25 February 2016
EMA/CHMP/190631/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Taltz

International non-proprietary name: ixekizumab

Procedure No. EMEA/H/C/003943/0000

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
AESI	adverse event of special interest
BSA	Body Surface Area
DLQI	Dermatology Life Quality Index
IBD	inflammatory bowel disease
IgG	immunoglobulin G
IL	interleukin (eg, IL-17A; a proinflammatory cytokine produced by Th17 cells)
MAb	monoclonal antibody
NAb	neutralising antibodies
NAPSI	Nail Psoriasis Severity Index
NMSC	non-melanoma skin cancer
NRI	nonresponder imputation
NRS	Numeric Rating Scale
PASI	Psoriasis Area and Severity Index
PPASI	Psoriasis Palmoplantar Severity Index
PSAB	Psoriasis Skin Appearance Bothersomeness
PSSI	Psoriasis Scalp Severity Index
Q2W	every 2 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology–Self Report (16 Items)
sPGA	static Physician Global Assessment
TE-ADA	treatment-emergent anti-drug antibodies
TNFα	tumour necrosis factor alpha

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 23 April 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Taltz, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

The applicant applied for the following indication: Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ixekizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0090/2012 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0090/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance ixekizumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19/05/2011. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application. A new application was filed in the USA.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Greg Markey

- The application was received by the EMA on 23 April 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2015.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 10 September 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2015.
- During the PRAC meeting on 3 December 2015, the PRAC endorsed the PRAC Rapporteur Assessment Report.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 10 February 2016.
- During the meeting on 25 February 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Taltz.

2. Scientific discussion

2.1. Introduction

Psoriasis is a chronic, relapsing / remitting skin disease affecting about 2% to 3% of the population worldwide (Christophers 2001; International Federation of Psoriasis Associations [IFPA] 2014), with rates varying across ethnic groups and geographic regions.

Psoriasis is characterized by red, scaly patches, papules and plaques that usually itch. Lesions vary in severity from minor localized patches to complete body coverage. The most common form, affecting up to 90% of people with psoriasis, is plaque psoriasis that appears on elbows, knees, scalp and back. Nail changes such as pitting or discolouration occur in up to 50% of people with psoriasis.

A diagnosis of psoriasis can be made through examination of the skin, scalp and nails. Special blood tests or diagnostic procedures such as skin biopsy are usually not needed to make the diagnosis. Skin biopsy, if obtained, typically shows excessive growth and thickening of the epidermal layer of the skin due to keratinocyte hyperproliferation with an inflammatory infiltrate of T-cells.

Psoriasis is known to have a negative impact on the quality of life of the affected person. Depending on the severity and location of outbreaks, individuals may experience significant physical discomfort and some disability. Itching and pain can interfere with basic functions, such as self-care and sleep. Participation in sporting activities and certain occupations can be difficult for those with plaques located on their hands and feet. Plaques on the scalp can be particularly embarrassing for cosmetic reasons because plaques flake.

There are 3 primary forms of treatment for psoriasis: topical therapy, phototherapy, and systemic therapy. Systemic therapies can further be classified as conventional agents and biologic agents. Topical therapies are insufficient for long-term therapy for patients with moderate-to-severe disease. Psoralen UVA therapy (PUVA) and narrowband ultraviolet B (NB UVB) phototherapy can be used for more extensive disease and/or when topical therapies have failed (Menter et al. 2010) but very high level responses are rarely obtained. Conventional systemic therapy, including methotrexate, cyclosporine, and acitretin, rarely provide the high level responses that are of greatest importance to patients who suffer from moderate-to-severe psoriasis. While these medications are effective in some patients many will need to transition to other therapies over time to achieve appropriate treatment goals. Available biologic agents include TNF antagonists (adalimumab, etanercept, infliximab), anti-IL-12/IL-23 (ustekinumab), and anti-IL-17A (secukinumab).

About the product

Ixekizumab is a humanised monoclonal antibody (MAb) designed to selectively inhibit interleukin 17A (IL-17A). IL-17A belongs to a family of 6 members: IL-17A, B, C, D, E (or IL-25), and F. The biologically active form of IL-17A consists of either IL-17A homodimers or IL-17A-IL-17F heterodimers.

The development of new products for the treatment of psoriasis is covered in the CHMP Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 2004) and was taken into account in the development of Taltz.

The applicant also received Scientific Advice on the development of ixekizumab from the CHMP. The Scientific Advice pertained to clinical aspects of the dossier.

Indication and dosage

The initially proposed indication was “Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy”.

The recommended indication is “Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy”.

The recommended posology is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.

2.2. Quality aspects

2.2.1. Introduction

Ixekizumab is a monoclonal antibody against the pro-inflammatory cytokine interleukin-17A (IL-17A). Ixekizumab is constructed as an IgG4 isotype, which is known to have low binding affinity to Fcγ receptors or components of the complement system. Ixekizumab is produced in CHO cells.

Ixekizumab active substance is formulated in a citrate-buffered solution containing citrate, NaCl, polysorbate 80, pH 5.4–6.0.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.2.2. Active Substance

General information

Ixekizumab is a humanised immunoglobulin G4 (IgG_4) isotype monoclonal antibody composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. Ixekizumab binds to and neutralises IL-17A. The binding affinity (KD) of ixekizumab to IL-17A is <1 pM at 25°C. Each heavy chain contains an N-linked glycosylation site at Asn296 which is modified with oligosaccharides.

The ixekizumab hinge sequence contains a Ser to Pro substitution (S228P based on EU-index numbering, or S227P based on the actual amino acid sequence of ixekizumab heavy chain). The S228P substitution reduces the frequency of half-antibody formation, or other heterologous antibody combinations, sometimes observed with IgG_4 antibodies. In addition, the terminal lysine of the wild type IgG_4 was removed (K447 deletion, desK447, EU numbering) to eliminate heterogeneity generated *in vivo* by the proteolytic clipping of the C-terminal lysine.

Manufacture, characterisation and process controls

Manufacture and process controls

Information on the manufacturing, storage and control facilities for ixekizumab active substance is provided in the dossier.

A cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) is used for the manufacture of the active substance. Following expansion of the cell culture in a production bioreactor, the active substance is purified with a series of chromatography, viral inactivation and filtration steps. The purified active substance is then dispensed and frozen for storage.

The compatibility and protection provided by the container closure system were confirmed.

Control of critical steps and intermediates

The principles applied in the development of the commercial active substance process and control strategy incorporate an enhanced, risk-based approach in the design of the manufacturing process. The manufacturing process is divided into the different unit operations where the performance in process is controlled throughout production using a combination of in-process tests, in-process specifications and defined operation ranges for process parameters.

Control of materials

Characterisation of cell banks was performed according to ICH Q5A to support genetic stability up to 55 population doublings, starting from MCB. Procedures for preparation and acceptance criteria of future WCBs were described. Overall, the quality of starting material and raw material is well defined.

Process validation

Process validation of the ixekizumab active substance manufacturing process was performed at the Lilly Kinsale manufacturing site to demonstrate that the commercial scale manufacturing process performs consistently and is capable of meeting pre-determined acceptance criteria. Process validation studies were conducted according to prospective protocols and encompassed the elements such as process characterisation, process verification, clearance of process impurities, process intermediate hold times, in-process microbiological monitoring, chromatography column life, reprocessing studies as well active substance shipping evaluation. All five validation batches fulfilled the acceptance criteria and showed good reproducibility.

Manufacturing process development

Comprehensive data are presented supporting comparability of active substance over time in development. Besides data from the release testing, results are reported from the analysis of the oligosaccharide profile, charge distribution of the antibody, hydrodynamic structure, thermal stability profile, reduced and non-reduced peptide map as well as orthogonal methods supporting comparable primary, secondary and tertiary structure.

Characterisation

The ixekizumab active substance was thoroughly characterised using state-of-the-art methods. Extensive studies are reported from the characterisation of the different product-related impurities resolved in the size-exclusion high-performance liquid chromatography (SE-HPLC) and capillary electrophoresis sodium dodecyl sulfate (CE-SDS) (reduced and non-reduced) analyses used for release control of purity, including identification of different structural variant and information of the analytical techniques applied.

Specification

Specifications

The in-house methods applied to specify active substance include the following: cell-based assay (potency, identity), UV (assay), cation exchange chromatography (identity, charge heterogeneity), size exclusion chromatography (purity, aggregates), reduced and non-reduced CE-SDS (purity).

Descriptions of analytical methods also include requirements for system suitability criteria and the methodology is well described. The in-house analytical methods were validated according to recommendations in ICH Q2. For tests also applied to finished product, validation reports include both

active substance and finished product. Batch data was provided from commercial scale batches. A comprehensive toxicological evaluation and data from manufacturing capacity was provided to support consistent removal of process-related impurities not included in the list of specifications. In addition, batch data was provided to support consistency in sulfhydryl content and carbohydrate pattern, which is not planned to be part of release testing of active substance. Overall, the provided batch data are supportive for a consistent manufacture of ixekizumab.

Reference standard

Primary and working reference standards were prepared from the same Phase 3 clinical trial active substance batch (BR101835). Acceptance criteria were provided for regular requalification of these standards. Whereas the primary standard is expected to last for indefinite time, defined acceptance criteria for future working standards are provided. In case of a new primary reference standard is required an application for change will be submitted. Any modifications to the list of specifications of active substance emanating from this evaluation should also be included in the acceptance criteria of reference standards.

Stability

Stability data at the long-term storage condition was provided to support the proposed shelf life for the active substance. All results have remained within the proposed acceptance criteria.

A comprehensive study on stressed material was also provided.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description and composition of the finished product

Ixekizumab injection, 80 mg/1 mL, is supplied as a sterile solution in a 1 mL type I glass syringe, intended for single use and subcutaneous administration. The commercial finished product formulation contains the active pharmaceutical ingredient, ixekizumab, in a matrix consisting of the inactive ingredients citrate buffer, sodium chloride, polysorbate 80, and water for injections.

Six pack sizes are proposed:

- One, two or three single use pre-filled syringes;

- One, two or three pre-filled pens (syringe encased in a disposable, single-dose pen).

Pharmaceutical Development

Quality by Design principles were implemented during development of the formulation and the manufacturing process for finished product. Extensive documentation was provided and the results were clearly presented. No design space was claimed.

The ixekizumab solution formulation was developed and optimised based on pre-formulation studies, pharmaceutical development experience and statistical Design of Experiments (DOE) studies.

Manufacturing Process Development

The manufacturing processes developed for the ixekizumab low and high dose lyophilised finished products for Phase 1 and Phase 2 utilised early phase platform processes and controls suitable for the manufacture of these clinical scale batches. The ixekizumab solution semi-finished syringe manufactured for Phase 3 clinical trials utilised a manufacturing process at commercial scale that was further optimised for finished product validation and commercial manufacturing. The manufacturing process for the ixekizumab finished product semi-finished syringe was developed based on development studies, experience in manufacturing and scaling up clinical trial supplies, and process characterisation studies designed to assess the robustness of the manufacturing process.

The manufacturing site for Phase 3 clinical supplies was changed during development. Based upon the results presented on comparability between batches produced at Vetter and Lilly, the finished product from both sites is judged as comparable. The analytical results presented on the biological, biochemical and biophysical as well as stability testing did not display any significant differences.

Container Closure System

The primary container closure system for ixekizumab injection is a 1 mL-long clear glass staked needle syringe barrel with a small round finger flange, and closed with an elastomeric plunger and rigid needle shield.

The container closure system was selected based on the results of screening, characterisation, and design verification and qualification studies intended to demonstrate the suitability of the container closure system for use with ixekizumab injection in the delivery device. The ixekizumab injection was supplied as an 80 mg/mL solution finished product in a 1 mL glass semi-finished syringe (SFS) assembled into a delivery device (prefilled syringe or auto-injector) for subcutaneous administration.

Manufacture of the product and process controls

The semi-finished syringe manufacturing process includes five processes steps: buffer excipient solution compounding, finished product formulation compounding, sterile filtration, aseptic syringe filling and plungering, and inspection. During the assembly process, the semi-finished syringe and the device components are combined into the ixekizumab injection delivery device, the prefilled syringe and/or the auto-injector.

Controls of critical steps and intermediates

Operating ranges for process parameters and acceptance criteria for controls are provided for the parameters/controls that were determined to be critical to ensuring that the Critical Quality Attributes are met (e.g., Critical Process Parameters (CPP), Critical In-Process Controls (CIPC), and In-Process Specifications (IPS)).

Ranges were also provided for a subset of non-critical process parameters and controls (e.g. Operational Process Parameters (OPP) and In-Process Controls (IPC)). These select OPPs and IPCs are included to ensure process consistency and were classified as non-critical (not impacting CQAs). Parameters and controls (critical and non-critical) are managed via the internal quality system, including change control management, deviation management, and routine process and product performance monitoring. Changes are reported in regulatory filings in accordance with applicable guidance and regulations.

Process validation

A product control strategy was established during the manufacturing process development. The process validation batch data presented demonstrate that all validation batches complied with the established in-process and release specifications and that the commercial manufacturing process is

robust and performs as intended, giving a finished product which meets the quality requirements. The validation was run at set points while the ranges of process parameters were challenged during the manufacturing process development.

Media fills were used to validate the aseptic filling process and results from process simulations show no contaminated vials. Results and requirements for the media fill validation cover the maximum duration of filling and are in line with current EU requirements.

Product specification

Relevant tests are included in the specification for the finished product. The specifications provided are based on the quality of ixekizumab used in toxicological and clinical testing, the stability of ixekizumab, the variability of the analytical methods used to analyse the finished product, and ICH guidelines. These specifications assure control of the finished product quality and device functionality at release and during storage respectively. The specifications for the ixekizumab semi-finished syringe, the pre-filled syringe and the auto-injector were provided.

Analytical methods have been appropriately validated. The same reference standard is used for active substance and finished product

Batch analysis data were provided for validation batches and primary stability batches for the semi-finished syringe. Batch analysis data were also provided for validation batches for finished product in prefilled syringe and in auto-injector. All batch results presented comply with the limits in the proposed specifications and demonstrate batch-to-batch consistency.

Stability of the product

The proposed shelf-life for ixekizumab finished product is 24 months when stored at the recommended storage condition (2-8ºC). Stability data was provided for the primary stability studies at 5°C and at 25°C/60% RH as well as supportive data at 5°C. The results presented support the proposed 24 month shelf-life at 2-8°C.

The Applicant provided evidence that the secondary packaging is able to protect the finished product from light.

Adventitious agents

Ixekizumab is produced from recombinant CHO cells and cultivated in serum-free media. Starting from the MCB, the manufacturing process is free from animal components. Insulin used as media additive is of recombinant source. During cell cloning, materials of animal origin were used which were shown to have a negligible TSE risk and to be sufficiently safe regarding adventitious virus.

Virus testing of cell banks (MCB, WCB and ECB) is extensive and shows no evidence of adventitious virus. The only type of virus detected is retrovirus-like particles (RVLP) which is a well-known feature of CHO cells. Capacity of the process to remove RVLP was shown by calculating RVLP levels in three commercial batches.

Routine viral testing of unprocessed bulk consists of *in vitro* viral testing (using three indicator cell lines, namely CHO, MRC-5 and Vero) as well as testing for Mouse Minute Virus (MMV).

The viral removal capacity was shown using XMuLV, PPV, PRV and Reo-3 model virus. The major contributing virus reduction steps consist of detergent viral inactivation (Triton X-100), low-pH

treatment and nanofiltration, depending on the nature of the model virus. Protein A chromatography was also shown to contribute to virus reduction to a lesser extent.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active Substance

A key concern identified in the initial assessment is that the descriptions of the commercial manufacturing process, process validation and development of the manufacturing process for the active substance were in parts only brief.

As requested, the Applicant extended the description of the manufacturing process to include further information on the procedures used and the control applied in the processing of product through the three cell culturing and the two chromatography steps. In addition, data was presented supporting control of deamidation and oxidation of active substance over the range in operation for process parameters defined in the dossier. The manufacturing process is now considered sufficiently well-defined to ensure production of active substance of consistent high quality, using procedures that were challenged in process development and evaluated in the process validation studies.

The Applicant has now re-evaluated active substance acceptance criteria with more recently available stability data that demonstrates no discernible trend during storage. The updated proposed active substance specification limits are also taking into account the revised proposed finished product criteria based on clinical experience. Altogether, the proposed specification for active substance is found acceptable (see also discussion on specification on finished product below for further details).

The claimed shelf life for the active substance is based on acceptable full time data.

Finished Medicinal Product

The composition of the finished product is described and Pharmacopoeia references were provided. The excipients in the finished product formulation are commonly used in protein pharmaceuticals; no novel excipients or any materials of human or animal origin are present. The formulation development describes and justifies the chosen commercial formulation (1 mL solution for injection containing 80 mg ixekizumab) and is comprehensive. The development of the container closure system is sufficiently presented. Detailed results from the human factor usability study for the auto-injector and the Instructions for use were provided.

The description of the manufacturing process and process controls and control of critical steps and intermediates is sufficiently described and documented in general. Information concerning the assembly process of the pre-filled syringe and the pre-filled pen was provided. The manufacturing process development was sufficiently described and justifies the commercial ixekizumab semi-finished syringe manufacturing process.

The process validation data is sufficient.

The manufacturing site for Phase 3 clinical supplies was changed during development. Based upon the results presented on comparability between batches produced at Vetter and Lilly, the finished product from both sites is judged as comparable. The analytical results presented on the biological, biochemical and biophysical as well as stability testing did not display any significant differences.

The Applicant provided the proposed specifications for the ixekizumab semi-finished syringe, the prefilled syringe, and the auto-injector. The test items in the proposed specification are in line with the CHMP guideline on monoclonal antibodies (EMEA/CHMP/BWP/157653/2007).

An issue was raised was raised on clinical qualification of limits for potency, purity tests (SEC, reduced and non-reduced CE-SDS) and charge heterogeneity (CEX) since they represent attributes that may impact safety and/or efficacy if outside their limits. For this reason the limits for these in the specifications of the active substance and finished product needed to be in line with what was qualified in clinical studies or qualified by other means. The Applicant re-evaluated the acceptance criteria for purity tests (SEC, reduced and non-reduced CE-SDS), charge heterogeneity and potency in the specifications for both the finished product and active substance. Recent stability data was incorporated in the calculations and levels that were qualified in human clinical trials presented and utilised to propose revised specification acceptance criteria. Clinically qualified limits were determined based upon batches used in human clinical studies and their observed release results, maximum age of each finished product at the time it was dispensed in the clinic and the change on stability. The level of each attribute qualified in human clinical trials is proposed as the finished product end-of-shelf-life specification acceptance criteria. The proposed finished product release criteria were then determined by adjusting the proposed end-of-shelf-life criteria by the change observed over the shelf life of the finished product. The proposed active substance acceptance criteria were revised to allow for potential changes during manufacture and storage of the finished product assuring that the clinically qualified levels will be maintained throughout the proposed finished product shelf life. The principle of adding a factor of measurement uncertainty of a method to the nominal clinical levels for the determination of clinically qualified levels is not considered acceptable in principle terms. However, since the variability of most methods are low and the differences between the revised end of shelf life specification acceptance criteria in the proposed specifications and the actual clinical levels presented are judged as small, the claimed acceptance criteria can be considered as acceptable since they are within the same range as the clinical experience and the small difference seen most likely of negligible impact.

Several limits for purity, charge heterogeneity, and potency were narrowed as requested and justified in relation to clinical experience. This approach was considered acceptable. The revised limits are clinically qualified and are considered satisfactory.

The proposed shelf life for ixekizumab finished product of 24 months when stored at the recommended storage condition, 2-8°C is considered acceptable.

Adventitious agents

An adequate evaluation was performed on the non-viral and viral safety of the animal-derived media components used in cell line development. The Applicant demonstrated that ixekizumab cell cultures are free of detectable adventitious agents. The tested batches met acceptance criteria. Based on the presented results the risk for bacterial, fungal or mycoplasma contamination is minimal.

The evaluation of viral clearance by the purification process focuses on three virus removal/inactivation unit operations.

Virus testing of cell banks (master cell bank (MCB), working cell bank (WCB) and extended cell bank (ECB)) and shows no evidence of adventitious virus. The only type of virus detected is retrovirus-like particles (RVLP) which is a well-known feature of CHO cells. Capacity of the process to remove RVLP was shown.

The relevant unit operations were evaluated for virus removal using four model viruses and a scaled-down laboratory model. As demonstrated the manufacturing process effectively removes enveloped and non-enveloped viruses. Overall, the results of the virus clearance studies are deemed acceptable.

To summarise, virus safety was sufficiently demonstrated.

Safety concerning other adventitious agents including TSE was sufficiently assured.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Taltz is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Taltz is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendations for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

In support of this submission the Applicant submitted data from *in vitro* pharmacology studies with ixekizumab, one *in vivo* pharmacology study, one pharmacokinetic study and multiple preclinical safety studies. The carcinogenicity assessment conducted by the Applicant was primarily based on a review of the literature with summary of evidence from toxicity studies with ixekizumab.

