 0.5)
Crohn's Disease	5 (0.5%)	(0.1, 1.0)	0.4	(0.2, 0.9)
Ulcerative Colitis	5 (0.5%)	(0.1, 1.0)	0.4	(0.2, 0.9)
IBD Confirmed by Adjudication	13 (1.4%)	(0.6, 2.2)	1.0	(0.6, 1.7)
Crohn's Disease Confirmed by Adjudication	7 (0.8%)	(0.2, 1.3)	0.5	(0.2, 1.1)
Ulcerative Colitis Confirmed by Adjudication	6 (0.6%)	(0.1, 1.2)	0.4	(0.2, 1.0)

Abbreviations: IXE = Ixekizumab; IR = incidence rate per 100 patient-years; N = number of patients in the analysis population; n = number of patients with at least one treatment-emergent adverse event (TEAE) in the specified category; TEAE = treatment-emergent adverse event; Total Patient-Years = total time patients were in the treatment period; MACE = major adverse cerebro-cardiovascular events; CI = confidence interval.

Immunogenicity

Analyses of the relationship between TEAEs and TE-ADA status over time were conducted for 2 specific AEs of special interest: allergic reactions/hypersensitivity events (anaphylaxis or non-anaphylaxis [immediate and non-immediate]) and Injection Site Reactions.

Allergic Reactions/Hypersensitivities

There were no confirmed cases of anaphylaxis in All axSpA Ixekizumab Exposures integrated Analysis Set. All reported allergic reactions/hypersensitivities cases were non anaphylaxis (immediate or non-immediate) in nature.

In the pooled ixekizumab treatment group, 69 (8.3%) TE-ADA-negative patients reported at least 1 non anaphylaxis TEAE (immediate, 18 patients; nonimmediate, 54 patients) and 5 (5.7%) TE-ADA-positive patient reported at least 1 non anaphylaxis TEAE (non-immediate, 5 patients). Of these 5 patients, 4 had the TEAEs occurred only during periods where TE-ADA were not present, and 1 patient had the TEAEs occurred during periods where TE-ADA was present. This patient was TE-ADA positive beginning approximately 8 months prior to the non-anaphylaxis TEAE, without events reported during that period.

Injection Site Reactions

In the pooled ixekizumab treatment group in All axSpA Ixekizumab Exposures Integrated Analysis Set, 127 (15.3%) TE-ADA-negative patients reported at least 1 Injection Site Reactions TEAE. A total of 26 (29.9%) TE-ADA-positive patients reported at least 1 Injection Site Reactions TEAE:

- 13 patients had events only when TE-ADA were not present. All events (Injection site reaction, Injection site erythema, Injection site pruritus) were mild in severity and did not re-occur after the development of TE-ADA
- 12 patients started reporting events before the detection of TE-ADA and continued to report the same type of events after the development of TE-ADA (at low titer in 7 patients, at moderate titer in 1 patient and both low and moderate titers in 4 patients). All events were mild (9 patients) or moderate (3 patients) in severity, with no increase in severity after the development of TE-ADA. In 2 patients, the events decreased in severity (from moderate to mild) after the development of TE-ADA, and
- 1 patient had mild events of Injection site hypersensitivity only when TE-ADA were present. This patient had a single TE-ADA-positive result (titer 1:10) on study Day 15 and reported the events on study Days 13 and 15.

TEAEs and Pharmacokinetic Analyses

Exposure-safety data were integrated across the 3 axSpA studies in the clinical development programme (Studies RHBV, RHBW, and RHBX) for analysis. According to the applicant, there was no apparent relationship between ixekizumab trough concentrations (Ctrough) at Week 16 and the overall incidence of TEAEs during the first 16 weeks of the double-blind period, nor specifically with infections or allergic reactions/hypersensitivity events within the range of concentrations observed across these studies. There was a trend for an exposure-response relationship between Ctrough and injection site reactions, although the incidence in the ixekizumab groups was lowest in Quartile 2 which was comparable to the placebo group. According to the applicant, the incidences of the AEs of special interest of Infections (Candida, herpes, staphylococcal, and infections reported as SAEs), hypersensitivity reactions (anaphylaxis), neutropaenia, MACE, and IBD were too small, thus, would not allow for an evaluation of the relationship to ixekizumab drug concentrations.

In general, these findings are consistent with findings in the Ps, and PsA populations where there is an overall lack of a relationship between concentrations and TEAEs and AEs of special interest, except for Injection Site Reactions.

Laboratory findings

Clinical laboratory assessments, including haematology, serum chemistry, and urinalysis, were performed as scheduled per protocol.

Cytopenias and hepatic events are discussed in the adverse events of special interest.

Haematology Laboratory Tests

The findings were consistent between the Placebo-Controlled AxSpA Integrated Analysis Set and the All AxSpA Analysis Set and were found consistent with the known safety profile of ixekizumab in other indications.

Chemistry Laboratory Tests

There were no clinically important changes in chemistry parameters. Any observed differences were considered unremarkable and unlikely to represent clinically meaningful differences. The findings from the All AxSpA Analysis Set were consistent with the Placebo-Controlled AxSpA Integrated Analysis Set and considered consistent with the known safety profile of ixekizumab.

Hepatic Laboratory Tests

In the Placebo-Controlled axSpA Integrated Analysis Set, the frequencies were comparable between the ixekizumab treatment groups and the placebo group with respect to the proportions of patients with elevations across the various baseline categories and prespecified elevation cut-offs for each parameter (that is, ALT, AST, ALP, or total bilirubin). Most patients did not experience shifts to different categories for ALT, AST, or total bilirubin. Supportive safety data from the All axSpA Analysis Set did not show new signals for hepatic laboratory test abnormalities.

The data do not suggest an increased risk for drug-induced liver injury with ixekizumab treatment, consistent with the previously reported safety profile for ixekizumab.

Safety in special populations

Intrinsic Factors

Subgroup analyses were performed in the Placebo-Controlled axSpA Integrated Analysis Set for Demographic Subgroups (Sex; Age Category Groups; Weight Category; Body mass index; Ethnicity) and Geographic Region Subgroups. These analyses included the proportion of patients with at least 1 TEAE, as well as the AEs of special interest specified for subgroup analyses, namely, Infections, Allergic reactions/hypersensitivity events, and Injection Site Reactions. Analyses were reviewed for the clinical importance of any findings, including evaluation of statistically significant findings.

The TEAE profile was not influenced by sex, weight and BMI, ethnicity and race or by geographic region. The TEAE profile was not influenced by age.