There were no separate safety pharmacology studies. General toxicity studies were all conducted in accordance with GLP. For the cross-reactivity studies, even though the development of the method was conducted in non-GLP conditions, the final study was in compliance with GLP.

The GLP aspects of this application were considered acceptable by the CHMP.

2.3.2. Pharmacology

Interleukin-17A (IL-17A; also known as IL-17) is a member of a 6-member family of cytokines. Biologically active IL-17A exists as a homodimer (A/A) or as a heterodimer (A/F) with IL-17F.

IL-17A is secreted by Th17 cells which are differentiated from CD4+ cells and which function at mucosal barriers and trigger pro-inflammatory signals leading to neutrophil mobilisation and responses that constitute an antimicrobial response: for instance, Th17 cells are involved in protection against pathogens such as *Klebsiella pneumoniae* and *Candida albicans*: IL-17 knockout mice were shown to be more susceptible to infection than normal mice.

Th17 cells also produce other pro-inflammatory cytokines such as IL-6, IL-21, IL-22, tumour necrosis factor-α (TNF-α), granulocyte macrophage colony-stimulating factor (GM-CSF), chemokine "C-X-C motif" ligand 1 (CXCL1; also referred to as growth-related oncogene-α (GRO-α) or keratinocyte chemoattractant (KC)2) and chemokine "C-C motif" ligand 20 (CCL20). In addition, some other cells also produce IL-17A: e.g. CD8+ T cells, CD4+Foxp3+ Treg cells, natural killer cells, neutrophils and mast cells.

Psoriasis is a disorder of keratinocyte hyperproliferation and there is evidence to suggest that IL-17A has a role in the pathogenesis of the disease. Cell types that respond strongly to IL-17A include keratinocytes and psoriatic plaques are known to contain elevated concentrations of T_h17 cells, which there produce excessive amounts of IL-17; IL-17 can directly activate over 40 genes in keratinocytes leading to excess production of several inflammatory cytokines. Other antibodies that target IL-17 pathways (e.g. secukinumab) have also shown activity in patients with psoriasis.

Primary pharmacodynamic studies

In vitro studies

Specificity of Ixekizumab (studybTDR09)

Binding of ixekizumab to human IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, mouse IL-17A, was determined by ELISA with results showing that ixekizumab binds specifically to IL-17A in a concentration-dependent manner but not to any other cytokine tested: including mouse IL-17A or human IL-22 (negative control).

In Vitro Binding Kinetics of Ixekizumab: Surface Plasmon Resonance Analysis

Binding kinetics and affinity of ixekizumab to human, cynomolgus monkey, rabbit, mouse, and rat IL-17A was assessed using surface plasmon resonance (SPR). Results are summarised in **Table 1.**

Table 1. *In Vitro* Binding Parameters of Ixekizumab to Human, Cynomolgus, Rabbit IL-17A Determined Using Surface Plasmon Resonance

IL-17A	*k_{on}	*k_{off}	*†K_D
Human	7.5 (± 1.4) $x10^{6}$	1.3 (± 0.8) $x10^{-5}$	1.8 (± 1.1) $x10^{-12}$
Cynomolgus	7.9 (± 0.3) $x10^{6}$	0.7 (± 0.9) $x10^{-5}$	0.8 (± 1.1) $x10^{-12}$
‡Rabbit	1.5 (± 0.6) $x10^{5}$ 9 (± 3) $x10^{6}$	1.7 (± 0.5) $x10^{-4}$ 1.1 (± 0.2) $x10^{-1}$	1.3 (± 0.6) $x10^{-9}$ 14 (± 4) $x10^{-9}$

* The value reported are averages ± standard deviations calculated from several independent measurements; human
n=11; cynomolgus n=2; rabbit n=4.
† KD is calculated using koff/kon for each measurement, and the final value is average of several independent measurements.

‡ Binding was biphasic and data was fit with heterogeneous ligand models.

Binding constants for ixekizumab for both of the commercially sourced purified recombinant homodimer IL-17A and the IL-17A/F heterodimer were also determined using SPR (**Table 2**).

Table 2. Ixekizumab versus Human IL-17A or IL-17A/F: In Vitro Binding Kinetics Determination Using Surface Plasmon Resonance at 37ºC

	K_{on} (1/Ms)	K_{off} (1/s)	K_D (pM)
IL-17A*	6.98 (± 0.18) x 10^6	≤2 x 10-5	≤ 3
IL-17A/F*	7.32 (± 0.07) x 10^6	≤ 2 x 10-5	≤ 3

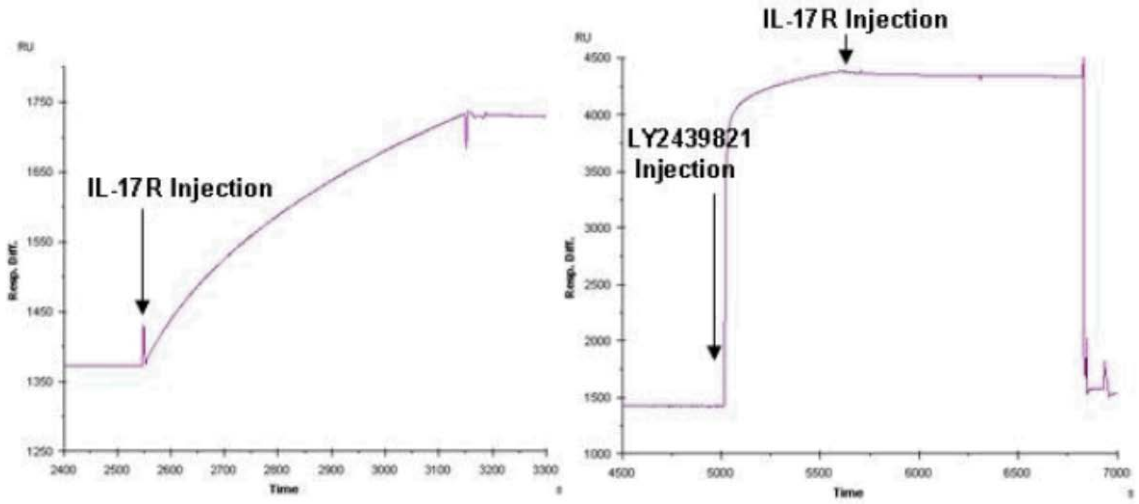
(Note: Data is the mean ± standard deviation from 3 assays. The K_{off} for each cycle of IL-17A or IL-17A/F was ≤ 2 x 10^{-5} which is the cutoff for measurable dissociation as tested. Therefore, the K_{off} is reported as ≤ 2 x 10^{-5}, and the KD is reported as ≤ 2 x 10^{-5} / Kon.)

Ixekizumab Blocks IL-17A Binding to the IL-17 Receptor: Surface Plasmon Resonance Analysis (Study bTDR68)

SPR was also used to test the effect of ixekizumab on the interaction between human IL-17 and the human IL-17 receptor. For this, human IL-17A was immobilised onto a chip. Binding of human IL-17 to human IL-17 receptor was shown by injecting 50 µl of a solution containing human IL-17A receptor and observing the change in SPR signal when this was done. Binding to reconstituted human IL-17 of ixekizumab was then assessed by injecting 50 µl of a solution of ixekizumab (500 nM). This was reported to nearly saturate IL-17A. Each of human IL-17A receptor and ixekizumab were able to bind to human IL-17A.

Ixekizumab was injected at 500 nM, followed by injection of human IL-17A receptor at 1 µM. In this circumstance, it was determined that once human IL-17A bound ixekizumab, it could not then bind any human IL-17A receptor (see **Figure 1**).

Figure 1. In vitro binding of IL-17R or ixekizumab (LY2439821) to immobilised human IL-17A.

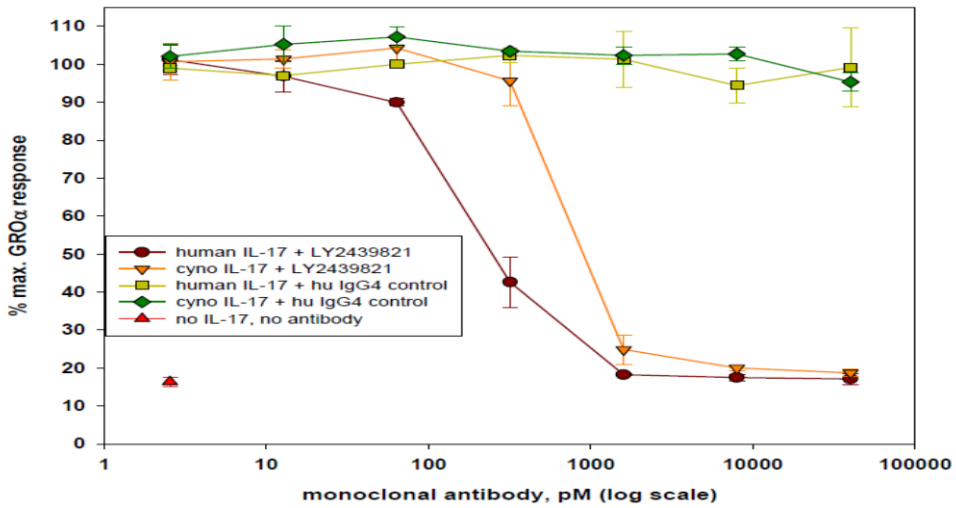


In Vitro Neutralization Assay for Ixekizumab (Study bTDR13 and bTDR130)

The effect of ixekizumab on IL-17A induced secretion of growth-related oncogene-α (GROα) from the human colorectal adenocarcinoma epithelial cell line HT-29 was analysed to determine functional inhibition of IL-17A. HT-29 cells were treated with a constant amount of either human IL-17A (60

ng/mL = 1875 pM), or cynomolgus monkey IL-17A (60 ng/mL = 1618 pM), in the presence of either ixekizumab or control human IgG4. After approximately 48 hours, levels of GROα in the culture media were measured by ELISA. Data presented are the mean ± standard deviation of triplicate wells per treatment (**Figure 2**).

Figure 2. Neutralization of IL-17A induced secretion of GROα by ixekizumab (LY2439821)



Similar results were obtained when assessing the ability of ixekizumab to inhibit IL-17A/F induced secretion of GROα by ixekizumab (data not shown).

In Vitro Analysis of Human Fc Receptor and Complement Binding of Ixekizumab (Study bTDR171)

Binding of ixekizumab to human Fcγ receptors (I [CD64], IIa [CD32a], IIIa [CD16a] and also to complement component C1q) was investigated to determine the potential for cell-mediated effects.

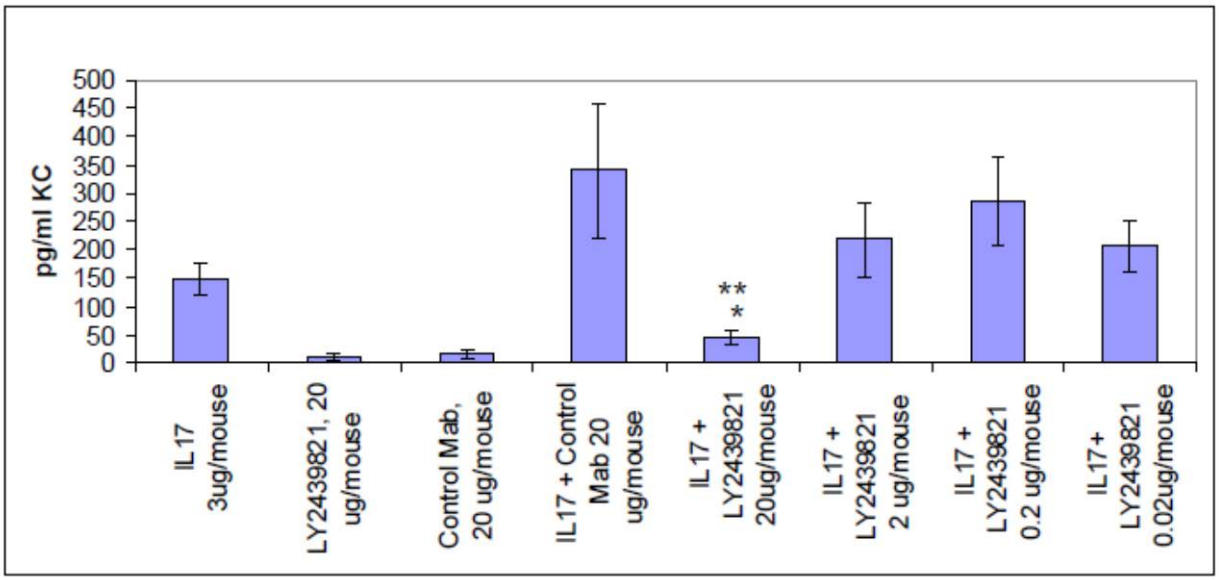
For these assays, 96-well plates were coated with each of the respective receptors with C-terminal His tags and after preparation were incubated with ixekizumab or with a positive control human IgG1 or with a negative control human IgG4 at concentrations of 6.25-200 µg/ml (for CD32a, CD16a and C1q). After allowing for binding to take place, bound antibody was detected after a washing step, using horseradish perioxidase-conjugated goat anti-human IgG Fab and use of the chromogenic substrate TMB with detection at 450 nm. Similar methods were applied to CD64 binding but antibodies were tested at concentrations of 0.001-300 µg/ml. Results indicated that ixekizumab does not bind to any of the tested receptors (data not shown).

In vivo studies

Neutralization of Human IL-17 by LY2439821: In Vivo Study Using Mice (Study bTDR08)

The purpose of this study was to demonstrate that ixekizumab is able to block the plasma increase of the mouse homologue of human GRO-α, keratinocyte chemoattractant chemokine (KC), mediated by the binding of human IL-17A to murine IL-17A receptors. Ixekizumab was administered intravenously to female C57BL/6 mice (n = 5/group; 8 to 12-week old) 1 hour prior to a subcutaneous injection of human IL-17A. At 2 hours post-IL-17A administration, blood samples were collected and KC levels in the plasma were determined by ELISA. Human IgG4 was used as a negative control antibody.

Figure 3. Ixekizumab suppresses human IL-17 induced Keratinocyte Chemoattractant in mouse plasma



The error bars represent the standard error.

*** p<.05 to IL-17A + 20 μg control IgG; * p<.05 to 3 μg IL-17A based on Students t-test.*

Secondary pharmacodynamic studies

The secondary pharmacodynamic studies were conducted with two available rat anti-mouse IL-17A antibodies (LSN2886817 and LSN2805474) and their main findings are summarised in **Table 3.**

Table 3. Secondary pharmacology studies and findings

Study	Method	Findings
In Vitro Binding Kinetics of Surrogate Antibodies: Surface Plasmon Resonance Analysis (bTDR69 and bTDR90)	In vitro; Antibody affinities to various species of IL-7A (KD = koff /kon) were determined using a BIAcore biosensor 2000 and BIAevaluation software with a 1:1 binding with mass transfer model.	LSN2886817 and LSN2805474 bound to murine IL-17A with calculated equilibrium dissociation constants (K_D) of 185 pM and 4 pM, respectively. LSN2886817 binds to rat IL-17A with a K_D of 470 pM. LSN2805474 shows a biphasic binding profile and was fit with a heterogeneous ligand model. The weak affinity binding site has a K_D of 5.2 nM , and the stronger affinity site has a K_D of 920 pM
In Vitro Neutralization Assay for Surrogate antibodies (bTDR79)	In vitro; 4T1 cells were treated with a constant amount of either mouse or rat IL-17A (5 ng/mL), in the presence of either LSN2805474 or LSN2886817 or isotype control antibodies 0.00096 to 75 µg/mL). After approximately 72 hours, levels of KC in the culture media were measured by	The mouse mammary gland epithelial tumor cell line 4T1 secreted KC when stimulated with mouse or rat IL-17A, in a dose-dependent manner. Both LSN2805474 and LSN2886817 inhibited mouse IL-17A-induced KC secretion from 4T1 cells, in a dose-dependent manner. LSN2886817 also inhibited rat IL- 17A-induced KC secretion. In contrast, LSN2805474 did not inhibit rat IL-17A-induced KC secretion from 4T1 cells. The isotype control antibodies did not inhibit mouse or rat IL-17A-induced KC secretion

	ELISA.	
Epitope Mapping for Surrogate Antibodies (bTDR114)	In vitro; Western blot under non-reducing and reducing conditions, hydrogen-deuterium exchange mass spectrometry (H/DXMS), amino acid alignment and in vitro cell-based bioassay (KC secretion from 4T1 cells)	Both LSN2805474 and LSN2886817 were able to recognize mouse IL-17A on a Western blot under non-reducing conditions. However, when mouse IL-17A was run under reducing conditions both antibodies recognized it poorly. H/DXMS data indicates that the LSN2805474 epitope lies within amino acids 49-102. Alignment of the amino acid sequences for human, mouse and rat IL-17A confirms many amino acid differences between human and the two rodent species in this region however, there is only a single amino acid difference between mouse and rat. Four mutants were created by changing the amino acid sequence from mouse to rat. Data suggest that LSN2805474 and LSN2886817 have overlapping but distinct amino acids that are critical contact points with murine IL-17A. Although the full epitope for LSN2805474 and LSN2886817 was not elucidated, they bind murine IL-17A with a distinct epitope compared with ixekizumab binding to human IL-17A

Safety pharmacology programme

Safety pharmacology endpoints were incorporated within 8-week and 39-week repeat-dose toxicity studies in young adult (2-to 4-year old) cynomolgus monkeys and are summarised in **Table 4**.

Table 4. Safety pharmacology studies

Species, Type of study, GLP, Study no	**Gender and no/grp**	**Method of Admin, Duration of dosing**	**Doses (mg/kg)**	**Safety pharmacology findings**
Monkey, Cynomolgus, Cardiovascular /Respiratory/Central nervous, GLP, 6180-918	3/sex/group	Iv, 8 weeks, ECG on day 8, week 4 and day 50	0, 5, 15, 50	No compound-related respiratory, neurological, or body temperature findings were observed. All the electrocardiograms were qualitatively within normal limits. No arrhythmias were found. There were also no statistically significant electrocardiographic findings considered attributable to the administration of Ixekizumab.
Monkey, cynomolgus, cardiovascular /central nervous, GLP, 7608-478	4/sex/group	Sc, 39 weeks, ECG 48-hours postdose on day 85, 176, and 260	0, 0.5, 5, 50	Animals were anesthetized with ketamine prior to ECG measurements. No effects on heart rate or on QT or corrected-QT intervals. All ECGs were qualitatively and quantitatively within normal limits and no arrhythmias were found. No effect on body temperature and all animals were observed as neurologically normal with no remarkable findings.

Pharmacodynamic drug interactions

No non-clinical drug-interaction studies have been performed with ixekizumab.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of ixekizumab (LY2439821, LA426-3C3) were evaluated following single and repeat-dose administration in Cynomolgus monkeys, as this was the primary species used for the toxicology program. In addition, the toxicokinetics were evaluated in pregnant monkeys in support of the developmental and reproductive toxicology studies. Both intravenous (IV) and subcutaneous (SC) routes of administration were investigated with ixekizumab in the PK and TK studies. For all TK studies, the concentrations of immunoreactive ixekizumab were determined by a validated antigen-capture enzyme-linked immunosorbent assay (ELISA).

Single-Dose pharmacokinetics

Single-dose pharmacokinetics of ixekizumab was evaluated in male cynomolgus monkeys following IV or SC administration of 1 mg/kg (Study 6180-791).

Table 5. Mean Pharmacokinetic Parameters of Ixekizumab in Cynomolgus Monkeys Following Intravenous or Subcutaneous Administration of 1 mg/kg

Parameter	Intravenous	Subcutaneous
AUC_{last} (µg•hr/mL)	2253 (2792/1714)	3314 (3771/2857)
t½ (hr)	156 (192/120)	246 (287/204)
CL (mL/hr/kg)	0.448 (0.323/0.573)	0.262 (0.207/0.317)
V_{ss} (mL/kg)	87.0 (88.7/85.2)	ND
C_{max} (µg/mL)	21.1 (18.2/24.0)	11.1 (12.4/9.8)
T_{max} (hr)	ND	72 (96/48)
n	2	2

Abbreviations: AUC_{last} = area under the concentration curve, t½ = half-life, CL = clearance, V_{ss} = volume of distribution at steady state, C_{max} = maximum concentration, T_{max} = time to maximum concentration, ND = not determined, n = number of animals. Individual animal data in brackets.

Repeat-Dose toxicity

The serum toxicokinetics of ixekizumab were determined in male and female cynomolgus monkeys over approximately 8-, 13-, and 39- weeks (**Tables 13, 14** and **15**).

Table 6. Summary of Mean Toxicokinetics in Male and Female Cynomolgus Monkeys Following Weekly Subcutaneous Administration of 5-, 15-, or 50-mg/kg Doses of Ixekizumab (LY2439821) for 8 Weeks (n = 3 unless otherwise indicated) (Study 6180-918)

		Administered Dose (mg Ixekizumab/kg)					
		5		15		50	
Parameter	Sex	M	F	M	F	M	F
Day 1							
C_{max} (µg/mL)		104	110	463	507	1700[a]	1670[a]
SD C_{max}		1.5	14.6	73.1	87.5	262	257
$AUC_{0\text{-}168hr}$ (µg•hr/mL)		7160	8580	30100	35100	104000[a]	109000[a]
SD $AUC_{0\text{-}168hr}$ (µg•hr/mL)		359	995	5370	5610	11600	16700
Day 57							
C_{max} (µg/mL)		NA	NA	NA	NA	2610	1900

SD C_{max}		NA	NA	NA	NA	81.4	356
$AUC_{0\text{-}168hr}$ (µg•hr/mL)		NA	NA	NA	NA	241000	180000
SD $AUC_{0\text{-}168hr}$ (µg•hr/mL)		NA	NA	NA	NA	25400	4000
Half-life (hr)		NA	NA	NA	NA	303	276
SD Half-life (hr)		NA	NA	NA	NA	71.6	61.5

Abbreviations: $AUC_{0\text{-}168hr}$ = area under the plasma concentration-time curve from 0 to 168 hours, C_{max} = maximum observed serum concentration, F = Female, M = Male, SD = standard deviation, NA = not applicable. [a] number of animals = 6.

Table 7. Summary of Mean Toxicokinetics in Male and Female Cynomolgus Monkeys Following Weekly Subcutaneous Administration of 0.5-, 5-, or 50-mg/kg Doses of Ixekizumab (LY2439821) for 39 Weeks (n = 4 unless otherwise indicated) (Study 7608-478)

		Administered Dose (mg Ixekizumab/kg)					
		5		15		50	
Parameter	Sex	M	F	M	F	M	F
Day 1							
C_{max} (µg/mL)		5.11	4.62	43.9	45.8	423[a]	450[a]
SD C_{max}		0.58	0.34	5.1	3.2	59	60
$AUC_{0\text{-}168hr}$ (µg•hr/mL)		705	615	6043	6166	57160[a]	58312[a]
SD $AUC_{0\text{-}168hr}$ (µg•hr/mL)		89	30	698	268	7322	4249
Day 267							
C_{max} (µg/mL)		NA	NA	NA	NA	1215[b]	855[b,c]
SD C_{max}		NA	NA	NA	NA	NA	NA
$AUC_{0\text{-}168hr}$ (µg•hr/mL)		NA	NA	NA	NA	168595[b]	119305[b,c]
SD $AUC_{0\text{-}168hr}$ (µg•hr/mL)		NA	NA	NA	NA	NA	NA
Half-life (hr)		NA	NA	NA	NA	337	188

Abbreviations: $AUC_{0\text{-}168hr}$ = area under the plasma concentration-time curve from 0 to 168 hours, Cmax = maximum observed serum concentration, F = Female, M = Male, SD = standard deviation, NA = not applicable. [a] number of animals = 6, [b] number of animals = 2, [c] One of the 2 females in the recovery group had a positive antidrug antibody response and decreased serum ixekizumab concentrations following the last dose on Day 267.

Table 8. Summary of Mean Toxicokinetics in Male and Female Cynomolgus Monkeys Following Weekly Subcutaneous Administration of 50- mg/kg Doses of Ixekizumab (LY2439821) for 13 Weeks (n = 6) (Study 20003965)

		Administered Dose (mg Ixekizumab/kg)	
		50	
Parameter	Sex	M	F
Day 1			
C_{max} (µg/mL)		426	456
SD C_{max}		63.9	60.6
$AUC_{0\text{-}168hr}$ (µg•hr/mL)		59995	63398
SD $AUC_{0\text{-}168hr}$ (µg•hr/mL)		10771	6686
Day 85			
C_{max} (µg/mL)		1238	1073
SD C_{max}		259	125
$AUC_{0\text{-}168hr}$ (µg•hr/mL)		179279	153865
SD $AUC_{0\text{-}168hr}$ (µg•hr/mL)		40962	18128

Abbreviations: $AUC_{0\text{-}168hr}$ = area under the plasma concentration-time curve from 0 to 168 hours, Cmax = maximum observed serum concentration, F = Female, M = Male, SD = standard deviation

Interspecies comparison

Table 9. Toxicokinetics interspecies comparison between cynomolgus monkeys and humans

Species Data Source	Dose	Steady-State Exposure (AUC) (mg*hr/mL)	Exposure (AUC) based Margin of Safety[a]
Human Population pharmacokinetic model	80 mg Q2W for 12 weeks following a 160 mg starting dose	2.366[b]	-
Monkey, Cynomolgus 39-Week repeat-dose toxicity study	50 mg/kg LOAEL 5 mg/kg NOAEL	144[c] 15.3[d]	61x 6.5x

Abbreviations: AUC = area under the serum concentration versus time curve, LOAEL = lowest-observed- adverse effect level, NOAEL = no-observed-adverse-effect level, SC = subcutaneous, Q2W = every 2 weeks.
[a] Monkey AUC / human AUC.
[b] Mean, steady-state AUC_{0-168} hours with 80 mg Q2W dosing, using simulations from the integrated population pharmacokinetic model. Lower steady-state AUC values were achieved following the starting dose of 160 mg or with the proposed maintenance dose of 80 mg every 4 weeks.
[c] Mean, steady-state AUC_{0-168} hours after multiple dosing (Day 267).
[d] Estimated steady-state AUC_{0-168} hours after multiple dosing (since a Day 267 AUC was not determined at 5 mg/kg, the Day 1 AUC was multiplied by 2.5, which was the extent of accumulation observed at 50 mg/kg).

Multiple-Dose Studies in Pregnant Monkeys

Serum exposure of ixekizumab was evaluated in pregnant Cynomolgus monkeys following weekly subcutaneous administration of 5 or 50 mg/kg on Gestation Days (GD) 20 to 139. Maternal and fetal serum and amniotic fluid samples were collected on the day of caesarean section, 24 to 72 hours after the last dose.

Table 10. Concentrations of Immunoreactive Ixekizumab (ng/mL) at Cesarean Section in Maternal Serum, Fetal Serum, and Amniotic Fluid of Cynomolgus Monkeys Following Weekly Subcutaneous Administrations of 5 or 50 mg Ixekizumab/kg (Study SNBL.010.15)

Dose	Day[a]	Maternal serum	Fetal serum	Amniotic fluid
5 mg/kg	140			
Mean		78655	19973	2086
SD		16579	6690	1701
n		11	10	10
50 mg/kg	140			
Mean		835909	153670	13565
SD		202042	32978	12051
n		11	10	10

Abbreviations: SD = standard deviation, n = number of animals. [a] Cesarean section preformed 24 to 72 hours after the final dose (Days 140 to 142).

Exposure to ixekizumab in pregnant adult females increased with dose, with mean serum concentrations of ixekizumab approximately 10-fold higher at 50 mg/kg relative to 5 mg/kg 48 hours post administration on GD 20 to 22, GD 70, and GD 140..

Table 11. Concentrations of Immunoreactive Ixekizumab (µg/mL) in Maternal Serum of Cynomolgus Monkeys Following Weekly Subcutaneous Administrations of 5 or 50 mg Ixekizumab/kg (Study 20018253)

Maternal Serum Concentrations (µg/mL) on Gestation Day					
	Day 20-22	Day 70		Day 140	
	48hr	0hr	48hr	0hr	48hr
5 mg/kg					
Mean	49.2	60.0	82.2	62.4	79.7
SD	12.8	29.7	35.5	27.8	34.6
n	18	16	16	15	15
50 mg/kg					
Mean	592	683	946	700	967
SD	142	242	285	298	298
n	18	18	18	16	16

Abbreviations: SD = standard deviation, n = number of animals.

Mean ixekizumab milk concentrations were detected on Postpartum Day (PPD) 14 and decreased over time through PPD 56 for the 5-mg/kg and 50-mg/kg dose groups. **Table 12** presents the mean ratios of ixekizumab concentrations of postpartum maternal milk compared to maternal serum.

Table 12. Mean Ratios of Ixekizumab Concentrations Postpartum in Cynomolgus Monkey Maternal Milk Compared to Maternal Serum (Study 20018253)

	Maternal Milk/Maternal Serum			
Dose (mg/kg)	**PPD14**	**PPD28**	**PPD42**	**PPD56**
5	0.0018	0.0019	0.0026	0.0019
50	0.0011	0.0012	0.00095	0.0020

Distribution

No nonclinical tissue distribution studies were conducted with ixekizumab, consistent with the guidance provided by ICH S6 R1.

Metabolism

No metabolism studies have been performed with ixekizumab. Ixekizumab is a large molecular weight protein and presumed to be degraded into component amino acids by general catabolism pathways.

Excretion

No nonclinical excretion studies were performed with ixekizumab. Ixekizumab is a large molecular weight protein and presumed to be degraded into component amino acids by general catabolism pathways.

Pharmacokinetic drug interactions

Nonclinical pharmacokinetic drug interaction studies were not conducted with ixekizumab.

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity studies of ixekizumab were not submitted.

Repeat dose toxicity

Repeat-dose toxicity studies and major findings are summarised in **Table 13**.

Table 13. Repeat-dose toxicity studies with ixekizumab

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
6180-918	Cynomolgus monkey/3M, 3F/grp	0, 5, 15, 50 mg/kg/week, iv	8 weeks (9 doses)+6 weeks recovery	50 mg/kg/week	There were no deaths or treatment-related findings
6180-478	Cynomolgus monkey/4M, 4F/grp	0, 0.5, 5, 50 mg/kg/week, sc	39 weeks (39 doses) +16 weeks recovery	5 mg/kg/week	One male of the 5 mg/kg dose group died on Day 140, 6 days after its 20th injection, not treatment related. Treatment-related findings were limited to the SC injection sites in animals of all ixekizumab dose groups. One female in the high dose group had more a pronounced injection-site reaction resulting in suspension of dosing potentially due to ixekizumab directed immunity.

Genotoxicity

In accordance with ICH S6 (R1), genotoxicity studies were not submitted because ixekizumab is a monoclonal antibody.

Carcinogenicity

Animal studies to assess the carcinogenic potential of ixekizumab were not submitted. Instead, a critical evaluation of the nonclinical ixekizumab data and published literature on IL-17A function was conducted.

The Applicant concluded that the overall weight-of-evidence indicates that the carcinogenic potential of ixekizumab is low and that carcinogenicity studies were not warranted. This conclusion was based on the following:

- There are no carcinogenic concerns based on the structure or metabolism of ixekizumab.
  - Since ixekizumab is a monoclonal antibody, this large protein is not expected to gain access to the nucleus and directly interact with DNA, but catabolised to peptides and constituent amino acids via well-defined processes.
- Animal studies indicate that ixekizumab does not cause cell proliferation or pre-neoplastic lesions.
  - Repeat-dose toxicity studies of up to 39 weeks duration in Cynomolgus monkeys did not indicate any such potential for ixekizumab. In addition, the lack of ixekizumab binding to

tissues, determined from an ex vivo tissue cross-reactivity study, suggest that off-target toxicity would not be expected.

- Animal studies indicate that ixekizumab is neither immune-toxic nor a potent immunosuppressive agent, nor does it potentiate expansion of any immune cell type.
  - Ixekizumab acts by inhibiting binding of IL-17A to the IL-17A receptor, thereby preventing IL-17A-mediated cellular responses, highlighted by the release of cytokines and chemokines designed to recruit and activate both neutrophils and memory T cells to the site of injury or inflammation and maintain a pro-inflammatory state. Nevertheless, assessments of immunotoxicity and immune-modulation in the repeat-dose toxicity studies in cynomolgus monkeys identified no remarkable changes. There was no alteration (reduction or increase) in lymphocyte subsets (total T cells, helper T cells, cytotoxic T cells, total B cells, NK cells), no change in NK cell function, no effects on T-cell-dependent primary immune response (IgG and IgM), and no histopathological changes in lymphoid organs.
- Though the scientific literature contains some divergent reports, the preponderance of data support a pro-tumour role for IL-17A in the development of carcinogenesis.
  - Cumulative evidence indicates high IL-17A expression in a variety of tumour types that is often associated with poor disease outcome.
  - Experimental data demonstrate the ability of IL-17A to induce angiogenesis, upregulate pro-inflammatory/pro-tumour cytokines and chemokines, recruit pro-inflammatory/tumour-supportive cells to the tumour site, and provide pro-survival signals to tumour cells.
  - Mechanistic studies using IL-17A- or IL-17RA-deficient mice and/or anti-IL-17A antibodies have largely demonstrated reduced tumorigenesis.

Reproduction Toxicity

The Reproductive and developmental toxicity studies with their main findings are summarised in **Table 14**.

Table 14. Reproductive and developmental toxicity studies

Study type / Study ID / GLP	Species; Number sex / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
Male/Female fertility, 20003965, GLP	Cynomolgus, 6/sex/group	Sc, 0/50 mg/kg, once weekly	13 weeks	There were no treatment-related findings on reproductive parameters. There were also no treatment-related macroscopic or microscopic alterations, or changes in the weights of male and female reproductive organs.	50 mg/kg
Embryo-foetal development, SNBL.010.15, GLP	Cynomolgus, 12/group	Sc, 0, 5, 50 mg/kg, once weekly	17 weeks (GD20 to GD139)	There was no maternal toxicity, no evidence of embryo/fetal toxicity or teratogenicity, and no effects on fetal immune system development.	50 mg/kg
Peri & postnatal, 20018253, GLP	Cynomolgus, 18/group	Sc, 0, 5, 50 mg/kg, once weekly	18 to 22 weeks, GD20-22 until	Seven infants, all from ixekizumab-treated groups, died or were euthanized within 6 days of birth. These mortalities were not considered treatment-related	50 mg/kg

	parturition	and also within the range of historical control data at the Testing Facility. In the surviving infants there were no treatment-related changes.

Local Tolerance

Local tolerance studies were not submitted and this was considered acceptable by the CHMP.

Other toxicity studies

The Applicant considered that specific studies to assess immunotoxicity, antigenicity, dependence, metabolites or impurities were not warranted, which was considered acceptable by the CHMP.

In Vitro Haemolysis and Plasma Compatibility

The purpose of this *in vitro study* (N00024) was to evaluate compatibility of the formulated test article for IV injection by assessing the potential of ixekizumab and the vehicle to cause hemolysis and serum flocculation in whole blood and sera, respectively, from Cynomolgus monkey and human.

No important compound-related haemolysis or serum flocculation occurred when ixekizumab concentrations of 5 and 25 mg/mL were mixed 1:1 with whole blood or 1:2 through 1:50 with serum of human or monkey.

***Ex Vivo* Tissue Cross-Reactivity Study**

The objective of this ex vivo study (KTA00027) was to determine the tissue binding specificity of ixekizumab in a panel of 35 normal tissues from humans and Cynomolgus monkeys.

Ixekizumab was applied to tissue cryosections at concentrations of 0.5 µg/mL(optimal concentration) or 2.5 µg/mL (5 times the optimal concentration) based on prior method development experiments. Ixekizumab binding was assessed immunohistochemically using a biotinylated mouse anti-human IgG4 secondary antibody and chromogenic detection reagent. Appropriate controls were included in the study to validate the adequacy of tissue sections for immunohistochemistry and to assist in the determination of specificity of ixekizumab binding.

No specific ixekizumab staining was observed in any human or Cynomolgus monkey tissues examined at either concentration.

2.3.5. Ecotoxicity / environmental risk assessment

Ixekizumab is a monoclonal anti-human Interleukin-17A antibody and therefore in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempt of the need for an environmental risk assessment.

2.3.6. Discussion on non-clinical aspects

Toxicity of ixekizumab was evaluated *in vitro* and *in vivo* in Cynomolgyus monkeys; studies were justified in Cynomolgus monkeys on the basis that other species did not show pharmacological sensitivity to ixekizumab whereas this was similar between humans and Cynomolgus monkeys.

General toxicity studies used intravenous dosing for up to 8 weeks and subcutaneous dosing up to 39 weeks with recovery groups for high dose and controls. In addition, one study was done over 13 weeks to assess the effect of ixekizumab on fertility in both male and female monkeys and two studies

were done in pregnant cynomolgus monkeys dosed over gestation days 20-~140, all these studies using the subcutaneous route.

Ixekizumab administration to Cynomolgus monkeys for 39 weeks at subcutaneous doses up to 50 mg/kg weekly produced no organ toxicity or undesirable effects on immune function (e.g. T-cell dependent antibody response and NK cell activity). A weekly subcutaneous dose of 50 mg/kg to monkeys is approximately 19 times the 160 mg starting dose of ixekizumab, and in monkeys results in exposure (AUC) that is at least 61-fold higher than the predicted mean steady-state exposure in humans administered the recommended dose regimen.

Ixekizumab has not been assessed for carcinogenic potential for several reasons. First, ixekizumab is a monoclonal antibody and therefore there is a low risk for direct interaction of ixekizumab against DNA, also proteins are catabolized to peptides and constituent amino acids via well-defined processes which are not considered to pose a risk for carcinogenesis. Second, data generated in monkey did not indicate a risk for pre-neoplastic lesions. Thirdly, the literature does not suggest an increased risk for tumorigenicity in relation to neutralisation of IL-17. Overall, the carcinogenic potential of ixekizumab was considered to be low. Nevertheless, as the risk for malignancies cannot be completely excluded due to the immunosuppressive properties of ixekizumab especially with long term use, this risk has been included in the Risk Management Plan as an important potential risk.

Ixekizumab produced no adverse effects on fertility or embryo-fetal development.

In developmental toxicity studies, ixekizumab was shown to cross the placenta and was present in the blood of offspring for up to 6 months of age. A higher incidence of postnatal mortality occurred in the offspring of monkeys given ixekizumab compared to concurrent controls. This was related primarily to early delivery or maternal neglect of offspring, common findings in nonhuman primate studies, and was not considered related to the mechanism of action of ixekizumab. In addition, use in pregnancy is included in the RMP as missing information.

Even though animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or post-natal development, as a precautionary measure, and due to the very limited experience of ixekizumab in humans, and the fact that treatment for psoriasis may be interrupted without detrimental effects it is preferable to avoid the use of ixekizumab during pregnancy.

Use in pregnancy is included in the RMP as missing information and further information regarding the potential risks with the use of ixekizumab during pregnancy will be collected through the US observational pregnancy study using medical record data.

In vitro data show that there is a low risk for haemolysis and similarly a low risk for unspecific tissue binding.