Table 53: Overview of Adverse Events by Age Category axSpA Safety Population All axSpA Ixekizumab Exposures Integrated Analysis Set - All Treatment Period

MedDRA Terms	75-84 years			>=85 years		
Event category	PBO (N=1) n(%)	IXE80Q4W (N=2) n(%)	IXE80Q2W (N=1) n(%)	PBO (N=0) n(%)	IXE80Q4W (N=0) n(%)	IXE80Q2W (N=0) n(%)
Total TEAE	1 (100.0%)	1 (50.0%)	0	0	0	0
Serious AEs	0	0	0	0	0	0
Fatal	0	0	0	0	0	0
Hospitalization	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Disability	0	0	0	0	0	0
Other	0	0	0	0	0	0
AE leading to drop-out	0	0	0	0	0	0
Psychiatric disorders (SOC)	0	0	0	0	0	0
Nervous system disorders (SOC)	1 (100.0%)	0	0	0	0	0
Accidents and injuries (SMQ)	0	0	0	0	0	0
Cardiac disorders (SOC)	0	0	0	0	0	0
Vascular disorders (SOC)	0	0	0	0	0	0

Cerebrovascular disorders (SMQ)	1 (0.4%)	1 (0.4%)	0	0	0	0
Infections and infestations (SOC)	44 (15.8%)	76 (27.8%)	65 (23.6%)	2 (14.3%)	1 (6.3%)	1 (16.7%)
Quality of life decreased (PT)	0	0	0	0	0	0
Hypotension, falls, fractures (LSC)	3 (1.1%)	3 (1.1%)	3 (1.1%)	0	1 (6.3%)	0
Fractures (LSC)	0	0	0	0	0	0

Abbreviations: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mgQ2W; IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients with at least one adverse event at the specified category; TEAE = treatment-emergent adverse event.

Extrinsic Factors

Subgroup analyses were performed for the following subgroups in the Placebo-Controlled axSpA Integrated Analysis Set for concomitant cDMARD (methotrexate, sulfasalazine, or hydroxychloroquine) Use, concomitant NSAID (including COX-2 inhibitors) Use, concomitant Oral Corticosteroid Use, concomitant Analgesic (systemic opioids and/or short acting analgesics with no anti-inflammatory effect) Use. These analyses included the proportion of patients with at least 1 TEAE, as well as the AEs of special interest specified for subgroup analyses, namely, Infections, Allergic reactions/hypersensitivity events, and Injection Site Reactions. Analyses were reviewed for the clinical importance of any findings, including evaluation of statistically significant findings.

According to the MAH, the TEAE profile was not influenced by concomitant use of cDMARD (methotrexate, sulfasalazine, or hydroxychloroquine), NSAID, oral corticosteroid or analgesic. 34.2% of patients were receiving a concomitant cDMARD85.5% of patients were receiving a concomitant NSAID, 11.9% of patients were receiving a concomitant oral corticosteroid 23.4% of patients were receiving a concomitant analgesic during the Placebo-Controlled Blinded Treatment Dosing Period (Weeks 0 to 16).

Upon request, the MAH provided TEAEs for patients treated with or without SSZ for patients treated with Ixekizumab 80mg Q4W or placebo (**Table 54**).

Table 54: Treatment-Emergent Adverse Event by SOC Patients Treated with and without Sulfasalazine AxSpA Safety Population Placebo-Controlled axSpA Integrated Analysis Set - Blinded Treatment Dosing Period Weeks

	Patients Treated with Sulfasalazine		Patients Treated without Sulfasalazine	
System organ class	Placebo (N=56) n (%)	Ixe 80 mg Q4W (N=65) n (%)	Placebo (N=238) n (%)	Ixe 80 mg Q4W (N=226) n (%)
Patients with at least 1 TEAE	24 (42.9)	33 (50.8)	114 (47.9)	129 (57.1)
Infections and infestations	9 (16.1)	16 (24.6)	37 (15.5)	61 (27.0)
General disorders and administration site conditions	7 (12.5)	5 (7.7)	19 (8.0)	31 (13.7)
Musculoskeletal and connective tissue disorders	2 (3.6)	3 (4.6)	23 (9.7)	22 (9.7)
Gastrointestinal disorders	1 (1.8)	2 (3.1)	20 (8.4)	22 (9.7)
Skin and subcutaneous tissue disorders	0	5 (7.7)	10 (4.2)	14 (6.2)
Investigations	5 (8.9)	3 (4.6)	11 (4.6)	9 (4.0)
Eye disorders	1 (1.8)	5 (7.7)	8 (3.4)	10 (4.4)
Nervous system disorders	0	3 (4.6)	12 (5.0)	9 (4.0)
Respiratory, thoracic and mediastinal disorders	0	3 (4.6)	6 (2.5)	8 (3.5)
Vascular disorders	4 (7.1)	1 (1.5)	6 (2.5)	6 (2.7)
Metabolism and nutrition disorders	0	1 (1.5)	9 (3.8)	5 (2.2)
Renal and urinary disorders	2 (3.6)	0	6 (2.5)	5 (2.2)
Injury, poisoning and procedural complications	2 (3.6)	0	4 (1.7)	5 (2.2)
Psychiatric disorders	1 (1.8)	0	5 (2.1)	4 (1.8)
Blood and lymphatic system disorders	3 (5.4)	1 (1.5)	3 (1.3)	2 (0.9)
Surgical and medical procedures	0	0	4 (1.7)	2 (0.9)
Reproductive system and breast disorders	1 (1.8)	0	3 (1.3)	1 (0.4)
Ear and labyrinth disorders	0	0	2 (0.8)	2 (0.9)
Cardiac disorders	1 (1.8)	0	3 (1.3)	0
Hepatobiliary disorders	0	1 (1.5)	2 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.4)	2 (0.9)
Immune system disorders	0	0	3 (1.3)	0
Congenital, familial and genetic disorders	0	0	1 (0.4)	0

Adverse Events by Starting Dose

According to the MAH, in Studies RHBV, RHBW , RHBX, as well as in the Placebo-Controlled axSpA Integrated Analysis Set, the ixekizumab starting dose (160 mg versus 80 mg at Week 0) had no impact on the overall safety profile, as evaluated by TEAEs, SAEs, AEs leading to discontinuations, and AEs of special interest.

Because Injection Site Reactions are the AEs of special interest that occur most often in the first few weeks of ixekizumab treatment, additional analyses investigating the impact of the ixekizumab starting dose on the frequency of Injection Site Reactions from Weeks 0 to 4 were performed. While the percentage of patients reporting at least 1 Injection Site Reactions TEAE was greater for those patients in the ixekizumab 80 mg Q2W group receiving the 160-mg starting dose (n = 21 [15.0%]) compared with those receiving the 80-mg starting dose (n = 13 [9.1%]), this finding did not hold true for the ixekizumab

80 mg Q4W group where the percent of patients reporting an injection-related event was similar for each starting dose (160-mg starting dose: n = 8 [5.6%]; 80-mg starting dose: n = 9 [6.0%]). Taken together, the MAH considers that although the numbers of patients are small, the results suggest that the additional 80-mg injection at Week 0 (that is, 160-mg starting dose) does not impact the frequency of Injection Site Reactions in the first 4 weeks of treatment.

Use in Pregnancy and Lactation

Pregnant and lactating women were excluded from entering the clinical studies. Seven pregnancies were reported cumulatively as of the data cut-off date of the submission. Five pregnancies were reported in female partners of male patients in Studies RHBV, RHBW, and RHBY. Outcome was available for one pregnancy (a male neonate was reported to be born at 37 weeks and 3 days of gestation, with no abnormalities detected) in this case exposure period was reported as first and second trimesters and study drug was discontinued approximately 1.5 months after a pregnancy was confirmed. The outcomes for the remaining pregnancies is not available. In all other 4 cases the blinded study drug was continued.