2.3.7. Conclusion on the non-clinical aspects

There are no specific non-clinical issues that require further action post-marketing and the non-clinical profile of ixekizumab is considered sufficiently characterised.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant 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 15. Clinical pharmacology studies and analyses for ixekizumab

Study	Data Obtained to Support Analyses (Duration of Data Available)	Dose Regimen as Applicable to Analyses
RHAG CSR/	Single-Dose PK Population PK Histology (PD) Bioavailability Exposure-Efficacy (All data for RHAG analyses were available to Week 16)	Q2W given on 3 occasions: SC injection(s) of 5, 15, 50, and 150 mg or IV infusion of 15 mg
RHAJ Population PK Report/	Population PK Exposure-Efficacy Immunogenicity	Part A: SC injection(s) of 10, 25, 75, and 150 mg at 0, 2,4, 8, 12, and 16 weeks
RHBL CSR/	Single-Dose PK (up to Day 14 only, after the 160-mg starting dose) Effect of Intrinsic and Extrinsic Factors on PK	SC by PFS or autoinjector: 160-mg starting dose, 80-mg Q2W up to Week 12
Primary Population PK and Exposure Response Analyses: Data from studies **RHAG, RHAJ, RHAZ/**	Population PK (all studies) Exposure-Efficacy (data from RHAJ through Week 32 and RHAZ through Week 60) Immunogenicity – from RHAJ (through Week 32) and RHAZ (through Week 60) Safety data from RHAZ (through Week 60)	RHAG: as above RHAJ: as above RHAZ: SC starting dose of 160 mg SC 80-mg Q2W or Q4W up to 12 weeks (Induction) SC 80-mg Q4W or Q12W Week 12 to Week 60 (Maintenance)

Secondary Exposure-Response Analyses: Observed Data from Studies **RHAZ, RHBA, RHBC**/	Exposure-Efficacy Exposure-Safety Effect of Immunogenicity on PK (RHAZ data were available through Week 60; RHBA data were available up to Week 36 in all patients and Week 60 in a subset of patients; RHBC data were available up to Week 12)	RHAZ: as above RHBA: SC Starting Dose of 160 SC 80-mg Q2W or Q4W up to Week 12 (Induction) SC 80-mg Q4W or Q12W up to Week 60 (Maintenance) RHBC: SC Starting Dose of 160 mg SC 80-mg Q2W or Q4W up to Week 12 (Induction)
RHAT CSR/	Descriptive PK (data up to Week 52)	SC starting dose of 160 mg 80-mg Q2W up to Week 12 (Induction) 80-mg Q4W Weeks 12 to 52 (Maintenance)

Table 16. Pivotal phase 3 trials of ixekizumab in moderate to severe plaque psoriasis

Study Code Sites Countries	Total Number of Pts Randomised (Pts Randomised to Ixekizumab in Induction Period)	Induction Dosing Regimens and Controls	Maintenance Dosing Regimens	Psoriasis Population	Co-Primary Endpoints	Study Period: Duration
RHAZ 108 sites 11 countries	1296 (865)	• 80 mg Q2W[a] • 80 mg Q4W[b] • Placebo	• 80 mg Q4W[d] • 80 mg Q12W[d] • Placebo[d]	BSA ≥10% sPGA ≥3 PASI ≥12	sPGA (0,1) at 12 wks PASI 75 at 12 wks	Db induction: 12 wks Db maintenance: 48 additional wks Ext: 3.9 yrs
RHBA 127 sites 12 countries	1224 (698)	• 80 mg Q2W[a] • 80 mg Q4W[b] • Etanercept[c] • Placebo	• 80 mg Q4W[d] • 80 mg Q12W[d] • Placebo[d]	BSA ≥10% sPGA ≥3 PASI ≥12	sPGA (0,1) at 12 wks PASI 75 at 12 wks	Db induction: 12 wks Db maintenance: 48 additional wks Ext: 3.9 yrs
RHBC 125 sites 10 countries	1346 (771)	• 80 mg Q2W[a] • 80 mg Q4W[b] • Etanercept[c] • Placebo	• Not applicable[e]	BSA ≥10% sPGA ≥3 PASI ≥12	sPGA (0,1) at 12 wks PASI 75 at 12 wks	Db induction: 12 wks Ext: 4.8 yrs

Abbreviations: BSA = body surface area; PASI 75 = at least a 75% improvement from baseline in the Psoriasis Area and Severity Index; Pts = patients; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SC =subcutaneous; sPGA (0,1) = static Physician Global Assessment response of '0' (clear) or '1' (minimal); wks = weeks; yrs = years. Db = double-blind. Ext = extension

[a] *80 mg Q2W = Starting dose of 160 mg given as 2 SC injections at Week 0, followed by 80 mg as 1 SC injection every 2 wks in the Induction Dosing Period.*

[b] *80 mg Q4W = Starting dose of 160 mg given as 2 SC injections at Week 0, followed by 80 mg as 1 SC injection every 4 wks in the Induction Dosing Period.*

[c] *50-mg etanercept (1 SC injection) given twice weekly (every 3 to 4 days) in accordance with labelling of marketed product.*

[d] *Maintenance dosing regimens were used until relapse, defined as a loss of response equal to an sPGA score of ≥3; patients who relapsed were placed on the 80 Q4W dosing regimen. Patients switched from placebo to ixekizumab were given a starting dose of ixekizumab 160 mg (2 SC 80-mg injections) at the beginning of the Maintenance Dosing Period.*

[e] *Study RHBC did not include a Maintenance Dosing Period. Each patient who completed the Induction Dosing Period was permitted to enter a long-term extension period according to the judgment of the investigator. All patients in the long-term extension were assigned to 80 mg Q4W.*

Notes: The Phase 3 studies were multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies, with ongoing long-term extensions. The count of sites is based on sites obtaining informed consent from at least 1 patient. The number of patients treated is the number randomised to ixekizumab for the Induction Dosing Period; additional patients were treated with ixekizumab in subsequent study periods.

2.4.2. Pharmacokinetics

A population PK analysis was performed based on data from studies:

- RHAG phase I (sc injections 5, 15, 50 and 150 mg, i v 15 mg weeks 0, 2, 4).

- RHAJ phase II (sc injections 10, 25, 75, 150 mg weeks 0, 2, 4, 8, 12, 16)

- RHAZ phase III (s c starting dose 160 mg, induction 80 mg every 2 or 4 weeks, maintenance 80 mg every 4 or 12 weeks)

The objective of the PPK analysis was to characterize the pharmacokinetics (PK) of ixekizumab, determine the magnitude of within- and between-patient variability, and identify potential intrinsic and extrinsic factors that impact the PK of ixekizumab.

The population PK analysis included 6059 observed serum concentration samples from 1399 patients. Different formulations were used in each of the 3 studies: RHAG utilized a low dose lyophilized formulation, RHAJ used a high dose lyophilized formulation, and RHAZ used the proposed solution formulation for commercialization. Therefore different F estimates were explored for each study.

Table 17. Patient characteristics in the PPK analysis

Baseline Covariate	Overall	RHAZ	RHAJ	RHAG
Total Patient Count	1399	1247	115	37
Age (years) [a]	46.0 (17.0 – 88.0)	46.0 (17.0 – 88.0)	44.3 (18.2 – 72.2)	44.0 (20.0 – 65.0)
Body Weight (kg) [a]	88.9 (46.0 - 200)	88.7 (46.0 - 200)	89.9 (50.8 - 180)	89.7 (56.4 - 135)
Baseline C-Reactive Protein (mg/L) [a]	3.05 (0.100 – 149)	2.92 (0.200 – 149)	3.99 (0.250-35.8)	3.52 (0.100-36.9)
Baseline Cockroft-Gault Creatinine Clearance (mL/min) [a]	124 (35.9 – 342)	124 (35.9 -333)	122 (55.7 – 342)	NC
PASI [a]	17.4 (12.0 - 69.2)	17.6 (12.0 – 69.2)	16.2 (12.0 – 47.0)	17.4 (13.0 – 44.7)
sPGA [b]	3 (2 – 5)	3 (3 – 5)	3 (2 – 4)	NC
Percentages of BSA with Psoriasis involvement (%) [a]	21 (10 – 95)	21 (10 – 95)	17 (10 – 95)	-
Sex – Female (n(%))	450 (32.2)	395 (31.7)	48 (41.7)	7 (18.9)
Site/route of injection (%) [c]				
Abdomen - SC	66.1	68.2	23.7	33.9
Arm - SC	11.3	9.18	54.6	50.0
Buttock - SC	0.724	0	17.2	4.24
Thigh - SC	21.8	22.7	4.78	0.847
IV	0.0784	0	0	11.0
Race (n(%))				
Caucasian	1292 (92.4)	1156 (92.7)	104 (90.4)	32 (86.5)
Asian	61 (4.36)	56 (4.49)	4 (3.48)	1 (2.70)
African descent	31 (2.22)	26 (2.09)	5 (4.35)	-
Native American	5 (0.357)	3 (0.241)	2 (1.74)	-
Hispanic	4 (0.286)	-	-	4 (10.8)
Other	6 (0.429)	6 (0.481)	-	-
Ethnicity (%)				
Hispanic	4.86	3.53	17.4	10.8
Non-Hispanic	95.1	96.5	82.6	89.2
Geographical region (%)				
North America	57.0	52.0	97.4	100
Europe	37.9	42.3	2.61	-
Australia	2.93	3.29	-	-
Asia	2.14	2.41	-	-
Comorbidities (%)				
Dyslipidemia	15.2	17.0	-	NC
Hypertension	29.3	30.4	27.0	NC
Psoriatic Arthritis	26.2	26.5	31.3	NC
Type 2 diabetes	8.72	8.98	8.70	NC

A 2-compartment population PK model with first-order absorption and linear elimination best described the PK of ixekizumab administered SC in patients with psoriasis. Body weight was a significant covariate on clearance and volume parameters in the model and the effect was best described using an allometric relationship. Two factors influenced bioavailability and were included in the final model: study and site of administration. The bioavailability estimates for Study RHAG and Study RHAJ were similar so the final base model was described by one F parameter for these 2 studies and a separate F parameter for Study RHAZ.

The covariates tested in the model are depicted in **Table 18**.

Table 18. Covariates tested in the PPK analysis.

Covariate	Type	Parameters Tested
Bodyweight/Change from baseline in bodyweight	Continuous	CL, Q, V2, V3, F, KA
Body mass index (BMI)	Continuous	KA, F
Baseline CRP	Continuous	CL, V2
Age	Continuous	CL, V2, KA
Sex	Categorical	CL, V2
Geographic origin	Categorical	CL, V2
Ethnic origin	Categorical	CL, V2
Psoriatic arthritis	Categorical	CL, V2
Comorbidities (type II diabetes, dyslipidaemia, hypertension)[a]	Categorical	CL, V2,
Study (RHAG, RHAJ and RHAZ)	Categorical	F, V2, CL, KA
Creatinine clearance (estimated from Cockcroft-Gault formula)	Continuous	CL
Injection site (thigh, abdomen, arm, buttock)[b]	Categorical	F, KA
Concomitant medications occurring in at least 10% of patients	Categorical	CL
Immunogenicity (described below)	Categorical/Continuous	CL, F

Abbreviations: CL = clearance; Baseline CRP = baseline C-reactive protein; F = subcutaneous bioavailability; KA = first order absorption rate constant; V2 = central volume of distribution; V3 = peripheral volume of distribution.

[a] present in >10% of the population for dyslipidaemia and hypertension and 9% for type II diabetes.

[b] patients in each study were permitted to vary the site of injection during the course of the study

In addition to weight on clearance and volume terms, and study code on bioavailability, additional covariates that were retained in the final model were injection site on bioavailability and ADA titer and neutralising antibody status on clearance.

Based on simulations from the final PK model, the PK parameters after a 160 mg starting dose of ixekizumab followed by 80 mg Q2W or Q4W are shown in **Table 19**.

Table 19. Summary of Model-Predicted Ixekizumab PK Parameters Following a 160-mg Starting Dose Then 80-mg Q2W or Q4W Up to Week 12

PK Parameter	80-mg Q2W	80-mg Q4W
C_{max} after the 160-mg starting dose (µg/mL)	19.9 (8.15)[d]	19.9 (8.03)[d]
T_{max} after the 160-mg starting dose (days)	5 (1-14)[e]	5 (1-28)[e]
AUC 0-7 days after the 160-mg starting dose (µg*day/mL)	82.8 (35.9)[d]	82.5 (35.4)[d]
AUC 0-14 days after the 160-mg starting dose (µg*day/mL)	154 (58.1)[d]	154 (57.7)[d]
$C_{max,ss}$ after 80-mg Q2W or Q4W (µg/mL)[a]	21.5 (9.16)[d]	14.6 (6.04)[d]
$T_{max,ss}$ after 80-mg Q2W or Q4W (days)[a]	4 (1-14)[e]	4 (1-28)[e]
AUC 0-28 days (µg*day/mL)[b]	353 (150)[d]	187 (81.9)[d]
$C_{trough,ss}$ after 80-mg Q2W or Q4W (µg/mL)[a]	5.23 (3.19)[d]	1.87 (1.30)[d]
Time to steady state after 80-mg Q2W or Q4W dosing	8 weeks	8 weeks
Elimination half-life (days)[c]	12.8	12.8

Abbreviations: AUC = area under the curve; C_{max} = maximum serum concentration; $C_{max,ss}$ = maximum concentration of drug in serum at steady state; $C_{trough,ss}$ = steady state trough concentrations; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; T_{max} = time of maximum serum concentration; $T_{max,ss}$= time of maximum serum concentration at steady state.

a For the Q2W dosing regimen, data are summarized from Week 10 to Week 12 and for the Q4W dosing regimen, data are summarized from week 8 to week 12 after the starting dose at week 0.

b AUC0-28 days is calculated from week 8 to 12 for both the Q2W and Q4W dosing regimens

c Elimination half-life = (V2+V3)*0.693/CL; from final PK model parameter estimates.

d Mean (SD)

e Median (Range)

Absorption

Following a single subcutaneous (SC) dose of ixekizumab in patients with psoriasis, the rate of absorption was slow, achieving mean peak concentrations within 4 to 7 days, across a dose range of 5 to 160 mg. After multiple dosing, peak concentrations at steady state are predicted to be achieved in a similar time frame.

- **Bioavailability**

Studies **RHAG** and **RHAJ** used lyophilized formulations which were estimated to have the same bioavailability of 60%. In the phase 3 study, **RHAZ**, the final solution formulation (which is also the proposed commercial formulation) was used, and the bioavailability was estimated to be higher, 81%.

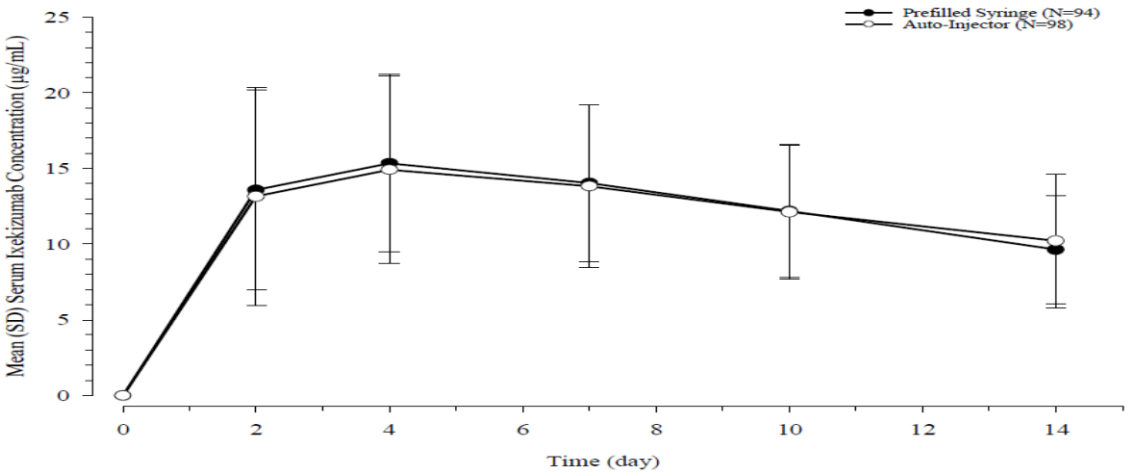
- **Effect of device**

Study **RHBL** was a Phase 3, multi-centre, parallel-group study in 204 patients with psoriasis (142 males, 62 females). The primary objective of the study was to evaluate the effect of drug delivery device, either by prefilled syringe or by autoinjector, on the PK of ixekizumab.

The study was performed in an outpatient setting. PK sampling was performed for 2 weeks after the 160 mg starting dose on day 2, 4, 7, 10 and 14. Treatment continued with 80 mg Q2W for 12 weeks, followed by a safety extension period with Q4W dosing. 180 patients were planned to be randomised 1:1 to receive ixekizumab by prefilled syringe (n=90) or autoinjector (n=90). Within the groups, the patients were also randomised to injection site arm, abdomen and thigh (n=30 group stratified into weight groups).

The PK of ixkizumab was similar following injection with prefilled syringe and autoinjector. Both geometric mean estimates of AUC and Cmax, as well as variability were similar between the devices (%CV on AUC for autoinjector 38%, prefilled syringe 36%, **Figure 4**).

Figure 4. Mean (± SD) serum ixekizumab concentration versus time profiles following a 160-mg subcutaneous (SC) dose using either a prefilled syringe or an autoinjector in patients with moderate-to-severe plaque psoriasis (Study RHBL)



A secondary objective of study RHBL was to investigate the effect of site of injection on the PK of ixekizumab. For both devices, injection in the thigh resulted in the highest drug exposure. For patients using the prefilled syringe, the arm and abdomen resulted in similar average AUC (151 and 135 ugxday/ml) whereas the average AUC after thigh administration was higher (190 ugxday/ml). After autoinjector use, thigh administration still showed the highest exposure (average AUC 178 ugxday/ml), followed by abdomen (159 ugxday/ml) and arm (124 ugxday/ml).

In the PPK analysis, four injection site areas were evaluated across the 3 studies: thigh, arm, abdomen, and buttock. Initially each site was evaluated separately for an effect on bioavailability. Refinement of the covariate effect showed that the thigh injection site resulted in higher bioavailability compared with the other areas of the body (arm, abdomen, or buttock).

Distribution

From the Primary Population PK Analyses (described later in this report) the geometric mean estimates (geometric coefficient of variation [CV]%) were V2 of 2.73 L (44%) and V3 of 4.28 L (19%), resulting in a total volume of distribution at steady-state of 7.11 L (29%), suggesting that ixekizumab has limited distribution into the peripheral compartments.

Elimination

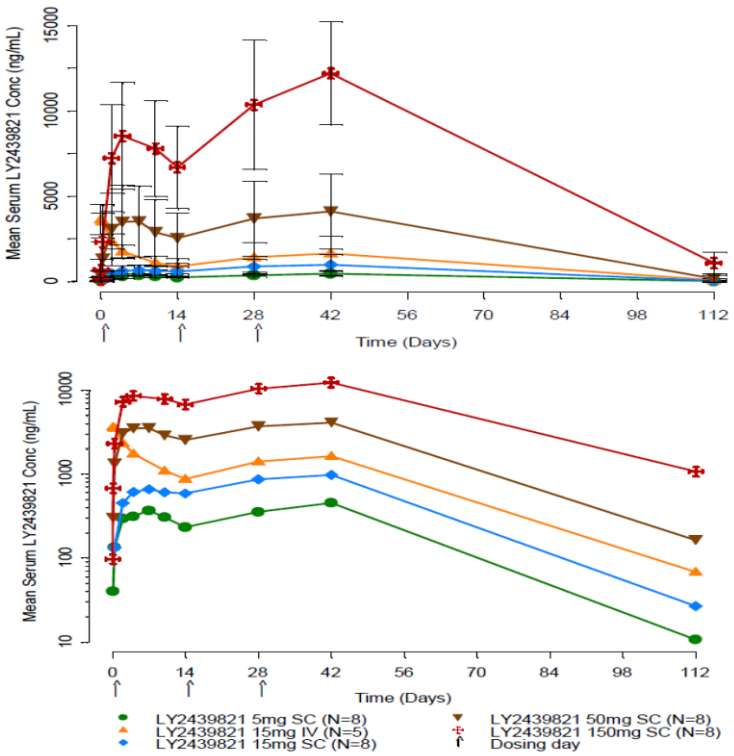
In the Primary Population PK Analyses, the geometric mean (geometric CV%) serum clearance was 0.0161 L/h (37%). Clearance was independent of dose. The geometric mean (geometric CV%) elimination half-life (t1/2) for ixekizumab was estimated at approximately 13 days (40%); this is within the typical range for an endogenous IgG antibody.

Dose proportionality and time dependencies

Study RHAG was a phase I dose escalation study in 46 patients with psoriasis vulgaris, where ixekizumab was administered SC (4 dose levels, 5, 15, 50 and 150 mg) and IV (1 dose level, 15 mg) for a total of 3 planned doses administered Q2W. 8 patients were included on each dose level, except for the IV dosing group where 5 patients were included. Of the 46 subjects randomized, 42 completed all 3 administrations of study drug.

The concentration-time profiles from this study are shown in **Figure 5.**

Figure 5. Ixekizumab mean plasma concentration-time profile following biweekly administration of 3 doses of LY2439821 in subjects with psoriasis vulgaris (study RHAG)



Abbreviations: conc = concentration; IV = intravenous; SC = subcutaneous. Arrows depict time of LY2439821 dosing.
Notes: Horizontal axis denotes time from first dose.

Anti-drug antibody positivity

In the PPK analysis including data from study RHAZ, ADA and NAb were found to be significant covariates on Cl. Using post-hoc estimates of clearance (CL) from the model, median clearance was approximately 2-fold higher in the moderate-to-high antibody titer (1:>160) group compared with patients who were ADA negative or had a low titer (<1:160), whereas being NAb positive resulted in an 8-fold increase in the typical value of CL in the PK model compared to CL in ADA negative patients. In the final PPK model, antibody titer was a significant covariate on Cl, with an additional effect due to NAb status. High titer and/or positive NAb status led to higher Cl. Only patients who were Nab positive had very large clearance values.

Special populations

Impaired renal/hepatic function

No study in patients with renal or hepatic impairment was submitted.

Gender

Sex was tested as a covariate on Cl in the PPK model (32% of the patients were female), but was not found to be relevant.

Race

Race was tested as a covariate on Cl in the PPK model, but 92% of the patients were Caucasian and only 4 and 2 % were Asian and African descent, respectively. Race was not a relevant covariate in the analysis. The study in Japanese patients (RHAT) was however not included in the PPK analysis, and the

average steady state concentrations given in the CSR were around twice as high as the steady state estimates given in the SmPC.

Elderly

Age was tested as a covariate on Cl in the PPK model (range 17-88 years), but was not found to be a significant predictor of CL, V or Ka.