Maternal exposure

Two pregnancies were reported in female patients of Study RHBX at the data cut-off date for this type II variation.

The first case involved a 24-year-old female patient. The patient's maternal medical history included 2 therapeutic abortions (2013 and 2014) 1 child of 12 months in good health, obesity, no excessive weight gain during pregnancy, and no previous macroscopic baby. The patient was not using any contraceptive method during her participation in the study. The patient had a positive urine pregnancy test prior to dosing at Week 20 study visit (second trimester exposure). The patient discontinued study drug permanently and developed polyhydramnios of an unknown cause on an unspecified date during the pregnancy. The patient was reported to have no complications during the pregnancy and no diagnostic tests were performed during the pregnancy. The patient delivered a female infant at 39 weeks of gestation via caesarean section due to polyhydramnios and high weight of the baby; the infant did not experience any complications.

The second case involved a 28-year-old female patient. The patient never consumed tobacco or alcohol and had a history of 3 other pregnancies which resulted in preterm live births. The patient became pregnant during the study after discontinuing study drug. The study drug discontinuation was decided by the investigator because the patient was not benefiting from study drug. The patient had slight hypertension at the end of the pregnancy and had no other diagnostic tests performed during the pregnancy other than ultrasounds and regular labs. The patient delivered a male infant by vaginal birth after 39 weeks of gestation. The infant was normal and weighed 7 pounds and measured at a length of 19.5 inches; APGAR scores were 10 at 1 minute and 10 at 5 minutes. No complications as a result of treatment with blinded study drug were reported by the patient.

Safety related to drug-drug interactions and other interactions

According to the MAH, there are no known interactions of ixekizumab with other medicines. Two population pharmacokinetic analyses were performed and results are included in this submission: one analysis in patients with r-axSpA using data from studies RHBV and RHBW and one analysis in patients with nr-axSpA using data from Study RHBX. In both population PK analyses, concomitant treatment with the following drugs was determined to have no impact on the clearance of ixekizumab: oral corticosteroids, NSAIDs (including COX-2 inhibitors), cDMARDs evaluated together (sulfasalazine, methotrexate, or hydroxychloroquine), and sulfasalazine and methotrexate evaluated individually.

Discontinuation due to adverse events

Placebo-Controlled axSpA Integrated Analysis Set

A higher percentage of ixekizumab-treated patients (n = 17 [3.0%]) reported an AE that led to study drug discontinuation compared with placebo-treated patients (n = 4 [1.4%]).

The SOCs in which study drug discontinuation due to an AE were reported most frequently in ixekizumab-treated patients were the General disorders and administration site disorder SOC, Gastrointestinal disorders SOC, and Infections and infestations SOC.

Reasons for treatment discontinuations due to TEAEs are provided in **Table 55**

Table 55: Reasons for Treatment Discontinuations due to TEAE, Double-Blind Treatment Period AxSpA Safety Population, Placebo-Controlled axSpA Integrated Analysis Set (Studies RHBV, RHBW, and RHBX)

Category	Overall AEs resulting DC			AEs resulting DC and related to study drug and as determined by investigators		
	Placebo (N=294) n (%)	Ixe 80mg Q4W (N=291) n (%)	Ixe 80mg Q2W (N=283) n (%)	Placebo (N=294) n (%)	Ixe 80mg Q4W (N=291) n (%)	Ixe 80mg Q2W (N=283) n (%)
TEAEs	3 (1.0)	9 (3.1)	7 (2.5) [a]	1 (0.3)	7 (2.4)	5 (1.8)
Mild	0	1 (0.3)	2 (0.7)	0	1 (0.3)	1 (0.4)
Moderate	0	6 (2.1)	3 (1.1)	0	4 (1.4)	3 (1.1)
Severe	3 (1.0)	2 (0.7)	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.4)
Death	0	0	1 (0.4)	0	0	0
SAE	3 (1.0)	3 (1.0)	1 (0.4)	1 (0.3)	2 (0.7)	0
AESIs:						
Infection	0	2 (0.7)	1 (0.4)	0	2 (0.7)	0
Injection-site reactions	0	1 (0.3)	3 (1.1)	0	1 (0.3)	3 (1.1)
Allergic reactions/hypersensitivities	1 (0.3)	0	1 (0.4)	1 (0.3)	0	1 (0.4)
Malignancies	0	1 (0.3)	0	0	1 (0.3)	0
Depression	0	0	1 (0.4)	0	0	0
IBD Confirmed by Adjudication	0	2 (0.7)	0	0	1 (0.3)	0

All axSpA Ixekizumab Exposures Integrated Analysis Set

In the All axSpA Analysis Set, 52 (5.6%) patients had an AE that led to study drug discontinuation. The SOCs in which study drug discontinuation due to an AE were reported most frequently in ixekizumab-treated patients were the Infections and infestations SOC, Gastrointestinal disorders SOC, and General disorders and administration site disorder SOC

Post marketing experience

The first marketing approval for ixekizumab occurred on 22 Mar 2016 when the United States FDA approved ixekizumab for the treatment of adults with moderate-to-severe plaque Ps. Ixekizumab has also been approved by the FDA for the treatment of adults with active PsA on 01 Dec 2017. The Initial Marketing Authorisation Application (EMEA/H/C/003943) for Taltz for use in patients with

moderate-to-severe Ps was approved by the EU Commission on 25 Apr 2016. The Type II variation procedure to add the indication for active PsA was approved by the EU Commission on 18 Jan 2018. The use of Taltz in axSpA has not been approved as yet and therefore, there is no postmarketing data available for patients with axSpA. As noted in PSUR 1, a signal for serious immediate hypersensitivity reactions consistent with anaphylaxis was identified from postmarketing spontaneous AE reports of ixekizumab, leading to a review of data for serious immediate hypersensitivity reactions. Based on findings from postmarketing spontaneous reports and mechanistic plausibility, the MedDRA Preferred Term of Anaphylaxis was added to the "Special warnings and precautions for use". Following PSUR2 the "Special warnings and precautions for use" and "Undesirable effects" sections of the SmPC were updated to reflect this information.

2.5.1. Discussion on clinical safety

Currently, the ixekizumab safety database comprises a total of 8421 ixekizumab-treated patients with Ps, PsA, r-axSpA, and nr- axSpA equating to 21,064.1 patient-years of exposure. In total 8953 patients have been treated with IXE in blinded and open-label clinical studies in plaque Ps, PsA, axial spondyloarthritis, and other autoimmune conditions combined. Of these, 6343 patients were exposed to IXE for at least 1 year, cumulatively representing 19,772.1 patient-years of exposure. The most common adverse events associated with ixekizumab includes infections, neutropenia, thrombocytopenia, allergic reactions, gastrointestinal disorders and injections site reactions.

A total of 929 patients with axial spondyloarthritis have been exposed to ixekizumab, whereof 738 (79.4%) for more than 1 year. Of note only 82 of 302 patients with nr- axSpA were exposed to IXE for ≥1yr of which only 38 IXE 80 mg Q4W were exposed to the intended treatment dose at the time of this submission. These patients were all bDMARD-naive. This dataset makes up less than 12 % of the total number of axSpA patients exposed for one year. The extent of exposure of all axSpA population to ixekizumab complies with the requirements described in ICH E1 Population Exposure (300-600 exposed for 6 months and 100 patients exposed for a minimum of one-year. However, the population of nr-axSpA falls well short of this. The MAH clarified that 130 patients with nr-axSpA reached 1-year ixekizumab exposure after entering extension study RHBY. Since Non-radiographic-axSpA is also considered to be a subset of a single disease entity, axSpA, which includes r-axSpA/ ankylosing spondylitis and nr-axSpA, safety in patients with r-axSpA exposed to IXE can be taken into consideration in the overall safety evaluation of IXE in the nr-AxSpA population.

The proportion of subjects with AEs, SAEs, infections, allergic reaction and injection site reactions in the 16-week placebo-controlled period of the pivotal studies appeared similar in the adalimumab and ixekizumab groups and not remarkably higher than in the placebo group. During the placebo-controlled parts of the study, adverse events were reported for 162/291 subjects (55.7%) treated with ixekizumab Q4W, 163/283 subjects (57.6%) treated with ixekizumab Q2W and 138/294 subjects (46.9%) treated with placebo. The corresponding number of subjects for adalimumab-treated subjects in RBHV were 44/90 subjects (48.9%). It should be noted that the population studied in RBHV were bDMARD-naïve, and in this population adverse events were less frequent for ixekizumab than for adalimumab. Also, serious adverse events were reported less frequently for ixekizumab than for adalimumab (1.2% vs 3.3%). Overall TEAES were slightly higher in the nr-AxSpA group (59.1%) compared to the total r-axSpA population (54.2%). The overall bDMARD naive nr-axSpA rate of TEAE (59.1%) was more comparable with the TNFi experienced r-axSpA populations (62.7%) rather than the bDMARD naïve axSpA population (45.7%). This difference was driven by a higher rate of mild to moderate TEAES. A dose related increase in TEAEs across the three studies was only seen in the study with patients with nr-axSpA in which, 63.7% of the 80 mg Q2W compared with 54.2% of the IXE80 mg Q4W treated patients experienced TEAEs. Of note, the frequencies of Injection Site Reactions (high level term) were highest in treatment naïve

patients with nr-axSpA in Study RHBX, however these frequenciesremain within the ranges previously reported in psoriasis and PsA studies.

There were 3 deaths among ixekizumab-treated subjects in this development programme. One due to suicide, one due to infection and one possibly due to murder. No particular concerns with regards to safety of the drug are evoked by these three cases. There were no deaths in the placebo group.

SAE were reported by 10 (1.7%) Ixekizumab treated patients and 6 (2.0) placebo treated patients.

Adverse events of special interest

Infections

Infections are included in the SmPC Sections 4.3, 4.4 and 4.8. Infections occurred with a similar frequency in the Ixekizumab Q2W, Q4W (23.3% and 26.5%) and adalimumab (21.1%) groups. The most frequent infections were nasopharyngitis and upper respiratory tract infections. There were no cases of TB reported. The findings in the 16-week placebo-controlled period does not evoke any further concern, neither did the additional provided exposure adjusted incidence rates.

The overall rates of OI were lower than placebo in the ixekizumab-treated patients (0.7% vs 0.5% respectively) in the 16-week placebo-controlled analysis and 1.6% in the all AxSpA analysis. There were slightly more reports of Herpes Zoster (2 (0.7%) patients) in the ixekizumab 80 mg Q4W compared with the placebo group (1 (0.3%) patient). Eleven (1.2%: IR 0.8/100PY) patients in the all axSpA reported Herpes zoster infection. All cases were mild to moderate in severity. Although the rates are low the incidence rate for Zoster in patients under 50 is of the order of 0.3-0.5/100 persons years with a steep rise after 50 years of age (Kawai et al 2014). The MAH clarified that the incidence rate of herpes zoster observed in the axSpA clinical development programme (0.8 per 100 patient-years) is consistent with the incidence rate of zoster in patients with axSpA identified in the two studies performed within US administrative insurance claims databases (0.9 per 100 person-years patients with ankylosing spondylitis Yun et al and 0.7 for patients(psoriasis, PsA, and ankylosing spondylitis) initiating a non-biologic DMARD (mean age 48.8 years) and 0.4 for patients starting a TNFi (mean age 52.2 years) (Winthrop et al. 2013). Thus, it is agreed by CHMP that the incidence rate of herpes zoster observed in the axSpA clinical development programme (0.8 per 100 patient-years) is consistent with the background rate of zoster reported in the literature.

The profile of infections in AxSpA populations is considered generally consistent with the prior experience of ixekizumab, however reports of UTI including pyelonephritis and infectious diarrhoea was further discussed by the MAH and although there were not sufficient data to require an update in the SmPC, the MAH commits to monitor these events in the next PSUR.

Upon request by CHMP, the warning in Section 4.4 of the SmPC regarding the use in patients with chronic infections and when a chronic infection starts whilst on treatment was revised, to state that the warning applies also to patients with history of recurrent infections and to clarify the instructions to the HCP.

Injection site reactions

Injection site reactions were reported for a higher proportion of patients treated with ixekizumab Q2W than for adalimumab in the direct comparison (RHBV). During the placebo-controlled 16 weeks of the studies, injection site reactions were noted among 7.1% of ixekizumab-treated patients. In the PsA studies, injections site reactions were observed among 12% of ixekizumab-treated subjects during the first 24 weeks, and therefore the current findings do not constitute a new safety concerns. Among subjects treated with ixekizumab, allergic reactions/hypersensitivity events were more frequent among ADA-negative than among ADA-positive patients. Injection site reactions, however, were observed with a higher frequency among ADA-positive patients. However, most of these reactions were reported during

periods when ADAs were not present. Injections site reactions are considered sufficiently covered by the current SmPC.

Cytopenias

Neutropenia and thrombocytopenia were observed among ixekizumab-treated subjects. In the placebo-controlled axSpa analysis set 8.9% in the Ixekizumab group and 3.4% in the placebo group experienced neutropenia and 2.1% in the Ixekizumab group and 3.4% in the placebo group experienced thrombocytopenia. In the all axSpa analysis set 15.9% and 5% of the ixekizumab treated patients experienced neutropenia respectively thrombocytopenia. Most of these cases were transient and mostly occurred with low-grade changes (grade 1 and 2). Two patients (4.3%) who had a treatment-emergent Grade 1 thrombocytopenia reported bleeding-related TEAE. The preferred terms for these cases were haematuria (in combination with vascular rupture in one case). It is noteworthy that both patients reported haematuria, however, the number of cases is too small to draw any conclusions. The findings in these studies appear consistent with what has been previously described, and these risks are considered sufficiently covered by the SmPC.