The number of elderly subjects included in the studies submitted in support of this application are summarised in **Table 20.**

Table 20. Number of patients included in the ixekizumab studies by age group

	Age <65 years	Age ≥65 to <75	Age 75≥ to <85	Age ≥85
Patients Involved in the Primary Population PK Analyses, n (%)	1305 (93.3%)	82 (5.86%)	11 (0.8%)	1 (0.07%)
All Psoriasis Ixekizumab Exposure Integrated Analyses Set, n (%)	3903 (92.8%)	265 (6.3%)	34 (0.8%)	2 (0.0%)

Pharmacokinetic interaction studies

Effect of other drugs on the PK of ixekizumab

No *in vitro* or *in vivo* studies have been performed. In the population PK analysis, HMG Co-A reductase inhibitors, ACE inhibitors and NSAIDs were taken by >10% of the patients, but none of these were significant covariates on ixekizumab clearance.

Effect of ixekizumab on the PK of other drugs

Previous data have shown that cytochrome P450 (CYP450) enzymes may be suppressed by increased levels of proinflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNFα) during chronic inflammation. Therefore, two in vitro studies were performed to investigate the possibility that ixekizumab, which act by neutralizing IL-17A, like, could indirectly normalize the activities of CYP450 enzymes by reducing cytokine levels. In the first study, three days incubation of IL-17A or the positive control IL-6 was performed in preparation of human hepatocytes. The positive control IL-6 in very high concentrations ((≥ 10 000 pg/ml) resulted in a decrease in enzyme activity and/or mRNA levels for many of the enzymes tested. In general, the effect of IL-17 appeared smaller, with a tendency to decrease mRNA expression of CYP3A4, but not consistently of other enzymes. No consistent effect of IL-17 on enzyme activity was observed. The other in vitro study used HepatoPac 3-dimensional hepatocyte cultures with Kupffer cells. The HepatoPac cultures responded concentration-dependently to IL-6 with down-regulation of the mRNA of many CYP450 enzymes, but with no obvious effect of Kupffer cells. A smaller and more variable effect of IL-17 was seen.

Use with Vaccines and Other Psoriasis Therapy

Controlled clinical studies of co-administration of ixekizumab with live vaccines, other biologic therapies, or systemic oral therapies approved for psoriasis were not submitted in support of this application.

Pharmacodynamics

Mechanism of action

Ixekizumab is an immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds with high affinity (<3 pM) and specificity to interleukin-17A (IL-17A). Ixekizumab does not bind the other five members of the IL-17 cytokine family (IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), or IL-17F).

IL-17A is a pro-inflammatory cytokine produced predominantly by a subset of CD4+ T cells, called Th17 cells, and has major roles in neutrophil homeostasis, host defence against extracellular bacteria and fungi, and chronic pathogenic inflammation. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases, including psoriasis.

Primary and secondary pharmacology

An exploratory evaluation on skin histopathology was conducted during the Phase 1 Study RHAG. At all dose levels tested (15 mg IV and 5, 15, 50, and 150 mg SC), there was a dose-related trend toward decreased epidermal thickness, number of patients with K16+ cells, numbers of CD3+ cells, and CD11c+ cells from baseline to Day 43, reflecting disease improvement (data not shown). Reductions in epidermal thickness, CD3+ cells, and CD11c+ cells from baseline were most persistent at the 15-mg IV dose level and at the 50- and 150-mg SC dose levels.

Exposure response analyses

The applicant has conducted a thorough PK/PD evaluation including both primary end-point evaluation (sPGA and PASI at weeks 12 and 60) as well as a time-course model of sPGA response.

Exposure response models were developed for sPGA(0,1) and sPGA(0) responders and PASI 75/90/100 responders at Week 12 and Week 60 and a time course model was also developed for sPGA scores.

An ordered categorical model best described the sPGA data and was used to determine the probability of a patient being a responder (defined as sPGA 0 or 1) or a non-responder (sPGA>1) after 12 weeks of treatment and another model after 60 weeks of treatment. For the PASI data, logistic regression modeling was used to estimate the probability of a patient achieving a particular PASI score (75, 90, or 100) after 12 weeks of treatment and after 60 weeks of treatment. Model-predicted Ctrough,ss estimates were determined from the PK model at Week 12 (Study RHAJ and Study RHAZ) and Week 60 (Study RHAZ only) and used as exposure inputs to the sPGA and PASI models.

The primary efficacy endpoints in the Phase 3 analyses were sPGA(0,1) and PASI 75 at Week 12 after the induction dosing regimens of 80 mg Q2W and Q4W. For both endpoints, there was an increase in the percent responders predicted from the exposure-response models for the Q2W versus the Q4W regimens; 87% verus 83% for sPGA(0,1) and of 94% versus 90% for PASI 75 response. These model predicted estimates were similar to the observed data, 84% verus 80% for sPGA(0,1) and of 92% versus 87% for PASI 75 response for the Q2W and Q4W dosing regimens, respectively. For the efficacy endpoints associated with the higher measures of response: sPGA(0), PASI 90 and PASI 100, there were greater responses predicted with the Q2W dosing regimen compared with the Q4W dosing regimen. The percentage of predicted responses for the Q2W and Q4W dosing regimens were 41% and 34%, 77% and 70%, 39% and 32%, for sPGA(0), PASI 90 and PASI 100, respectively, and were also consistent with observed data. These results indicate the more frequent induction dosing regimen of 80

mg Q2W provides additional benefit to patients with increases in the predicted percentage of responders in the range of 4 to 7%. The higher range of predicted concentrations for patients in the Q2W dosing regimen group ensured the majority of patients were on or closer to the plateau of the exposure response curve and thus were likely to achieve a response. This is compared with the Q4W dosing regimen group where the range of exposures was lower and encompassed more of the slope of the curve resulting in fewer patients predicted to achieve a response.

Weight

The PPK analysis identified body weight as a significant predictor of both Cl and V. Weight was also a covariate on Emax in the PKPD model where the model suggested a lower Emax in heavy patients. The net impact of body weight on both exposure and response according to the model is summarised in **Table 21.**

Table 21.Model Predicted Impact of Body Weight on Exposure and Response for the sPGA Week 12 Score in the PPKPD model

Weight Group[a]	$C_{trough,ss}$ (µg/mL) Q2W dosing	Percent of patients achieving response Q2W dosing		$C_{trough,ss}$ (µg/mL) Q4W dosing	Percent of patients achieving response Q4W dosing	
		sPGA(0,1)	sPGA(0)		sPGA(0,1)	sPGA(0)
Q1	13	93	57	4.5	90	48
Q2	10	90	49	4.1	87	40
Q3	8.6	87	41	3.0	82	32
Q4	6.7	83	33	2.3	74	23
<100 kg	11	90	48	4.1	86	39
≥100 kg	7.1	83	34	2.4	75	24

Abbreviations: $C_{trough,ss}$ = model-predicted trough concentration estimates; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment.

[a] Q = quartile; the median (range) weight of each quartile for Q2W dosing is 69 (48-76) kg for Q1, 83 (76-90) kg for Q2, 98 (90-104) kg for Q3 and 118 (105-191) kg for Q4. The median (range) weight of each quartile for Q4W dosing is 67 (47-76) kg for Q1, 83 (76-90) kg for Q2, 97 (90-105) kg for Q3 and 119 (106-170) kg for Q4.

When the Week 12 data were evaluated by body weight categories (<100 kg versus ≥ 100 kg), in general, the lighter weight patients had higher predicted response rates compared with the heavier patient group especially for the higher clinical response measures. When the Week 12 data were evaluated further by dosing regimen within each body weight category (<100 kg versus ≥ 100 kg), the benefit of the Q2W dosing regimen was apparent for both patient groups.

Several covariates were found to be predictors of response in the exposure-response analyses at Week 12 but not Week 60: palmoplantar involvement, baseline PASI score, baseline body weight and previous treatment with a biologic agent. It is possible that treatment for longer than 12 weeks may be needed in some sub-groups of patients to achieve the different clinical endpoints evaluated or that there are some sub-groups of patients who have a lower probability of responding. A time course model was also developed to evaluate the exposure-response relationship for sPGA scores over time. The Q2W dosing regimen in the induction dosing period (up to Week 12) is projected to achieve an 80% response rate by Week 12, whereas a Q4W dosing regimen is projected to achieve an 80% response rate by Week 19 (demonstrating the faster onset of response that is achieved with the Q2W induction dosing regimen). The Q4W and Q12W dosing regimens evaluated in the maintenance dosing period were predicted to result in differential sPGA response rates at Week 60. In terms of response

sustainability at Week 60, Q4W was superior to Q12W in the maintenance dosing period, where exposure in patients on the Q4W dosing regimen were associated with a 25 to 27% higher predicted sPGA(0,1) and sPGA(0) response rate as compared to Q12W dosing regimen. The model predicted results were consistent with the statistical analysis of efficacy data in the maintenance period, where significantly greater proportions of patients were maintained or achieved responses in the ixekizumab 80 mg Q4W group versus the 80 mg Q12W group across various efficacy endpoints.

Exposure safety analysis

Exposure relationships were explored for selected adverse events of special interest (injection site reactions, infections, hypersensitivity reactions, Candida, staphylococcal infections, MACE, and Crohn's disease) for data up to Week 12 (end of induction dosing period and the time of the primary efficacy endpoint assessment) and for data from Week 12 to Week 60 (maintenance dosing period). There appeared to be a concentration relationship with injection site reactions, with higher incidences of injection site reactions at higher ixekizumab concentrations; this occurred in both the induction and the maintenance dosing periods. When looking at incidence by induction dosing regimen, patients who received Q2W had more injection site reactions compared to the patients on the Q4W dosing regimen (N = 61 on Q2W versus 49 on Q4W for patients included in the exposure-safety analyses). There was no apparent ixekizumab concentration relationship with other adverse events of special interest investigated during either the induction or the maintenance dosing periods.

2.4.3. Discussion on clinical pharmacology

In general, the CHMP considered that the pharmacokinetic characterisation of ixekizumab appears adequate, and that the results were as would have been anticipated for an IgG antibody.

The pivotal studies were performed with the final formulation using the pre-filled syringe, but as the pharmacokinetics have been shown to be similar between the devices, efficacy and safety data can be extrapolated from the pre-filled pen. Although some difference in bioavailability was observed between different sites of injection, the PKPD model suggests that this difference is unlikely to impact the response to treatment. Information that the injection sites can be alternated has been included in the SmPC.

The PK-parameters of ixekizumab are comparable to reported parameters of known IgG antibodies. No dose- or time dependency in pharmacokinetics was observed, suggesting no major contribution of target mediated clearance in the dose range studied. Overall, ixekizumab exposure increased proportionally over a dose range of 5 to 160 mg given as an SC injection.

The PPK analysis suggests that with the proposed dosing, 80% of steady state in the induction phase is reached already after the loading dose (160 mg), and time to steady state after 80 mg 2QW or 4QW dosing is approximately 8 weeks. This is anticipated from the half-life.

The effect of organ impairment has not been studied, but no large effect on exposure is anticipated based on the assumption that ixekizumab exhibits general IgG pharmacokinetics. Nevertheless, use of ixekizumab in patients with severe hepatic and renal impairment is included in the RMP as missing information. The SmPC accordingly states that ixekizumab has not been studied in these patient populations and hence, no dose recommendations can be made.

In general, no drug-drug interactions are expected for an IgG antibody. Previous data have however suggested that cytochrome P450 (CYP450) enzymes may be suppressed by increased levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNFα) during chronic inflammation. Therefore, the Applicant submitted two *in vitro* studies to investigate if IL-17A could

influence CYP expression. Neither of the *in vitro* experiments performed suggests a role of IL-17A in the regulation of CYP enzymes. The regulation of enzymes by disease state and cytokine levels is however complex, and *in vitro* studies have up to now shown limited value in the qualitative and quantitative prediction of clinical interactions (Evers et al, Drug Metab Dispos, 2013). Considering therefore that enzyme regulation by cytokines appears to be difficult to study *in vitro*, the risk of a potential interaction risk is adequately reflected in the SmPC.

Interactions between MAbs and immunosuppressive agents have been reported in the published literature. In the scientific advice given by CHMP in 2011, a traditional drug-drug interaction study between ixekizumab and methotrexate or other DMARDS was recommended. However, this was not considered essential for the currently applied for indication of plaque psoriasis where concomitant treatment with DMARDs is unlikely. The lack of pharmacodynamic DDI studies with immunomodulatory agents or phototherapy is included in the SmPC. Furthermore, as no information is available with regards to co-administration of ixekizumab and live vaccines, it is recommended that live vaccines should not be administered to patients on ixekizumab. Available data is insufficient to conclude on an adequate immune response to inactivated vaccines following administration of ixekizumab and this is reflected in the SmPC. In addition, the Applicant is recommended to to further investigate the potential impact on the immune response following vaccination with inactive vaccines (e.g. meningococcal and/or influenza vaccines) in patients or healthy volunteers receiving ixekizumab. Immune responses to live and inactivated or non-live vaccines is also included in the RMP as missing information.

2.4.4. Conclusions on clinical pharmacology

The CHMP considered that overall the pharmacokinetics profile of ixekizumab was sufficiently characterised and was found to be in line with what is expected for a monoclonal IgG antibody. Further information will be collected, as described in the RMP, on the use of ixekizumab on patients with renal and hepatic impairment. From a pharmacodynamic perspective and given that Taltz will be used only in patients with plaque psoriasis the lack of DDI studies especially with other immunomodulators is considered acceptable. Use in patients receiving live and inactivated vaccines has been included in the RMP as missing information.

2.5. Clinical efficacy

The applicant submitted one phase 1 study (RHAG), one phase 2 study (RHAJ) (**Table 15)**, and three pivotal phase 3 clinical studies (RHAZ, RHBA, RHBC) (**Table 16**) in support of the application for Taltz in moderate to severe plaque psoriasis. In addition, there is one open-label study evaluating different injection devices (RHBL) and one open-label Japanese study (RHAT) that are considered supportive.

2.5.1. Dose response studies

Dose response data are available from the phase 1 study RHAG and the phase 2 study RHAJ. Different dosing regimens were also investigated in the phase 3 studies, i.e. dosing every 2 weeks vs. every 4 weeks during the induction phase and dosing every 4 weeks vs. every 12 weeks in the maintenance phase.

Study RHAG

Study RHAG was a randomized, double-blind, placebo-controlled, dose-escalation Phase 1 study that evaluated ixekizumab 5 mg, 15 mg, 50 mg, and 150 mg SC, and 15 mg intravenous (IV) (along with

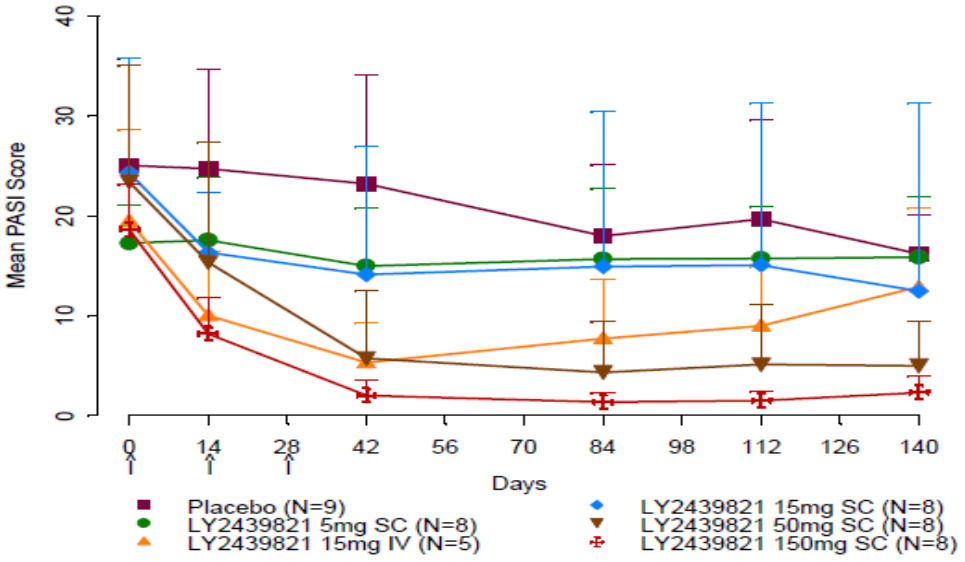
corresponding placebos) in patients with plaque psoriasis involving at least 15% body surface area, and a PASI total score of at least 13. Study drug was administered on Days 1, 15, and 29. Efficacy of ixekizumab was assessed as a secondary objective of the study, measured by a relative Physician Global Assessment (rPGA) and Psoriasis Area and Severity Index (PASI) on Days 15, 43, 85, 113, and 141.

A total of 46 patients were randomized and 33 completed this Phase 1 study.

For the rPGA, statistically significant improvements compared with placebo were achieved at all time points from Days 15 to 141 for the 50- and 150-mg SC groups, and the 15-mg IV group.

For PASI, statistically significant improvements in mean PASI score compared with placebo were achieved at all time points from Days 15 to 141 for the 50- and 150-mg SC groups (**Figure 6**).

Figure 6. Mean (SD) PASI score-time profile following biweekly administration of 3 doses of LY2439821 in subjects with psoriasis vulgaris for Study RHAG.



Abbreviations: IV = intravenous; PASI = Psoriasis Area and Severity Index; SC = subcutaneous; SD = standard deviation.
Horizontal axis denotes time from first dose.

Study RHAJ

Study RHAJ was a Phase 2 multi-center study designed to evaluate clinical activity, safety, tolerability, PK, PD, and immunogenicity of 4 ixekizumab SC dose groups compared with placebo in adults with plaque psoriasis.

The study had 2 parts:

- **Part A** was a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging design (approximately 20 to 40 weeks).

Five groups were evaluated in Part A: placebo (normal saline), 10, 25, 75, and 150 mg of ixekizumab, via SC administration. Study treatment was administered by the clinical staff at 0, 2, 4, 8, 12, and 16 weeks for a total of 6 administrations per patient. Ixekizumab for injection was supplied as a lyophilized powder in glass vials.

- **Part B** was an optional extension period with an open-label design (approximately 264 weeks).

Study treatment was administered as 120 mg ixekizumab Q4W until the implementation of an amendment, and thereafter, has been administered as 80 mg ixekizumab Q4W with a possibility of up to 60 administrations per patient.

The primary efficacy end-point was PASI 75 at week 12, reflecting a 75% improvement in the PASI score. PASI 90 and PASI 100 were also assessed.

Secondary Efficacy Measures included:

– sPGA: Physician's determination of the patient's psoriasis lesions overall at a given time point, with lesions graded for induration, erythema and scaling to obtain a final sPGA score (range 0 to 5). An sPGA responder was defined by a post baseline sPGA score of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline.

Primary and secondary efficacy analyses were conducted on the Modified Intent-to-Treat (mITT) population defined as all randomised patients who received at least 1 dose of study drug (ixekizumab or placebo) and had at least one post-baseline assessment. Patients in the mITT population were analysed by the treatment they actually received. The Per-Protocol (PP) population included patients who were compliant with study drug and who completed all visits up to Week 12 (Visit 8) with no major protocol violations. The PP population was used for secondary analyses of the primary efficacy endpoint.

All tests were conducted at a 2-sided alpha level of 0.05. There were no adjustments for multiple comparisons.

Analyses of the primary endpoint with pair wise comparisons between each ixekizumab dose and placebo were performed using a Fisher's exact 2-sided test. Missing data was imputed using last observation carried forward (LOCF).

Regarding secondary endpoints, the change from baseline in the sPGA score was analyzed using an ANCOVA model at each time point and at Week 12 (LOCF). An analysis of the sPGA scores was also conducted to examine rates of responders.

Results

142 patients were enrolled/randomized in Part A. Four (3%) patients discontinued the study treatment due to AEs. A total of 120 patients entered Part B. Twenty-two patients did not enter Part B; of which 5 (3.5%) patients completed Part A of the study and 17 (12%) patients discontinued from Part A.

Most patients were male (57%) and white/Caucasian (91%). The majority of patients were from the US (98%). The mean age was 46 years, and patients had a mean BMI of 31.5 kg/m^2. Patients had a mean disease duration of 16.5 years and mean % BSA of 21%. Mean baseline sPGA was 3.3, and the mean PASI score at Week 0 was 17.8. The majority of patients (92%) had at least 1 previous psoriasis medication. A prescription topical agent was the most commonly used medication (59%). Biologic and systemic therapies (non-biologic agents) were used by 42% and 35%, respectively.

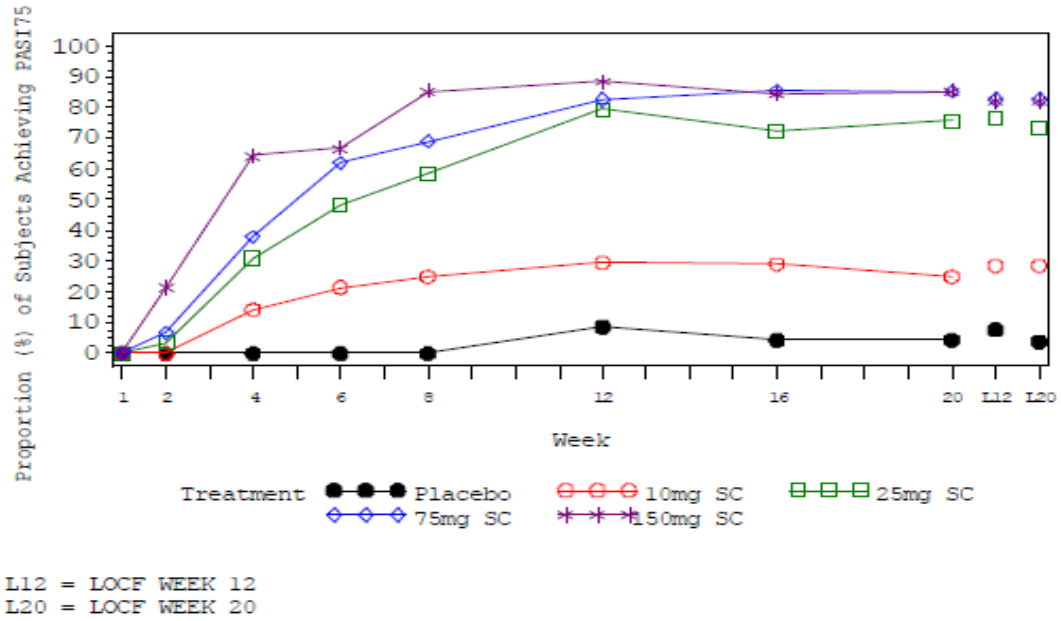
No statistically significant differences between groups were observed in any of the patient demographic or baseline disease characteristics.

Primary end-point (PASI 75 at week 12, mITT)

In the mITT population, a statistically significantly greater percentage of patients in the 25 mg (77%), 75 mg (83%), and 150 mg (82%) ixekizumab dose groups achieved PASI 75 at Week 12 (LOCF)

compared with placebo (8%; p<0.001). The results were similar when all observed values were considered.

Figure 7. PASI 75 response rate by treatment and time (mITT Population)



L12 = LOCF WEEK 12
L20 = LOCF WEEK 20

A significant dose-response relationship (p<0.001) was detected based on percent improvement of PASI at Week 12 (LOCF) using a predefined Emax model.

PASI 90 and PASI 100 at Week 12

The percentage of patients who achieved PASI 90 at Week 12 (LOCF) was statistically significantly greater in the 25 mg (50%), 75 mg (59%), and 150 mg (71%, p<0.001) ixekizumab dose groups compared with placebo (0%). This effect was maintained through Week 20 (LOCF).

The percentage of patients who achieved PASI 100 at Week 12 (LOCF) was statistically significantly greater in the 75 mg (38%), and 150 mg (39%, p<0.001) ixekizumab dose groups compared with placebo (0%). This effect was maintained through Week 20 (LOCF). The 25 mg ixekizumab dose group had statistically significantly greater percentage (23%) of patients at Week 20 (LOCF) compared with placebo (0%).

sPGA

The percentage of sPGA (0,1) responders at Week 12 (LOCF) was statistically significantly (p<0.001) greater compared with placebo (8%) for the 25-mg (70%), 75-mg (72%), and 150-mg (71%) ixekizumab dose groups. This effect was maintained through Week 20 (LOCF). The 10-mg ixekizumab dose group had a statistically significantly greater percentage of sPGA (0,1) responders (29%) compared with placebo (4%) at Week 20 (LOCF).

For sPGA (0) response at Week 12 (LOCF), a statistically significantly greater response compared with placebo (0%) was observed for the 25 mg (p=0.025, 20%), 75 mg (p<0.001, 38%) and 150 mg (p<0.001, 46%) ixekizumab dose groups. This effect was maintained through Week 20 (LOCF).

2.5.2. Main studies

RHAZ: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period and a Long-Term Extension Period to Evaluate the Efficacy and Safety of LY2439821 in Patients with Moderate-to-Severe Plaque Psoriasis

Methods

Study Participants

Main inclusion criteria:

The study enrolled male or female patients aged 18 years or older who had;

- a confirmed diagnosis of chronic plaque psoriasis for at least 6 months;
- who were candidates for phototherapy and/or systemic therapy, and
- who had ≥10% BSA involvement, an sPGA score of ≥3, and PASI score ≥12 at screening and at baseline.

Male patients had to agree to use a reliable method of birth control during the study.

Female patients could be women of childbearing potential who test negative for pregnancy and agreed to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer, or were women of non-childbearing potential, (e.g. had surgical sterilization, were aged ≥60 years; or women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and a FSH test confirming non-childbearing potential.

Main exclusion criteria:

Patients were excluded if they:

- had pustular, erythrodermic, and/or guttate forms of psoriasis; a history of drug-induced psoriasis; or a clinically significant flare of psoriasis during the 12 weeks prior to baseline.
- Therapies that caused patients to be excluded from study entry included systemic non-biologic psoriasis therapy or phototherapy (within 4 weeks of baseline), certain classes of topical psoriasis treatment (within 2 weeks of baseline), previous biologic therapies (within pre-specified washout periods; etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; golimumab <90 days; ustekinumab <8 months; rituximab or efalizumab <12 months; or any other biologic agent <5 half-lives prior to baseline), agents that target alpha-4-integrin, or previous use of ixekizumab or any other IL-17A antagonist.
- Patients were also excluded if they received or intended to receive certain vaccinations within specified time periods;
- had current or history of lymphoproliferative disease or malignant diseases (exception: successful treatment of basal cell carcinoma (no more than 3), squamous cell carcinoma of skin, or cervical carcinoma in situ with no recurrence within 5 years of baseline);
- had significant uncontrolled cerebro-cardiovascular, neurological, neuropsychiatric, renal, hepatic, respiratory, gastrointestinal, endocrine, or hematologic disorders;

– had a serious infection (within 12 weeks prior to baseline), active or latent tuberculosis (TB), human immunodeficiency virus, hepatitis C or some presentations of hepatitis B; or met specific laboratory criteria

– Had any other active or recent infection within 4 weeks of baseline that could pose an unacceptable risk to the patient or had a body temperature ≥38ºC at baseline; these patients could be rescreened (1 time) 4 or more weeks after documented resolution of symptoms.

Prior and Concomitant Therapy

All medications (other than study drug) taken during the study were recorded on the electronic case report form (eCRF). Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements. Any use of excluded medication as stated in the protocol was a violation of the protocol and was documented.

During the study, limited use of topical therapies was allowed, as was the use of non-live seasonal vaccinations (such as influenza) and/or emergency vaccination (such as rabies or tetanus vaccinations). Patients were able to continue their usual medication for other concomitant diseases throughout the study, unless specifically excluded in the protocol.

- **Treatments**

At Week 0 (baseline, Visit 2), patients who met all criteria for enrolment during the Screening Period (Visits 1 and 1A) were randomized into the Induction Dosing Period at a 1:1:1 ratio to 1 of 3 treatment groups:

- **80 mg ixekizumab Q2W:** A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10)
- **80 mg ixekizumab Q4W:** A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q4W (Weeks 4 and 8). Placebo given as 1 SC injection at Weeks 2, 6, and 10
- **Placebo:** Placebo given as 2 SC injections followed by placebo 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10)

The study consisted of 5 periods. The study is currently ongoing and the study report included in the MAA presents data from an interim 60-week database lock.

The **Screening Period** (Period 1) encompassed 4 to 30 days prior to the Induction Dosing Period (baseline; Week 0). The purpose of the screening period was to assess patient eligibility.

The **Induction Dosing Period** (Period 2) was a double-blind treatment period from Week 0 (baseline) to Week 12. The purpose of Period 2 was to compare the efficacy and safety of ixekizumab with that of placebo.

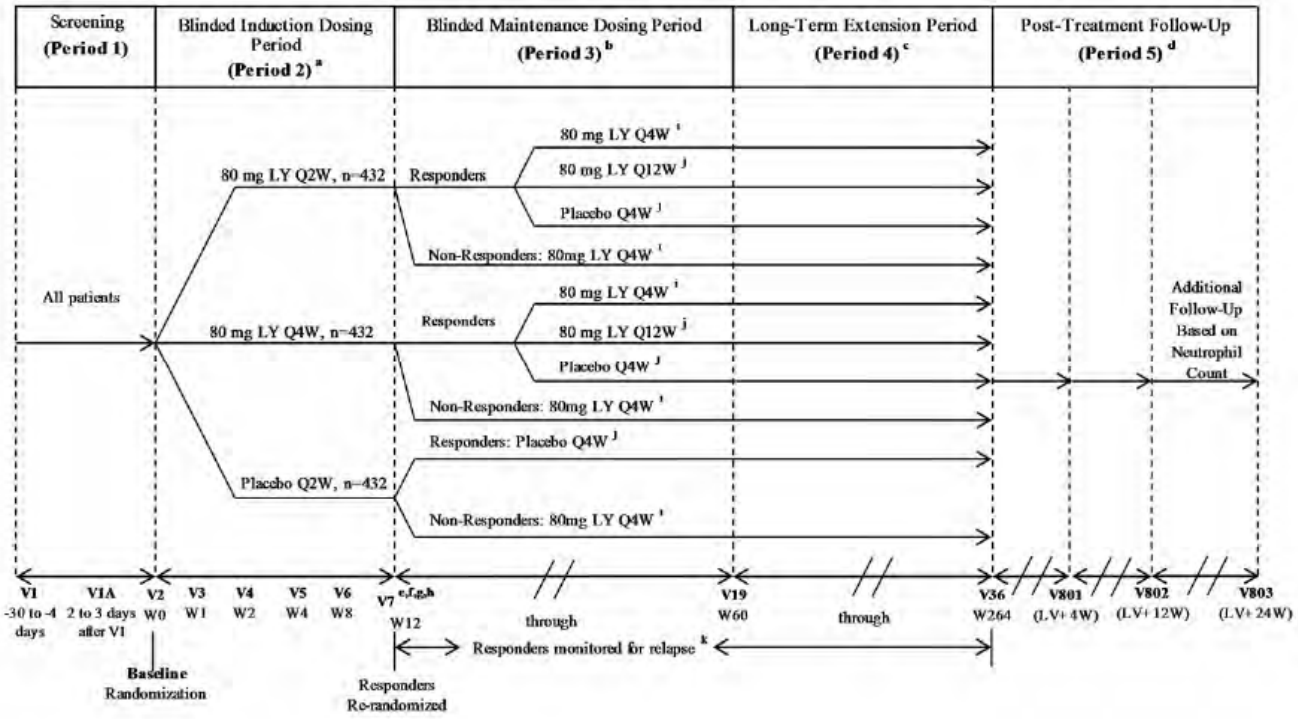
The **Maintenance Dosing Period** (Period 3) was a double-blind treatment period from Week 12 to Week 60. The purpose of Period 3 was to evaluate the optimum dosing interval, the maintenance of response/remission, relapse or rebound following treatment withdrawal, and response to re-treatment with ixekizumab following relapse in a re-randomized patient population.

The **Long-Term Extension Period** (Period 4) is for long-term evaluation of safety and efficacy parameters from Week 60 to Week 264. This period was blinded until after all patients reached Week 60 or discontinued (moved into the Post-Treatment Follow-Up Period), after which the study became open-label.

The **Post-Treatment Follow-Up Period** (Period 5) is for safety monitoring after treatment discontinuation for any patient receiving at least 1 dose of investigational product. Period 5 takes place from the last treatment period visit or Early Termination Visit up to a minimum of 12 weeks after that visit.

The study design is depicted in **Figure 8**.

Figure 8. Study design RHAZ



Abbreviations: LV = date of last visit; LY = ixekizumab (LY2439821); n = number of patients; Pbo = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous; sPGA = static Physician's Global Assessment; V = study visit; W = study week.

a All patients received 2 SC doses of investigational product at Week 0 (Visit 2) and 1 SC dose Q2W from Week 2 (Visit 4) through Week 10.
b All patients received 2 SC doses of investigational product at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 60 (Visit 19).
Study visits occurred at least Q4W during Period 3.
c Study visits occurred at least Q12W during Period 4. Treatment remained blinded to investigators, study site personnel, and patients until all patients reached Week 60 (Visit 19) or discontinued from the study (moved into Period 5).
d All patients who received investigational product entered into Period 5 and completed through Visit 802. Patients were to be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed or if determined by the sponsor/investigator that additional monitoring was needed.
e Responders to ixekizumab at Week 12 (Visit 7; responders were defined as those who achieved an sPGA score of 0 or 1) were randomly assigned at a 1:1:1 ratio to ixekizumab Q4W, Q12W, or placebo.
f Nonresponders to ixekizumab at Week 12 (Visit 7; nonresponders were defined as having an sPGA score of >1) received ixekizumab 80 mg Q4W.
g Responders to placebo at Week 12 (Visit 7) received 2 injections of placebo at Week 12 and remained on placebo Q4W until relapse.
h Nonresponders to placebo at Week 12 (Visit 7) received 2 injections of ixekizumab (starting dose) at Week 12 followed by ixekizumab 80 mg Q4W.
i Patients who experienced loss of treatment efficacy (relapse) during Period 3 remained on 80 mg ixekizumab Q4W to maintain the blind.
j Patients who experienced loss of treatment efficacy (relapse) during Period 3 were switched to 80 mg ixekizumab Q4W.
k Relapse occurring after Week 12 (Visit 7) was defined as a loss of response equal to an sPGA score of ≥3.

The primary efficacy endpoints of the study were evaluated at Week 12 and at this time point, patients who entered the Maintenance Dosing Period were classified as either responders or non-responders according to the following criteria:

- **Responder:** sPGA score of "0" or "1"
- **Non-responder:** sPGA score of >1

Patients who were receiving ixekizumab and were classified as "responders" were re-randomized at a 1:1:1 ratio to 1 of 3 treatment groups: **80 mg ixekizumab Q4W, 80 mg ixekizumab Q12W or placebo**.

Patients who were classified as "non-responders" were given 80 mg ixekizumab Q4W.

Patients who maintained their efficacy response with adequate overall safety during the Maintenance Dosing Period, as deemed by the investigator, were permitted to enter the Long-Term Extension Period in which efficacy and safety continued to be monitored.

- **Objectives**

The co-primary objectives of the study were to assess whether ixekizumab 80 mg Q2W or 80 mg Q4W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis as measured by the proportion of patients with a sPGA of 0 or 1 with at least a 2-point improvement from baseline and the proportion of patients achieving PASI 75 from baseline.

- **Outcomes/endpoints**

Primary efficacy end-points

The co-primary efficacy endpoints were the proportions of patients with an sPGA (0,1) and PASI 75 response at Week 12 (NRI) compared to placebo.

Secondary efficacy end-points

- Proportion of patients achieving an sPGA (0) at Week 12 (NRI) compared to placebo
- Proportion of patients with PASI 90 at Week 12 (NRI) compared to placebo
- Proportion of patients with PASI 100 at Week 12 (NRI) compared to placebo
- Proportion of patients maintaining an sPGA (0,1) from Week 12 after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) compared to placebo for ixekizumab-treated patients who had an sPGA (0,1) at Week 12 and were re-randomized (NRI)

Other secondary efficacy measures used in this study were the Nail Psoriasis Severity Index (NAPSI), the Psoriasis Scalp Severity Index (PSSI), and the Psoriasis Palmoplantar Severity Index (PPASI). The NAPSI was used only if the patient had fingernail psoriasis at baseline. Similarly, if the patient had palmoplantar psoriasis at baseline, the PPASI was used.

Health Outcomes Measures (selection)

- The Itch Numeric Rating Scale (NRS) was used to capture information on the overall severity of a patient's itching due to psoriasis. A responder analysis was made defined as the proportion of patients achieving an Itch NRS ≥4-point reduction from baseline for patients who had baseline Itch NRS ≥4.
- The Dermatology Life Quality Index (DLQI) was used to evaluate patient's health-related quality of life.

Itch Numeric Rating Scale (NRS)

The NRS is a single-item, patient-reported outcome (PRO) tool developed and validated by the applicant. Patients rate the worst severity of itching in the previous 24 hours on an 11-point numeric rating scale, ranging from 0 (no itching) to 10 (worst itching imaginable). A clinically meaningful itch response was determined by the Applicant to be a 4-point Itch NRS reduction. This was based on analyses obtained with the compound baricitinib as well as ixekizumab and the ability of the Itch NRS to predict a sPGA (0,1) response.

- **Sample size**

The total sample size for the study was planned at 1296 patients randomised in a 1:1:1 ratio to 80 mg Q2W, 80 mg Q4W, or placebo. In order to account for multiple testing for the 2 ixekizumab groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. With 432 patients per treatment group, this study had >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0,1) and PASI 75 at Week 12 (Visit 7).

The following assumptions were used for the power calculations for both sPGA and PASI 75 response rates at Week 12 (Visit 7): 70% for each ixekizumab treatment group and 10% for the placebo group. These assumptions were based on the Phase 2 Study RHAJ results and a review of historical clinical studies in psoriasis.

Assuming 70% of the ixekizumab patients were re-randomized in the Maintenance Dosing Period (Period 3) at Week 12 (Visit 7) in a 1:1:1 ratio to 80 mg Q4W, 80 mg Q12W, or placebo, approximately 100 patients were expected to be included in each treatment group.

- **Randomisation**

At Week 0 (Visit 2), patients who met all criteria for enrolment at Visits 1/1A and 2 were randomized at a 1:1:1 ratio to double-blind treatment groups (80 mg ixekizumab Q2W, 80 mg ixekizumab Q4W, or placebo) as determined by a computer-generated random sequence using an interactive voice response system (IVRS). The IVRS was used to assign double-blind investigational product to each patient. Patients were stratified by geographic regions, previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥3 conventional systemic therapies), and weight (<100 kg or ≥100 kg).

At Week 12 (Visit 7), patients who entered the blinded Maintenance Dosing Period were classified as a responder or non-responder based on sPGA. Patients who received ixekizumab during the Induction Dosing Period (Period 2) and who were responders were re-randomized at a 1:1:1 ratio using the IVRS to 80 mg Q4W, 80 mg Q12W, or placebo. Patients were stratified by weight (<100 kg or ≥100 kg) and by ixekizumab induction dosing regimen (80 mg Q2W or 80 mg Q4W).

Patients who received placebo during the Induction Dosing Period and who were responders were assigned using the IVRS to continue to receive placebo until relapse (defined as a loss of response equal to an sPGA score of ≥3) occurred.

Non-responders who received any investigational product (assigned to any treatment group) during the Induction Dosing Period were assigned using the IVRS to receive treatment with 80 mg Q4W.

- **Blinding (masking)**

This was a double-blind study.

- **Statistical methods**

The main efficacy population used for analyses for the Induction Dosing Period (up to week 12) was the intent-to-treat population (ITT) defined as all randomised patients. For sensitivity purpose, the primary analyses were repeated using the per-protocol set (PPS), defined as all randomised patients who were compliant with therapy, who did not have significant protocol violations, and whose study site did not have significant GCP issues that required a report to the regulatory agencies prior to Week 12.

A gatekeeping testing strategy for the analyses of the primary and a number of major secondary endpoints were implemented to control the overall type I error rate at a 2-sided α level of 0.05. The underlying procedure was derived using the methodology developed in Dmitrienko and Tamhane (2011). In order to account for the 2 ixekizumab groups, tests were to be performed stepwise at a 2-sided α level of 0.025 using the Bonferroni procedure with each test for a particular dose performed only if all prior tests of that dose were statistically significant.

For analyses of categorical efficacy endpoints, including the co-primary and a number of the major secondary endpoints, logistic regression was used with treatment, geographic region, previous non-biologic systemic therapy and baseline weight category in the model. For the categorical efficacy analysis, patients who did not meet clinical response criteria or had missing data at Week 12 were considered non-responders.

As sensitivity analyses for the co-primary efficacy endpoints a placebo Multiple Imputation (pMI) approach was used. Multiple imputations were used to replace missing outcomes for patients, irrespective of treatment arm, who had discontinued using multiple draws from a posterior predictive distribution estimated from the placebo arm. The binary outcomes, sPGA (0,1) and PASI 75, were then derived from the imputed data and the primary analyses repeated.

The primary analyses for all continuous efficacy endpoints were performed using a mixed effect repeated measures (MMRM) model. In the MMRM analyses, treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, baseline value, visit, and treatment-by-visit interaction terms were fitted as fixed factors.

For sensitivity purpose, treatment comparisons for continuous outcomes variables were also performed based on an analysis of covariance (ANCOVA).The ANCOVA model included treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline value.

Subgroup analyses were conducted for the co-primary endpoints with subgroups defined based on e.g. demographics, geographic regions, baseline disease severity and previous psoriasis therapy. Treatment group differences were evaluated within each subgroup using Fisher's exact test. A logistic regression analysis with treatment, subgroup, and the interaction of treatment by subgroup included as factors was used with treatment-by-subgroup interaction tested at the 10% significance level.