Hepatic event

The proportion of subjects with hepatic events was not higher for ixekizumab than for placebo during the placebo-controlled part of the studies. This is reassuring. One subject experienced a ≥5-fold increase in liver enzymes, ALT and AST levels were found to be elevated to 223 U/L (reference 6 to 43 U/L) and 201 U/L (reference 11 to 36 U/L). Approximately a month later, the patient's ALT and AST levels returned to normal. The elevated liver enzymes were noted 5 days after starting ciprofloxacin, which may be a confounder. No information on bilirubin values has been found, however, the applicant states that no patients met the laboratory screening criteria for potential drug-induced liver injury (ALT ≥3xULN and maximum total bilirubin ≥2xULN).

Cerebro- cardiovascular disease and MACE

In this application, in the placebo-controlled analysis the incidence of MACE was highest in the 80 mg Q2W group (0.5%) but similar between the placebo (0.3%) and 80 mg Q4W treated group (0.3%). The overall exposure adjusted incidence for MACE was 0.1E/100PY.

In the placebo-controlled analysis over 16 weeks there were 2 cases of cases of atrial arrhythmia in the IXE treated population compared with none in the placebo group, one of which was a SAE. In the longer-term integrated safety analysis, the all axSpA analysis there were 5 cases adjudicated as atrial arrhythmia and 4 cases of ventricular arrhythmia. AxSpA is associated with a higher prevalence of aortic valve disorders and conduction disorders. The MAH provided an overview of these cases of arrhythmia. There was no clear temporal association between initiation of treatment or most recent treatment and onset of any of the arrythmia events. In addition, in all cases (except 2 cases of ventricular arrythmia), there were confounding medical histories that could plausibly have contributed to the event. No new safety concern was thus identified from the review of the cases.

Cerebral haemorrhage and subarachnoid haemorrhage were reported as SAEs in the pooled AxSpA IXE safety population. The case of cerebral haemorrhage was not adjudicated to meet the criteria for MACE. Both events were reported by the same patient and were the result of a fall and unlikely to be related to the study drug.

Malignancy

Rates of malignancy in patients treated with IXE are low (0.4E/100PY). The IR increased slightly from 0-12 to 36-48 weeks (0.5E-0.6E/100PY). From week 48 -60, IR was 1.2E/100PY and from week 108, the IR was 2.6 E/100PY. No events were reported in the other time intervals. There is limited long term data in this axSpA population particularly in patients with nr-axSpA. An incidence rate of 0.7 per 100 patient-years was

identified from clinical studies of certolizumab in nr-axSpA and 0.4 for r-axSpA. An incidence rate of 0.6 per 100 patient-years was identified from clinical studies of secukinumab over 52 weeks of follow up with no additional malignancies up to 2yrs. There is no clear evidence of an increased risk for developing malignancies from the clinical trial data presented in this application but there was a slight trend toward increased IR over longer term use. The latency period for malignancy may limit identification in the time frame of these clinical trials. Evidence is inconclusive regarding the risk of malignancy associated with nr-axSpA and AS.

Depression and Suicide/Suicidal behaviour

Although a higher proportion of patients in the placebo treatment group (1.7%) than the IXE (0.9%) treated group reported depression related or suicidal/self-injury related TEAEs during the placebo-controlled period, all reports in the IXE population were in patients treated with the 80 mg Q2W regimen accounting for 1.8% of this population. In the C-SSRS analysis, 6 (1%) IXE treated patients compared with one (0.3%) of placebo treated patient reported suicidal ideation or behaviour. There were two significant suicide events (1 completed suicide and attempted suicide), both in the IXE treated population. Patient who committed suicide had a history of mild depression and was being treated with duloxetine. He was being treated with the IXE Q2W regimen and was intoxicated when he died. Although this case is confounded by his past history, treatment with an SNRI and the alcohol consumption, this patient did not appear to be at high suicide risk. There was no evidence of suicidal behaviour on the QIDS-SR16 and C-SSRS. Although it is recognised that there are increased background rates of depression and suicide in patients with axSpA, there appeared to be a slight a trend towards increase reports of suicidal behaviour in IXE treated patients. Overall, the data did not suggest an increased risk of depression and suicide/self-injury behaviour associated with ixekizumab use. However, the MAH commits to monitor depression-related or suicide/self injury-related AEs in subsequent PSUR.

IBD

In the Placebo-Controlled axSpA Integrated Analysis Set, 4 (0.7%) ixekizumab-treated patients and 2 (0.7%) placebo-treated patient reported at least 1 IBD-related TEAE. In the All axSpA Analysis Set, 16 (1.7%) patients reported at least 1 IBD-related TEAE. The frequency of IBD-related TEAEs in the axSpA clinical development programme was higher than that observed in the previously reported data in patients with plaque Ps or PsA. Possible explanations for this observation include the higher prevalence of Crohn's disease and Colitis ulcerative in the axSpA (4% to 16%) population compared with the plaque Ps (1.6%) or PsA (3.0%) populations. Inflammatory bowel disease is included in the Special Warnings and Precautions for Use section of the currently approved SmPC and included as a potential risk in the RMP; no update to the SmPC was proposed by the MAH. Upon CHMP's request, the higher rate of IBD in the b-DMARD experienced Q4W treated r-axSpA population was further discussed by the MAH and the unexpected finding of a higher reporting rate of IBD in the b-DMARD treated r-axSpa treated with the lower Q4W dose in the placebo-controlled integrated analysis was not apparent in the extension period (Weeks 16 to 52), where all 4 cases reported occurred in the bDMARD naive population. . No update to the existing wording was deemed necessary by the CHMP.

Hypersensitivity and Allergic reactions

Rates of hypersensitivity and allergic reactions were low (8%). Most reactions were non-immediate and mild or moderate in severity. Slightly higher rates of non-anaphylactic hypersensitivity reactions were noted in the TNFi experienced r-axSpa population. There were no reported anaphylactic reactions in the IXE population. There was no clear association between TE-ADA status and allergic reaction/hypersensitivity. This is consistent with the profile seen in the PS and PsA. Hypersensitivity

(including anaphylaxis) is appropriately reflected in sections 4.4 and 4.8 of the SmPC and no updates are deemed necessary by the CHMP.

To facilitate the interpretation of the figures from the "All axSpA ixekizumab Exposures Integrated Analysis Set", the MAH was asked to provide tables with exposure-adjusted incidence rates of all AEs of special interest. These additional data were in line with the data already presented.A higher percentage of ixekizumab-treated patients (3.0%) reported an AE that led to study drug discontinuation compared with placebo-treated patients (1.4%). The SOCs in which study drug discontinuation due to an AE were reported most frequently in ixekizumab-treated patients were the General disorders and administration site disorder SOC, Gastrointestinal disorders SOC, and Infections and infestations SOC. Upon request, the MAH provided reasons for discontinuations per treatment regimen in a tabulated form and the data provided did not evoke additional concerns. In the All axSpA Analysis Set, 52 (5.6%) patients had an AE that led to study drug discontinuation. According to the MAH, the data demonstrated that there was no trend for an increase in the incidence rate of discontinuation over longer durations of exposure to ixekizumab, consistent with the known safety profile of ixekizumab, which is agreed by CHMP.