Analyses for the Maintenance Dosing Period were performed using the Maintenance Dosing Period Primary Population. This population was defined as all re-randomized patients (i.e. patients who had been randomized to ixekizumab in the Induction Dosing Period who achieved an sPGA [0,1] and were re-randomized at Week 12) who received at least 1 dose of study treatment during the Maintenance Dosing Period. For patients who met relapse criteria and were re-treated with ixekizumab, only data up to the time of relapse was included in the maintenance of effect analyses. These patients were considered non-responders to categorical assessments per the NRI imputation method. Overall, the analysis approach as used for the analyses for the Induction period was used also for the Maintenance Dosing Period; logistic regression (NRI) for categorical endpoints and, MMRM and ANCOVA

(mBOCF/LOCF) for continuous endpoints. Time to relapse, i.e. loss of response defined as a sPGA ≥3, through Week 60 was summarized using Kaplan-Meier estimates. Besides for the proportion of patients maintaining an sPGA (0,1) from Week 12 (after re-randomization) to Week 60 (NRI), defined as a major secondary endpoint and hence included in the gatekeeping strategy, there was no adjustment for multiple comparisons for any other analyses.

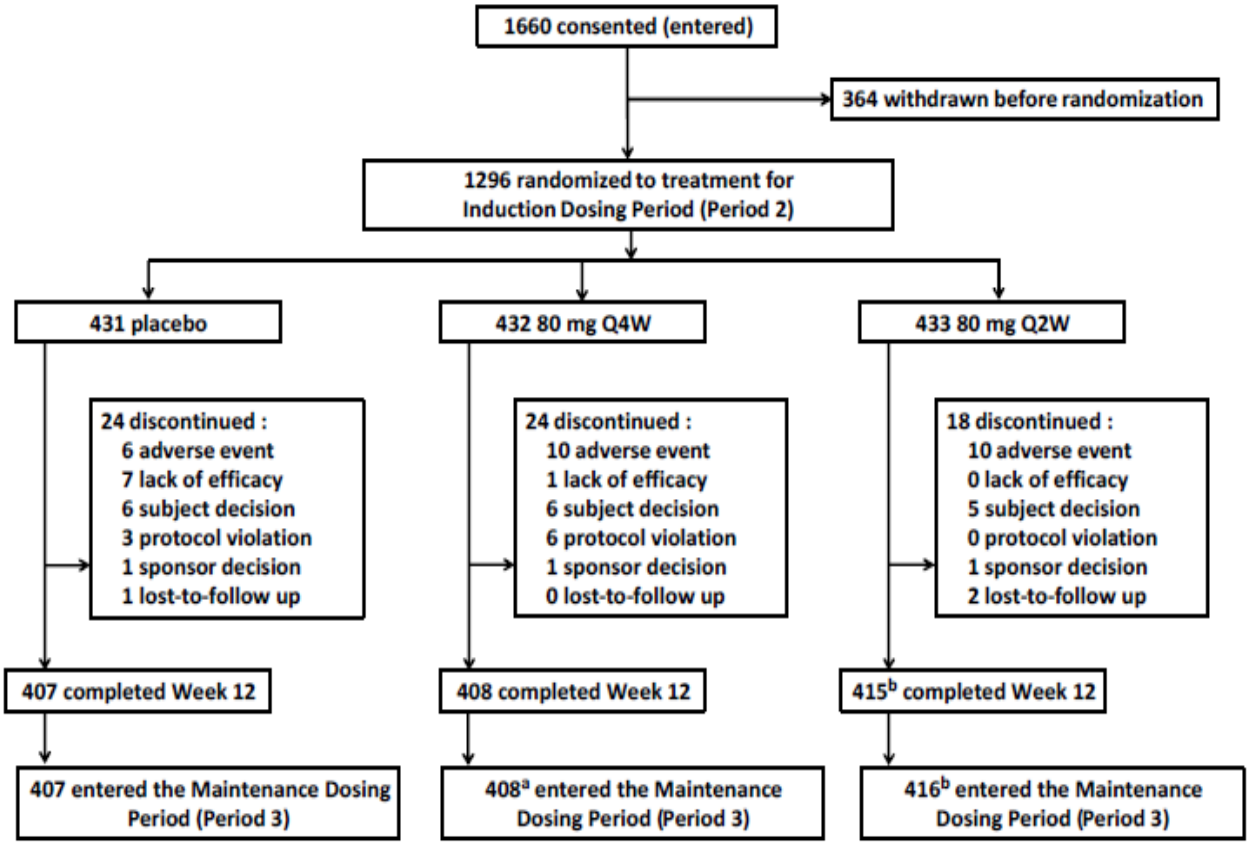
The SAP was approved on 20 Apr 2012 and subsequently amended on 20 Dec 2012 and 19 May 2014. After unblinding there was one change made to planned analyses deemed to have negligible impact on the interpretation of data. The analyses presented in this report are based on data contained in the reporting database that was validated and locked for analysis on 07 Aug 2014.

Results

- **Participant flow**

The patient disposition in the induction and the maintenance dosing periods are depicted in **Figures 9-11**.

Figure 9. Patient disposition Induction Dosing Period, ITT Population, Study RHAZ



Abbreviations: IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; SAP = statistical analysis plan.
a This figure shows 408 patients in the IXE 80-Q4W group who finished the Induction Dosing Period and entered the Maintenance Dosing Period; whereas the figure below shows 407 patients because 1 patient completed the Induction Dosing Period and was re-randomized to the Maintenance Dosing Period at Visit 7 but discontinued at Visit 8 because of investigator decision and did not contribute data to the Maintenance Dosing Period.
b One more patient was recorded as entered the Maintenance Dosing Period than completed the Induction Dosing Period because

1 patient discontinued at Week 12 due to subject decision, but at the same visit on the same day was also re-randomized and took the first dose of Maintenance Dosing Period study drug. Per the SAP definition, the patient was qualified for the Maintenance Dosing Period Primary Population even though he/she discontinued at Week 12.

Figure 10. Patient disposition Maintenance Dosing Period ITT Population, patients treated with ixekizumab 80 mg Q4W in the Induction Dosing Period.

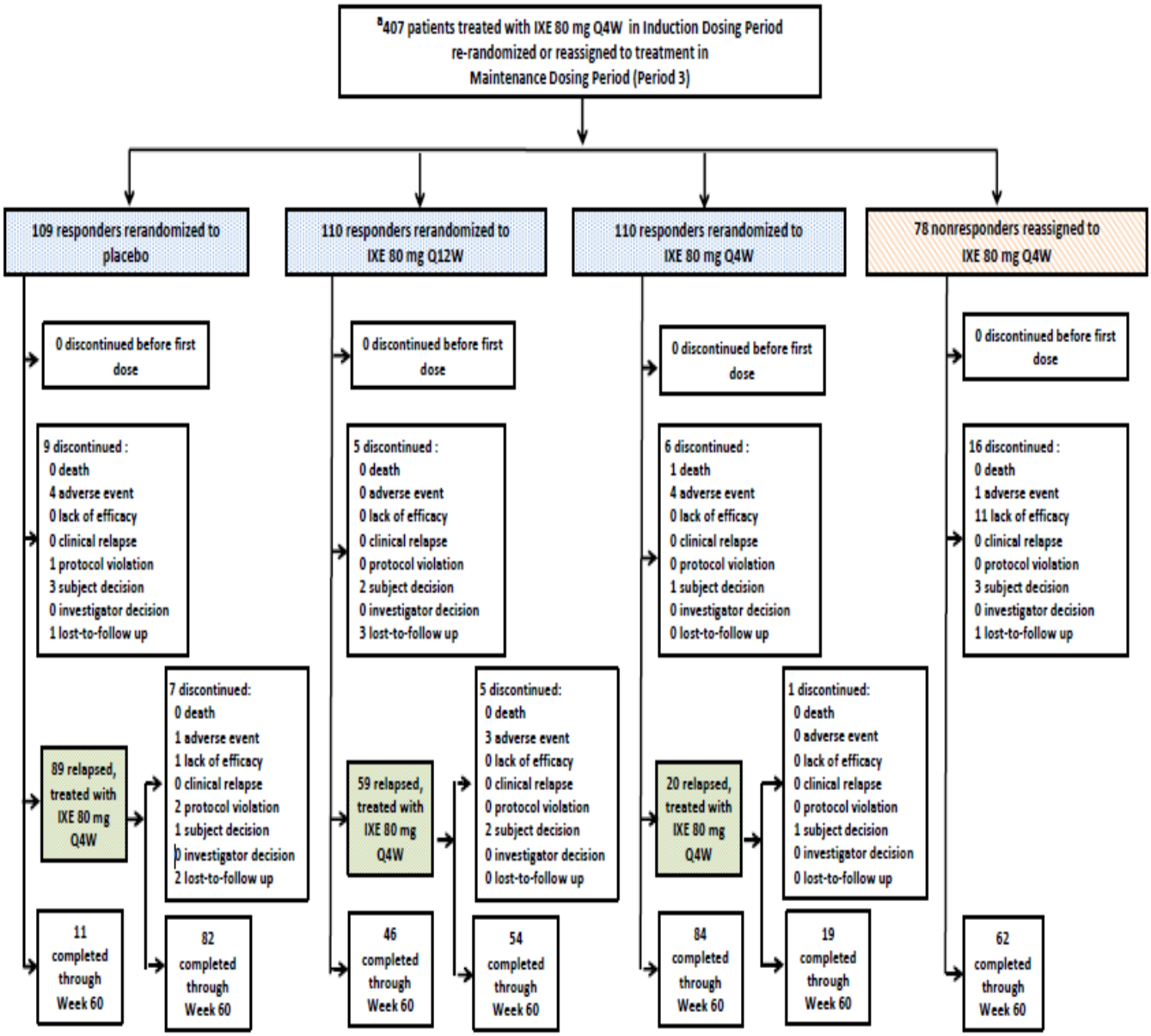
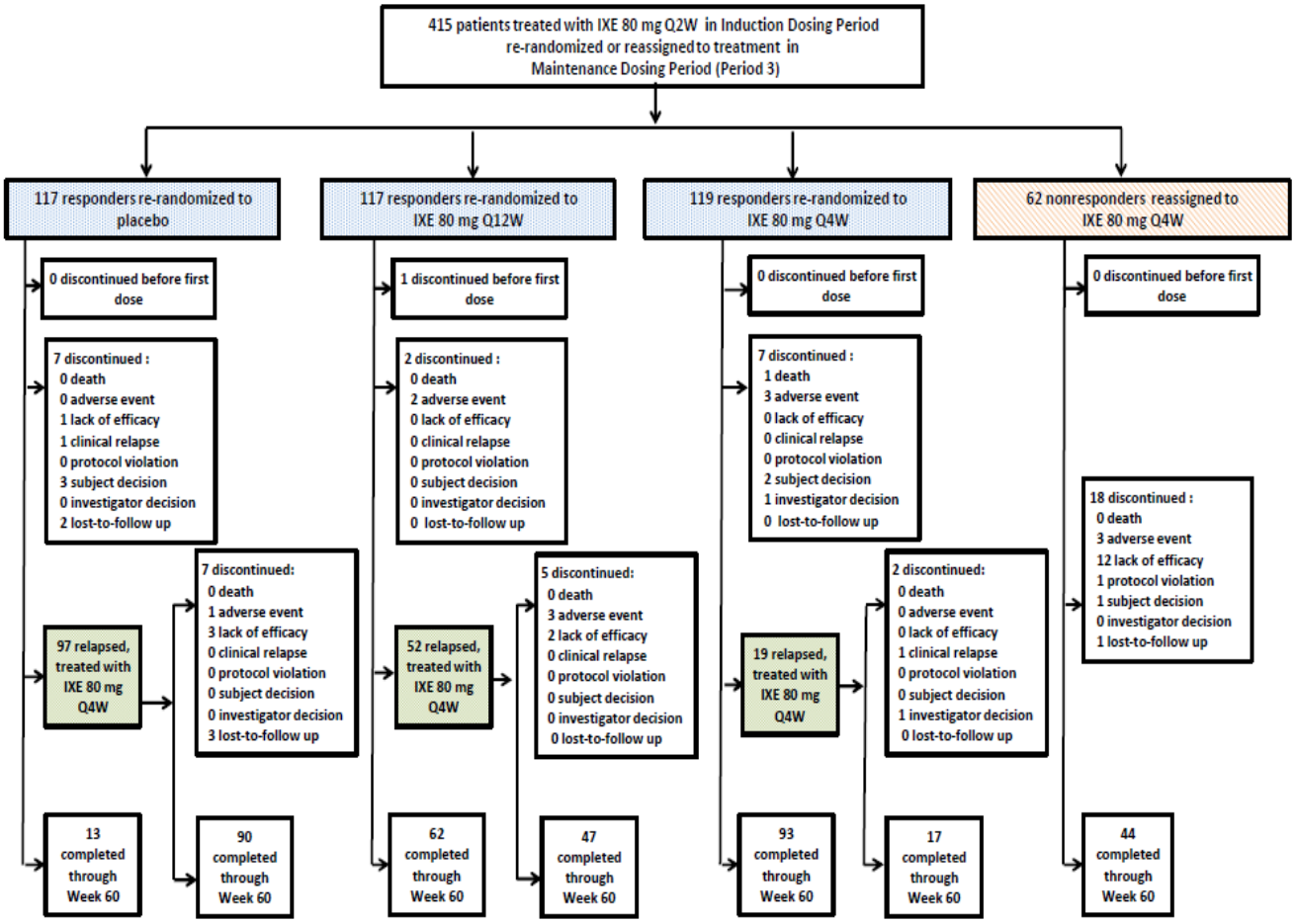


Figure 11. Patient disposition Maintenance Dosing Period ITT Population, patients treated with ixekizumab 80 mg Q2W in Induction Dosing Period.



There were statistically significantly higher percentages of patients who completed the Maintenance Dosing Period in the ixekizumab 80 mg Q4W or Q12W groups than in the placebo group; when summarized by pooled dose, the completion rates were 77.3%, 47.6%, and 10.6%, respectively ($p<.001$ for both comparisons). When comparing the patients who relapsed, there were statistically significantly lower percentages of patients who relapsed in the ixekizumab 80 mg Q4W or Q12W groups than in the placebo group; the relapse rates were 17.0%, 48.9%, and 82.3%, respectively ($p<.001$ for both comparisons). There were no statistically significant difference in the proportions of patients who discontinued across treatment groups.

- **Recruitment**

Study RHAZ was initiated on 06 December 2011 (first patient enrolled/assigned to therapy). The last patient visit prior to database lock for the study report was 24 June 2014 (database lock date 7 Aug 2014).

- **Conduct of the study**

The protocol for this study was approved on 24 August 2011 and was amended on 15 March 2012 and 30 October 2012, two addenda were also made. No changes to the conduct of the study were made after the time of the first unblinding. There was a change made to the planned analyses, but this change did not impact the interpretation of study results.

The revisions in the first amendment included clarification that patients who had no response (that is, patients who remained at or above their baseline sPGA score at both Weeks 12 and 24) were to be discontinued from further treatment, providing further definition of concomitant topical products and clarification of the use of such agents during the study and concomitant therapy analyses, changing the definition of "rebound" to add an evaluation of PASI so that rebound was now defined in terms of sPGA, PASI, and disease phenotype and some changes to the statistical analyses. The second amendment included changes to the statistical analyses.

Protocol deviations

A total of 14% of patients had a major protocol deviation during the Induction Dosing Period; the most common protocol deviation was for missing data (7.3% of patients). There were also low numbers of protocol deviations in the categories that were prospectively identified to exclude patients from the PPS analyses. For patients in the Maintenance Dosing Period Primary Population, 16% had a major protocol deviation during the maintenance period; the most common being missing data (7%). Additional deviations were observed through monitoring, the most common category of other deviations for all study periods combined was improper re-consent (5.5% of patients).

Compliance

A patient was considered non-compliant if he or she missed ≥2 consecutive doses of study drug, missed >20% of the expected doses during the treatment period, or had an occurrence of double dosing (took more injections at the same time point than specified in the protocol). Overall compliance was 98% the Induction Dosing Period and >97% for the Maintenance Dosing Period, with no significant differences between treatment groups.

Baseline data

Patient Demographics and Baseline Characteristics in Study RHAZ are summarised in **Table 22**.

Table 22. Patient Demographics and Baseline Characteristics, Study RHAZ, ITT Population

	RHAZ (N=1296)
Age (Years)	
Mean (SD)	45.7 (12.93)
Gender, n (%)	
Male	883 (68.1)
Female	413 (31.9)
Race, n (%)	
American Indian or Alaska Native	3 (0.2)
Asian	62 (4.8)
Black or African American	26 (2.0)
Native Hawaiian or Other Pacific Islander	1 (0.1)
White	1199 (92.5)
Multiple	5 (0.4)
Geographic Region, n (%)	
Asia	33 (2.5)
North America	673 (51.9)
Europe[a]	548 (42.3)
Central America/South America	0
Australia	42 (3.2)
Weight Category, n (%)	
<100 kg	867 (66.9)
≥100 kg	429 (33.1)
Previous Systemic Therapy, n (%)	
Never Used	372 (28.7)
Nonbiologic Only	402 (31.0)
Biologic Only	168 (13.0)
Biologic and Nonbiologic	354 (27.3)
Previous Nonbiologic Systemic Therapy, n (%)	
Used 1 Therapy	360 (27.8)
Used 2 Therapies	177 (13.7)
Used ≥3 Therapies	219 (16.9)
Previous Nonbiologic Systemic Therapy: Inadequate Response, Intolerance, or Contraindication	
Used <3 Therapies	1145 (88.3)
Used ≥3 Therapies	151 (11.7)
Previous Biologic Therapy, n (%)	
Used 1 Therapy	285 (22.0)
Used 2 Therapies	123 (9.5)
Used ≥3 Therapies	114 (8.8)
Previous Biologic Agent, n (%)	
Tumor Necrosis Factor (TNF)-α Inhibitor (infliximab, etanercept, adalimumab, golimumab)	342 (26.4)
Interleukin (IL) 12/23 Inhibitor (ustekinumab)	161 (12.4)
Other (efalizumab, alefacept, or other)	217 (16.7)
Previous Phototherapy Therapy, n (%)	
Never Used	705 (54.4)
Ever Used	591 (45.6)
Duration of Psoriasis Symptoms in Years	
Mean (SD)	19.6 (11.85)
Baseline static Physician Global Assessment (sPGA), n (%)	
Number of Patients with sPGA = 3	632 (48.8)
Number of Patients with sPGA = 4,5	664 (51.2)
Baseline Psoriasis Area and Severity Index (PASI) Score	
Mean (SD)	20.2 (7.99)
Baseline Itch Numeric Rating Scale (NRS) Score	
Mean (SD)	7.1 (2.49)
Baseline Itch NRS Score, n(%)	
<4	152 (11.7)
≥4	1144 (88.3)
Baseline Dermatology Life Quality Index (DLQI) Score	
Mean (SD)	13.1 (7.05)
Baseline Nail Psoriasis Severity Index (NAPSI) Total Score	
Mean (SD)	25.0 (19.24)

Abbreviations: ITT = intent-to-treat; N = number of patients; n = percentage of patients; SD = standard deviation.

[a] Europe's geographic region includes patients from European Union (EU) member states (1576 patients, 95.3% across all treatment arms [including etanercept], in Austria, France, Netherlands, Spain, United Kingdom, Germany, Italy, Denmark, Poland, Romania, Czech Republic, Hungary, and Bulgaria), and from Russia (77 patients, 4.7% across all treatment arms [including etanercept]), which were combined due to the small number of Russian patients and the preponderance of investigative sites in the west of Russia.

- **Numbers analysed**

Table 23. Study Analysis Populations - Period 2 Induction Dosing, Study RHAZ

Period Population and Status	PBO n (%)	IXE80Q4W n (%)	IXE80Q2W n (%)	Total n (%)
Randomized Patients	431	432	433	1296
Intent to Treat (ITT)	431	432	433	1296
Completed Week 12 (% Relative to ITT)	407 (94.4%)	408 (94.4%)	415 (95.8%)	1230 (94.9%)
Per Protocol Set (PPS) (% relative to ITT)	404 (93.7%)	391 (90.5%)	406 (93.8%)	1201 (92.7%)
Completed Week 12 (% Relative to Above Row)	390 (96.5%)	377 (96.4%)	393 (96.8%)	1160 (96.6%)
Safety (% Relative to ITT)	431 (100.0%)	432 (100.0%)	433 (100.0%)	1296 (100.0%)
Completed Week 12 (% Relative to Above Row)	407 (94.4%)	408 (94.4%)	415 (95.8%)	1230 (94.9%)

Notes: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W;

Table 24. Study Analysis Populations - Period 3 Maintenance Dosing

	PBO		IXE80Q4W				IXE80Q2W				
	Resp	Non-Resp	Resp	Resp	Resp	Non-Resp	Resp	Resp	Resp	Non-Resp	
Period Population and Status	PBO	IXE80Q4W	PBO	IXE80Q12W	IXE80Q4W	IXE80Q4W	PBO	IXE80Q12W	IXE80Q4W	IXE80Q4W	Total
Maintenance Dosing Period Primary Population			109	110	110		117	117	119		682
Maintenance Dosing Period Secondary Population	16	391				78				62	547

Notes: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q12W = Ixekizumab 80 mg Q12W; Resp = responder; Non-Resp = non-responder.
Column header: line 1 - treatment during induction dosing period; line 2 - response status at Week 12 as recorded in interactive voice response system (IVRS); line 3 - assigned treatment for maintenance dosing period.