Laboratory findings

Some increases in total cholesterol, VLDL, HDL and triglyceride and fasting glucose were noted in IXE treated patients compared with placebo. The MAH was requested to clarify significance of these findings. The magnitude of the changes was not considered clinically meaningful by the MAH and the changes were not long-lasting. No evidence of dose-dependent increases were observed. Also, the MAH stated, that in UNCOVER-1, -2, and -3 ixekizumab psoriasis studies, in which fasting lipid profiles were obtained through 60 weeks, no significant changes were observed versus placebo for total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, or triglyceride at 60 weeks (maintenance dosing period). Importantly, LDL to HDL ratios remained stable during the induction and maintenance periods. Although transient changes were observed for some parameters during the induction period, these changes did not persist into the maintenance period. The MAHs reasons for not adding increased lipid levels as an ADR in the SmPC are accepted by CHMP. The MAH will continue to monitor total cholesterol, VLDL, HDL, and triglycerides in the context of cerebro-cardiovascular events in the next PSUR.

Safety data in subgroups

Subgroup analyses indicated that the TEAE profile was not influenced by age, sex, race, BMI/body weight, concomitant DMARD, NSAID, corticosteroid and analgesic use.

The MAH proposed initially a claim in Section 4.2 of SmPC that there were no evident safety concerns when ixekizumab was concomitantly administered with cDMARDs (mainly sulfasalazine), corticosteroids, NSAIDs, or analgesics. However, the CHMP requested justification on the proposed statement. Indeed, these treatments form part of the current standard of care for AS, concomitant use of these drugs had no evident impact on efficacy in studies RHBV, RHBW, RHBX. Only around 1/3 of the patients were receiving concomitant cDMARDs during the studies, the majority were receiving sulfasalazine (SSZ) (21.8%) followed by Methotrexate (12.8%) and Hydroxychloroquine (0.3%). Since the term DMARD is broad and the different DMARDs do not have similar safety profile, it was not considered appropriate by CHMP to evaluate them together. Of the cDMARDs allowed in the studies, only sulfasalazine is recommended (off label) in treatment guidelines on axSpA, and then in the setting of peripheral arthritis. In the response, the MAH removed the proposed statement in Section 4.2 of SmPC, however, the MAH was further requested by CHMP to provide safety data on ixekizumab and sulfasalazine in combination, compared to ixekizumab in monotherapy, since this is considered to be data of relevance to the prescriber. The provided data did not evoke any further concerns. No update of the SmPC was therefore recommended by the CHMP.

2.5.2. Conclusions on clinical safety

The most common adverse events associated with ixekizumab include infections, neutropenia, thrombocytopenia, allergic reactions, gastrointestinal disorders and injections site reactions. No new safety problems have been identified in these studies although some imbalance in a few AEs were observed. These events (UTI including pyelonephritis and infectious diarrhoea and depression-related or suicide/self-injury-related AEs) will be followed by the MAH in the next PSUR.

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 MAH proposed the reclassification of a number of risks (including laboratory findings or risks without serious clinical outcomes) following the guidance in GVP V rev2. No changes were made to the list of additional pharmacovigilance activities or risk minimisation measures.

The CHMP endorsed the Risk Management Plan version 6.3 with the following content:

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Serious infections	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Candida Infection Spontaneous Follow-up Form-Extrapulmonary Tuberculosis Spontaneous Follow-up Form-Herpes Zoster Spontaneous Follow-up Form-Pneumonia Spontaneous Follow-up Form-Pulmonary Tuberculosis Spontaneous Follow-up Form-Tinea Infection Spontaneous Follow-up Form-Unspecified Infection Spontaneous Follow-up Form-Viral Reactivation Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030)
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None proposed	detection: Spontaneous Follow-up Form-General Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030
MACE	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Cardiac Disorders Spontaneous Follow-up Form-Cerebrovascular Accident Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030
Malignancy	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Cancer/Neoplasm Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030
Long-term safety (such as events with a low frequency and/or long latency)	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Cancer/Neoplasm Spontaneous Follow-up Form-Cardiac Disorders Spontaneous Follow-up Form-Cerebrovascular Accident Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have

been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Estonia.

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: the revisions are not considered to significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton (SIJs and spine) with onset of symptoms that typically appear in the second or third decade of life. AxSpA is recognised as a single disease entity, with a patient subset defined by the presence of radiographically defined structural damage of the SIJs (r-axSpA) and a patient subset without clear structural damage radiographically (nr-axSpA) consisting of:

- Radiographic axSpA (r-axSpA; also termed ankylosing spondylitis [AS]), characterised by the presence of definitive structural damage of the SIJ on radiographs. These patients fulfil the radiologic criterion of the mNY criteria.
- Nonradiographic axSpA (nr-axSpA), characterised by the lack of definitive structural damage of the SIJ on radiographs. These patients do not fulfil the radiologic criterion of the mNY criteria.

AxSpA affects up to 1.4% of the Caucasian adult population worldwide. The proportion of patients with nr-axSpA among all patients with axSpA ranges from 40% to 60% according to several national and international referral programmes. Formerly, patients with axSpA without radiographically defined sacroiliitis but with evidence of sacroiliitis from magnetic resonance imaging (MRI) or other characteristics of disease have been less well diagnosed despite sharing a similar burden of disease and the same common features as patients with r-axSpA, such as spinal inflammation, chronic back pain, positivity for human leukocyte antigen (HLA)-B27, and The ASAS criteria for axSpA have been developed, in addition to a diagnostic algorithm (van den Berg et al. 2013), to facilitate earlier recognition of axSpA and to identify axSpA patients with and without radiographic sacroiliitis) using x-rays and MRI. Adoption of the ASAS criteria has the potential to lead to earlier identification of patients with axSpA early in the disease course, and to result in more timely therapeutic intervention and less disability.

AxSpA is characterised by chronic inflammation of the axial skeleton (SIJ and spine), as well as variable involvement of the peripheral joints. As the disease progresses, it can lead to new bone formation in the form of syndesmophytes and joint ankylosis, primarily in the axial skeleton. Patients with axSpA may also

have extra-articular manifestations of the disease such as enthesitis, anterior uveitis, psoriasis (Ps), and inflammatory bowel disease (IBD), as well as comorbidities of aortitis or cardiac conduction abnormalities.

In summary, Ixekizumab, a IL-17A-inhibitor, is approved for plaque psoriasis and PsA. This application aims to extend the indication to treatment of active axial spondyloarthritis (axSpA); including both radiographic (r-axSpA) and non-radiographic disease (nr-axSpA). Plaque psoriasis, PsA and axSpA are related and sometimes overlapping conditions; both with regards to clinical features and available treatment options.

3.1.2. Available therapies and unmet medical need

Nonsteroidal anti-inflammatory drugs are the first line of drug treatment in patients with axSpA, although they are not effective or well tolerated in all patients. Treatment of NSAID-refractory axSpA is hampered by the lack of efficacy of cDMARDs (Braun and Sieper 2009), although peripheral arthritis associated with axSpA may respond to sulfasalazine. Patients with more advanced disease requiring biologic therapy have limited options. Although TNF inhibitors have demonstrated efficacy in both r-axSpA and nr-axSpA, up to 40% of patients fail to achieve adequate disease control or may be intolerant to TNFi, and switching patients to a second or third TNFi may not be effective (Lie et al. 2011). Other than TNF inhibitors, the only available targeted treatment is secukinumab (another interleukin-17 [IL-17] inhibitor), which is only registered in patients with r-axSpA.

For patients with nr-axSpA, the only currently approved therapy is TNF inhibition. Antagonism of IL-17 by ixekizumab represents a novel approach to interfere with the chronic inflammatory process by selectively targeting the predominant cytokine of the unique subset of helper Th17 cells, as well as other cells that play a predominant role in the inflammation associated with axSpA. The subgroup of patients with nr-axSpA with objective signs of inflammation (defined as active inflammation on MRI and/or elevated C-reactive protein [CRP]) is considered the appropriate target population for biologic treatment given the higher observed progression rates (up to 20% over a 2-year period) relative to approximately 10% progression over the same period in patients with nr-axSpA without such objective signs of inflammation. In addition, studies from TNF inhibitors in nr-axSpA demonstrated that minimal treatment effect is observed in patients with nr-axSpA without objective signs of inflammation at baseline (Poddubnyy et al. 2012; Rudwaleit and Sieper 2012; Sieper and van der Heijde 2013; Sieper et al. 2013).

In summary, although there are several approved drugs for axSpA, there is still a high unmet need for additional targeted treatment options since all patients do not respond to or tolerate the available alternatives.

3.1.3. Main clinical studies

The applicant has conducted 3 pivotal clinical studies in 960 adult patients with axSpA axial: 2 studies in patients with r-axSpA (RHBV and RHBW) and 1 study in patients with nr-axSpA (RHBX). All three studies have a randomized, double blind, parallel group design, testing two different dose regimens of Ixekizumab (80mg Q2W or 80mg Q4W) with or without a bolus dose of 160 mg. One study (RHBV) also included an active comparator, Adalimumab 40mg Q2W. The placebo-controlled period was 16 weeks in the two r-axSpA studies (RHBV, RHBW) and 52 weeks in the nr-axSpA study (RHBX). In all three studies, the primary endpoint, ASAS 40, was measured at week 16.

The design and conduct of these studies essentially follow the relevant EMA GL and received Scientific Advice.

Study **RHBV** was a randomized, double-blind, active and placebo-controlled, study in **bDMARD-naive patients** with active **rad-axSpA**, with a double-blind, 16-week treatment period. In addition, long-term

efficacy and safety were evaluated up to 52 weeks for patients who participated throughout the entire 1-year study.

Study **RHBW** was a, randomized, double-blind, placebo-controlled, study with a double-blind, 16-week treatment period in **tumor necrosis factor inhibitor (TNFi)-experienced patients** with **rad-axSpA**. In addition, long-term efficacy and safety were evaluated up to 52 weeks for patients who participated throughout the entire 1-year study.

Study **RHBX** was a randomized, double-blind, placebo-controlled, study in **bDMARD-naive patients** with active **nr-axSpA** that included a 52-week treatment period.

In all three studies the study population consisted of adult subjects with a diagnosis of axSpA and a history of prior therapy for axSpA of at least 12 weeks and an inadequate response or intolerance to NSAID.

3.2. Favourable effects

All three phase III studies met the primary endpoint of superiority over placebo in ASAS 40 response rate at week 16. In addition, most major secondary endpoints (evaluating disease activity, objective signs of inflammation, function and patient reported quality of life) were achieved. Effects were observed as early as after one week and seemed to be maintained over time.

ASAS 40 response at week 16; the primary endpoint of the three main studies

In Study RHBV that included 341 TNF-inhibitor naive r-axSpA, ASAS 40 response at week 16, was reached for 48% of the patient treated with Ixekizumab 80mg Q4W and for 52% of the patient treated with Ixekizumab 80 mg Q2W. Among the patients treated with placebo, 18% reached ASAS 40 at week 16. In the Adalimumab 40mg Q2W group, 36% reached ASAS 40 response. The study was not designed to test non-inferiority of Ixekizumab compared to Adalimumab.

In study RHBW that included 316 TNF-inhibitor experienced r-axSpA, ASAS 40 response at week 16 was achieved for 30.6% in the Ixekizumab 80mg Q2W group, 25.4% Ixekixumab 80mg Q4W and 12.5% Placebo.

In study RHBX that included 303 patients with non-radiographic axial spondyloarthritis, ASAS 40 response at week 16 was achieved for by 40.2% in the Ixekizumab 80mg Q2W, 35.4% Ixekixumab in the 80mg Q4W and in the 19.0% Placebo group.

ASDAS change; a major secondary endpoint of special interest in the three main studies

ASDAS Change from Baseline week 16, LSM (SE) in study RHBV were in the groups IXE 80 mg Q4W, IXE 80 mg Q2W, ADA 40 mg Q2W and PBO: -1.43 (0.102), -1.37 (0.101), -1.30 (0.096) and -0.46 (0.099).

ASDAS Change from Baseline week 16, LSM (SE) in study RHBW were in the groups IXE 80 mg Q4W, IXE 80 mg Q2W and PBO: -1.16 (0.094), -1.13 (0.103) and -0.11 (0.099).

ASDAS Change from Baseline week 16, LSM (SE) in study RHBX were in the groups IXE 80 mg Q4W, IXE 80 mg Q2W and PBO: -1.12 (0.097), -1.26 (0.095) and -0.58 (0.095).

The proposed posology is a bolus dose of 160 mg, followed by 80 mg by subcutaneous injection every 4 weeks which is acceptable by CHMP.

3.1. Uncertainties and limitations about favourable effects

It is not established whether all patients with axSpA will benefit from ixekizumab since all patients in the 3 pivotal studies had previous treatment with conventional therapy for at least 12 weeks and had not responded or was intolerant to NSAID. Thus, the initially broad indication proposed by the applicant was considered not justified and has been revised at the CHMP's request to adequately reflect the intended population.

In study **RHBX**, examining patients with nR-axSpA eligible subjects were requested to have objective signs of inflammation, specified as sacroiliitis on MRI or elevated C-reactive protein (CRP). At the CHMP's request, the MAH added "as indicated by elevated CRP and / or MRI", to the indication wording for patients with nR-axSpA for clarification.

In nr-axSpA in particular, it is not established whether treatment in a well responding patient should be continued on a chronic basis, or whether dose tapering or even treatment discontinuation can be considered at some point. The MAH indicated to currently collect randomised withdrawal data in the ongoing study RHBY. The MAH has committed, based on CHMP's recommendation, to submit the results post-approval in line with the EU Guideline on axSpA.

3.2. Unfavourable effects

Currently, the ixekizumab safety database comprises a total of 8421 ixekizumab-treated patients with Ps, PsA, r-axSpA, and nr- axSpA equating to 21,064.1 patient-years of exposure. The most common adverse events associated with ixekizumab includes infections, neutropenia, thrombocytopenia, allergic reactions, gastrointestinal disorders and injections site reactions.

A total of 929 patients with axial spondyloarthritis have been exposed to ixekizumab, whereof 738 (79.4%) for more than 1 year. The proportion of subjects with AEs, SAEs, infections, allergic reaction and injection site reactions in the 16-week placebo-controlled period of the pivotal studies appeared similar in the adalimumab and ixekizumab groups and not remarkably higher than in the placebo group. During the placebo-controlled parts of the study, adverse events were reported for 162/291 subjects (55.7%) treated with ixekizumab Q4W, 163/283 subjects (57.6%) treated with ixekizumab Q2W and 138/294 subjects (46.9%) treated with placebo. The corresponding number of subjects for adalimumab-treated subjects in RBHV were 44/90 subjects (48.9%).

Infections occurred with a similar frequency in the ixekizumab (23.3% and 26.5%) and adalimumab (21.1%) groups. The most frequent infections were nasopharyngitis and upper respiratory tract infections. There were no cases of TB reported. The findings in the 16-week placebo-controlled period does not evoke any further concern. Infections are included in the SmPC 4.3,4.4 and 4.8.

The warning in Section 4.4 of the SmPC regarding the use in patients with chronic infections and when a chronic infection starts whilst on treatment is updated to state that the warning applies also to patients with history of recurrent infections and to clarify the instructions to the HCP.

Injection site reactions were reported for a higher proportion of patients treated with ixekizumab Q2W than for adalimumab in the direct comparison (RHBV). During the placebo-controlled 16 weeks of the studies, injection site reactions were noted among 7.1% of ixekizumab-treated patients. In the PsA studies, injections site reactions were observed among 12% of ixekizumab-treated subjects during the first 24 weeks, and therefore the current findings do not constitute a new safety concern.

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.

3.3. Uncertainties and limitations about unfavourable effects

About 1/3 of the patients were on concomitant treatment with DMARD, the most common being Sulfasalazine (SSZ). The term DMARD is broad and different DMARDs do not have the same mode of action or safety profile. Of the cDMARDs allowed in the studies, only sulfasalazine is recommended (off label) in treatment guidelines on axSpA, and then in the setting of peripheral arthritis. The MAH was requested to provide safety data on ixekizumab and sulfasalazine in combination, compared to ixekizumab in monotherapy and the provided data did not evoke any further concerns.

No new safety concerns have been identified in these studies although some imbalance in a few AEs were seen. These events (UTI, Diarrhoea infectious and Depression related or suicide/self injury) will be followed by the MAH in the next PSUR.

3.4. Effects Table

Table 56: Effects Table for Taltz for axSpA.

Effect	Short description	Unit	Treatment		Control		Uncertainties / Strength of evidence	References
			Favourable Effects					
			IXE 80 mg Q4W	IXE 80 mg Q2W	ADA 40 mg Q2W	PBO		
ASAS40 week 16	Clinical response in bDMARD-naïve r-axSpA	%	48.1%	51.8%	35.6%	18.4%	p<.05 for comparison vs placebo for both doses of IXE	RHBV
ASAS40 week 16	Clinical response TNFi-Experienced r-axSpA	%	25.4%	30.6%		12.5%	p<.05 for comparison vs placebo for both doses of IXE	RHBW
ASAS40 week 16	bDMARD-Naive nr-axSpA	%	35.4%	40.2%		19.0%	p<.05 for comparison vs placebo for both doses of IXE	RHBX
ASDAS Change from Baseline week 16, LSM (SE)	Disease Activity Score change in bDMARD-naïve r-axSpA		-1.43 (0.102)	-1.37 (0.101)	-1.30 (0.096)	-0.46 (0.099)	p<.001 for comparison vs placebo for both doses of IXE	RHBV

Effect	Short description	Unit	Treatment		Control		Uncertainties / Strength of evidence	References
ASDAS Change from Baseline week 16, LSM (SE)	Disease Activity Score change in TNFi-Experienced r-axSpA		-1.16 (0.094)	-1.13 (0.103)		-0.11 (0.099)	p<.001 for comparison vs placebo for both doses of IXE	RHBW
ASDAS Change from Baseline week 16, LSM (SE)	Disease Activity Score change in bDMARD-naïve r-axSpA		-1.12 (0.097)	-1.26 (0.095)		-0.58 (0.095)	p<.001 for comparison vs placebo for both doses of IXE	RHBX
			Unfavourable Effects					
TEAE	Patients with ≥TEAE, PBO-controlled period; week 1-16	%	55.7%	57.6%		46.9%		Placebo Controlled axSpA Integrated Analysis Set
Infections			26.5%	23.3%		15.6%		
Allergic reactions/hypersensitivity			2.4%	4.2%		1.7%		

Abbreviations: ASDAS = Ankylosing Spondylitis Disease Activity Score; Q2W = every 2 weeks; Q4W = every 4 weeks; r-axSpA =Radiographic Axial Spondyloarthritis, nr-axSpA= Non-Radiographic Axial Spondyloarthritis. ASDAS = Ankylosing Spondylitis Disease Activity Score; LSM = least squares mean; SE= standard error

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

Clinically relevant and statistically significant effects have been shown for ixekizumab in the treatment of r-axSpA in both bDMARD naïve and bDMARD experienced patients. In addition, clinically relevant efficacy has been shown for ixekizumab in nr-axSpA patients.

The initially proposed indication targeted all subjects with active axSpA, although the studied populations were restricted to subjects with prior experience of conventional treatment. At the CHMP's request, the MAH has revised the indication for both the r-axSpA and nr-axSpA populations to reflect the intended population.

In study **RHBX**, examining patients with nR-axSpA eligible subjects were requested to have objective

signs of inflammation, specified as sacroiliitis on MRI or elevated C-reactive protein (CRP). At the CHMP's request, the MAH added "as indicated by elevated CRP and / or MRI", to the indication wording for patients with nR-axSpA for clarification.

The wording of the indication is as follows:

Axial spondyloarthritis

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis

Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

The proposed posology is a bolus dose of 160 mg, followed by 80 mg by subcutaneous injection every 4 weeks which is acceptable by CHMP.

The safety profile for ixekizumab in the current application is considered overall consistent with prior experience in other indications and no new concerns have arisen.

Slight imbalances in some AEs, namely UTI, Diarrhoea infectious and Depression related or suicide/self-injury were observed. These issues will be followed by the MAH in the next PSUR.

3.5.2. Balance of benefits and risks

Ixekizumab has demonstrated a positive and clinically meaningful effect on the treatment of axial spondylarthritis. The identified risks in the pivotal Phase III studies for axSpA are considered to be consistent with those previous established in the psoriasis and psoriatic arthritis submissions.

3.6. Conclusions

The overall B/R of Taltz for the treatment of the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy and for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs) is positive.

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 - Changes to therapeutic indications - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with active axial spondyloarthritis; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC and relevant section of the PL are updated. The PI was also brought in line with the latest QRD template version 10.1. Furthermore, the applicant took the opportunity to update the local representative of Estonia in the PL. In addition, the RMP was updated to version 6.3.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

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

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Taltz-H-C-3943-II-0030'