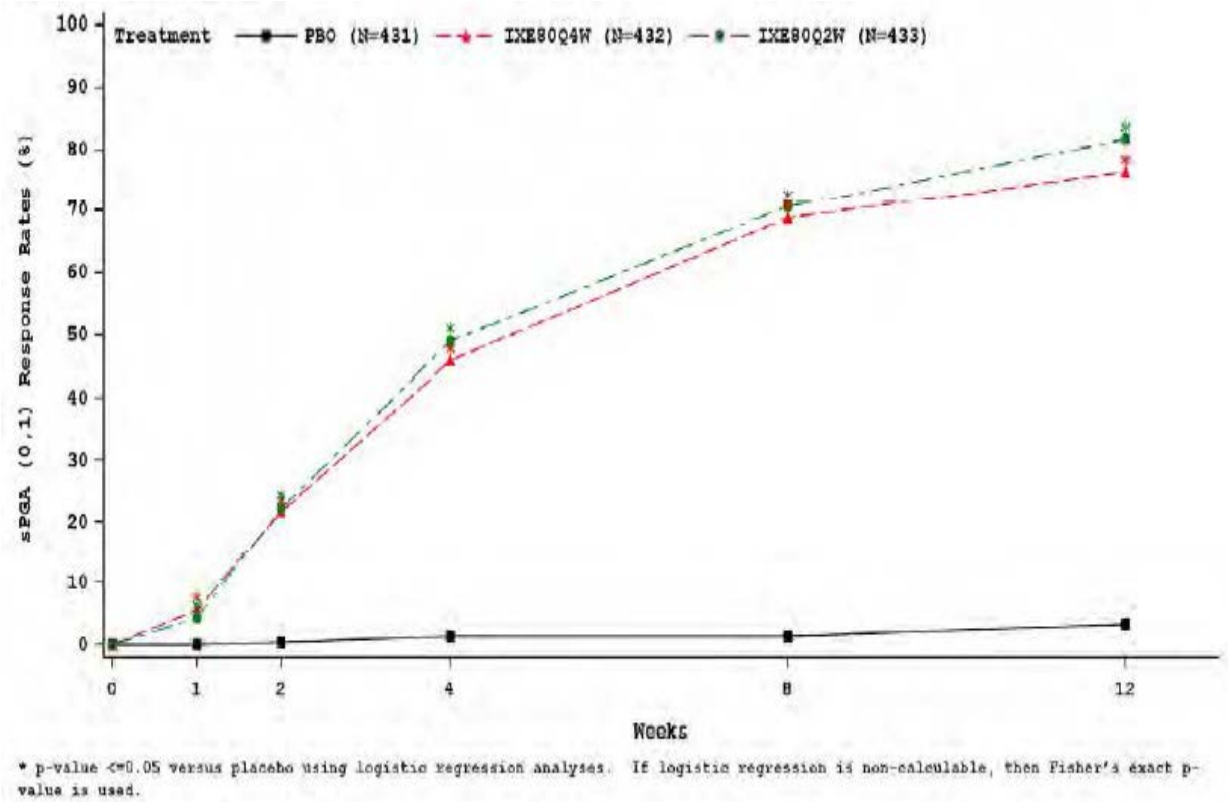
- **Outcomes and estimation**

Primary efficacy end-points

After 12 weeks of treatment, both ixekizumab treatment groups were superior to placebo as measured by the proportions of patients achieving sPGA (0,1) with at least a 2-point improvement from baseline and as measured by the proportion of patients achieving PASI 75.

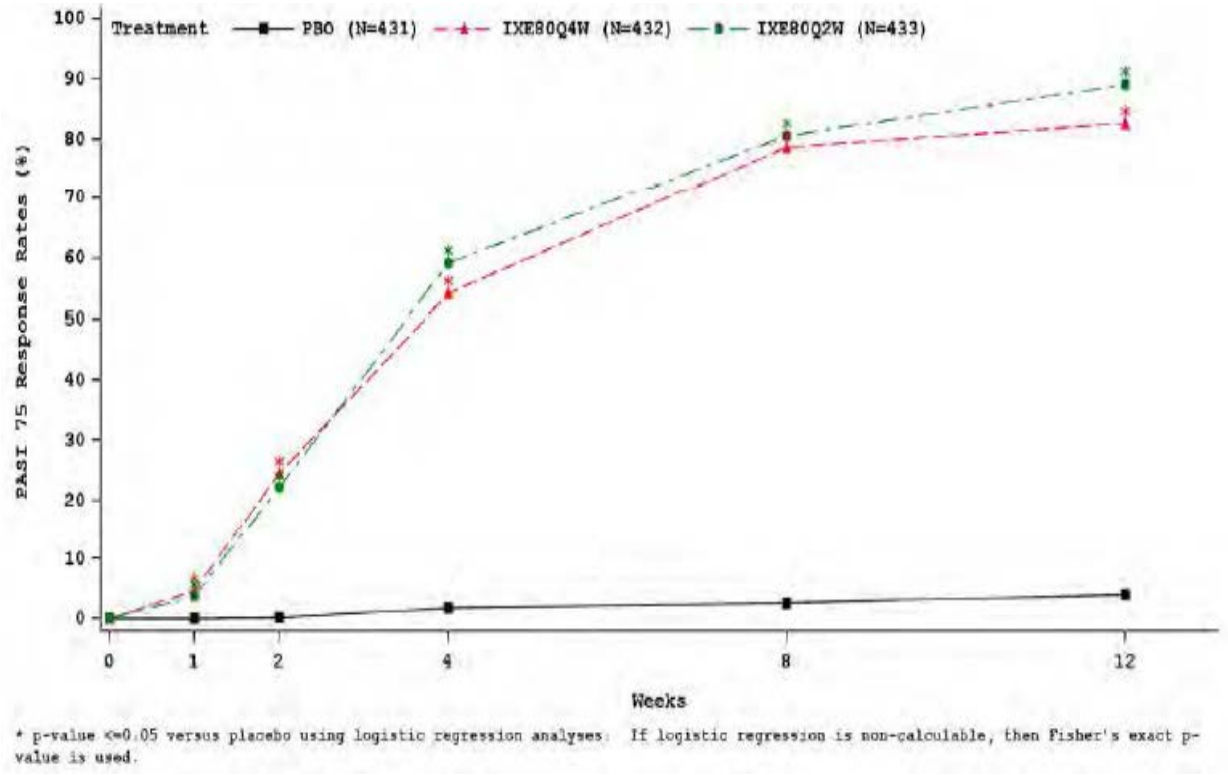
At Week 12, the response rates for sPGA (0,1) for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups were 81.8% 76.4%, and 3.2%, respectively (ITT, NRI). P-values for both ixekizumab doses were <0.001 compared to placebo. The response rates over time are shown in **Figure 12**.

Figure 12. sPGA (0,1) response rates at each post-baseline visit (NRI) Intent-to-Treat Population, Induction Dosing Period



At Week 12, the response rates for PASI 75 for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups were 89.1%, 82.6%, and 3.9%, respectively (ITT, NRI). P-values for both ixekizumab doses were <0.001 compared to placebo. The response rates over time are shown in **Figure 13**.

Figure 13. PASI 75 response rates at each post-baseline visit (NRI) Intent-to-Treat Population Induction Dosing Period



The primary efficacy analyses were repeated on the Per-Protocol Set. The PPS included 1201 patients (92.7% of the ITT Population). The results of these sensitivity analyses were consistent with the primary analyses.

Gated secondary efficacy end-points

sPGA (0) at Week 12

At Week 12, the sPGA (0) response rates for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups were 37.0%, 34.5%, and 0%, respectively (NRI).

PASI 90 at Week 12

At Week 12, the PASI 90 response rates for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups were 70.9%, 64.6%, and 0.5%, respectively (NRI).

PASI 100 at Week 12

At Week 12, the PASI 100 response rates for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups were 35.3%, 33.6%, and 0, respectively (NRI).

Itch NRS at Week 12

At Week 12, the proportion of patients achieving a 4-point reduction in the Itch NRS scale for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups were 85.9%, 80.5%, and 15.5%, respectively.

DLQI at Week 12

At baseline, mean (SD) DLQI total scores (on the 30-point DLQI) for patients randomized to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo were 13.4 (7.0), 13.2 (7.0), and 12.8 (7.1), respectively.

At Week 12, the LS mean changes in DLQI total scores were -11.1, -10.7, and -1.0 for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups, respectively.

NAPSI at Week 12

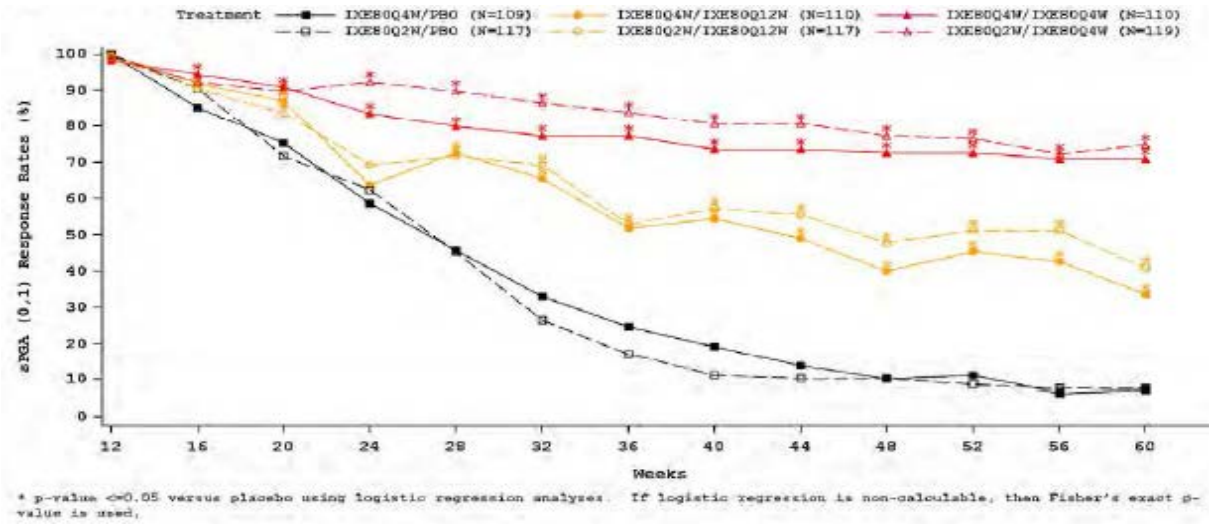
At baseline, mean (SD) NAPSI scores for patients who had fingernail involvement and were randomized to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo were 24.6 (18.9), 24.1 (18.2), and 26.1 (20.5), respectively.

After 12 weeks of treatment, both ixekizumab groups showed a statistically significant therapeutic advantage over placebo, as measured by change from baseline (MMRM) in NAPSI total scores. At Week 12, the LS mean changes from baseline in NAPSI scores were -7.24, -7.19, and 2.17 for the ixekizumab 80-mg Q2W, ixekizumab 80-mg Q4W, and placebo groups, respectively.

Maintenance of sPGA (0,1) at Week 60

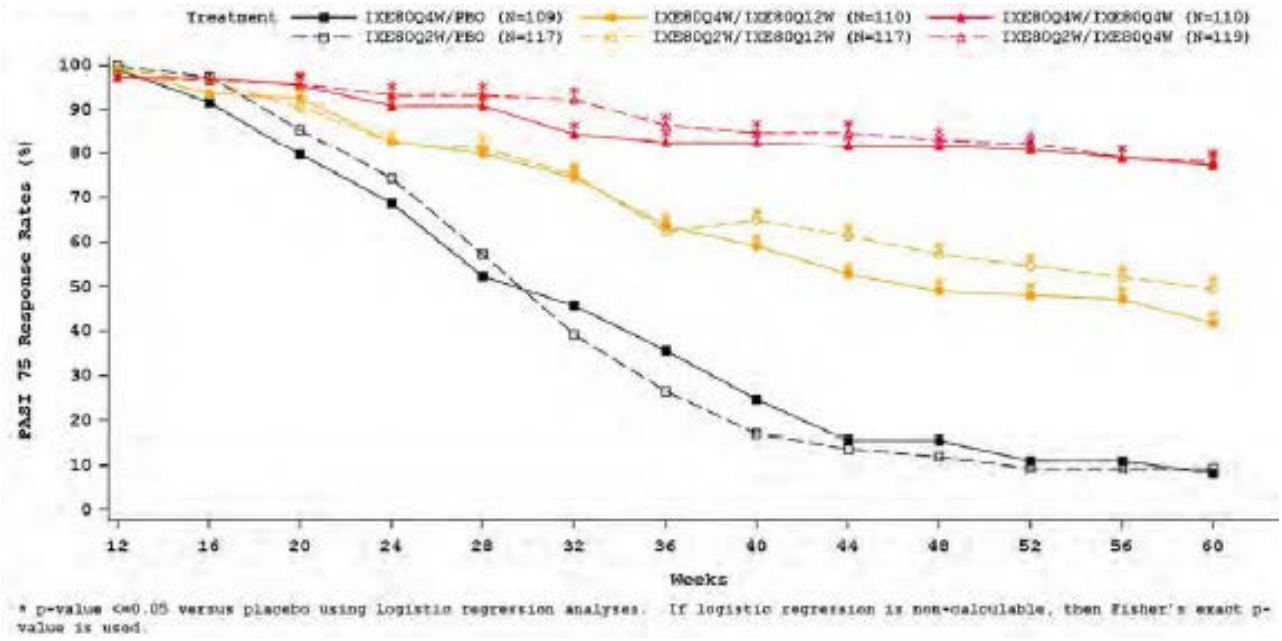
At Week 60, both ixekizumab groups showed a statistically significant therapeutic advantage over placebo, as measured by the proportion of patients maintaining sPGA (0,1) at Week 60. When analysed by individual dose group, sPGA (0,1) response rates at Week 60 among patients who had received ixekizumab 80 mg Q2W during the Induction Dosing Period were 74.8%, 41.0%, and 7.7% among those re-randomized to ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, and placebo, respectively. Response rates among patients who had received ixekizumab 80 mg Q4W during the Induction Dosing Period were 70.9%, 33.6%, and 7.3% among those re-randomized to ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, and placebo, respectively.

Figure 14. sPGA (0,1) response rates at each postbaseline visit (NRI) by dose (Maintenance Dosing Period Primary Population).



PASI 75 response rates during the Maintenance period

Figure 15. PASI 75 response rates at each postbaseline visit (NRI) by individual dose Maintenance Dosing Period Primary Population



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RHBA: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis

Methods

Study Participants

The main inclusion and exclusion criteria as well as prior and concomitant therapy were very similar to those in Study RHAZ with the exception that patients with prior etanercept use were excluded from this study.

- **Treatments**

Similar to Study RHAZ, this study consists of 5 periods; a Screening Period (Period 1), a Blinded Induction Dosing Period (Period 2) from Week 0 to Week 12, a Blinded Maintenance Dosing Period (Period 3), a Long-Term Extension Period (Period 4) up to Week 264 and a Post-Treatment Follow-Up Period.

At **Week 0** (baseline), patients who met all enrolment criteria during the Screening Period were randomized into the blinded Induction Dosing Period at a 2:2:2:1 ratio to double-blind treatment groups:

- **80 mg ixekizumab Q2W:** A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10). Placebo for etanercept (1 SC injection) given twice weekly starting at Week 0 up to Week 12.
- **80 mg ixekizumab Q4W:** A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q4W (Weeks 4 and 8). Placebo for ixekizumab given as 1 SC injection at Weeks 2, 6, and 10 and Placebo for etanercept (1 SC injection) given twice weekly starting at Week 0 up to Week 12.
- **Placebo:** Placebo for ixekizumab (Week 0) given as 2 SC injections followed by placebo for ixekizumab Q2W (Weeks 2, 4, 6, 8, and 10). Placebo for etanercept (1 SC injection) given twice weekly (every 3 to 4 days) starting at Week 0 up to Week 12.

- **Etanercept 50 mg twice weekly:** Etanercept 50 mg (1 SC injection) given twice weekly (every 3 to 4 days) starting at Week 0 and up to Week 12. Placebo for ixekizumab given as 2 SC injections (Week 0) followed by placebo for ixekizumab Q2W given as 1 SC injection (Weeks 2, 4, 6, 8, and 10).

At **Week 12**, patients who entered the blinded Maintenance Dosing Period were classified as either "responders" or "non-responders" according to the following criteria:

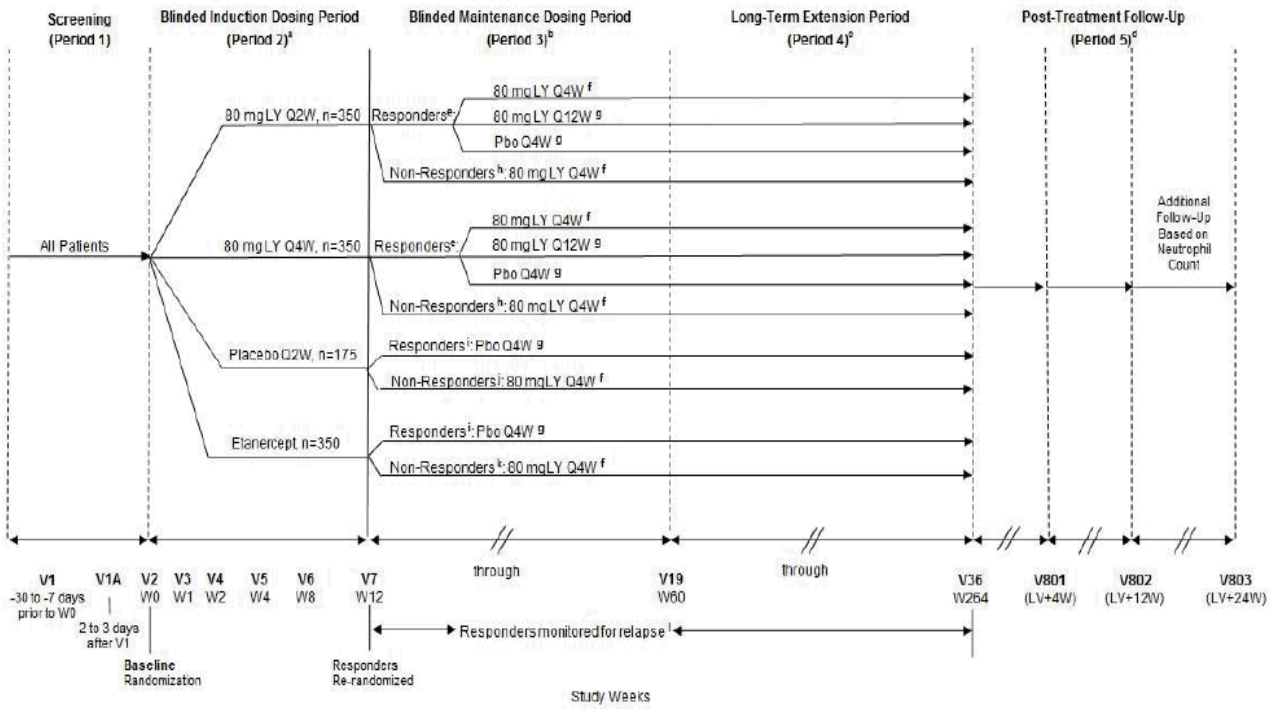
- **Responder:** sPGA score of "0" or "1" with at least a 2-point improvement from baseline
- **Non-responder:** sPGA score >1

Ixekizumab-treated patients who were classified as responders were re-randomized to treatment in the Maintenance Dosing Period at a 1:1:1 ratio to 1 of 3 treatment groups: **Ixekizumab 80 mg Q4W**, **Ixekizumab 80 mg Q12W**, or **Placebo**, and were considered the Maintenance Dosing Period Primary Population.

Placebo- or etanercept-treated patients who were classified as responders were assigned to placebo treatment and all patients who were classified as non-responders were given ixekizumab 80 mg Q4W in the Maintenance Dosing Period; these patients were considered the Maintenance Dosing Period Secondary Population.

Following relapse (regardless of group), a dose regimen of 80 mg Q4W (1 SC injection) was administered and continued to be administered for the remainder of the study to maintain the study blind and to see if study response can be regained with continued treatment (for the Q4W group) or on treatment with a higher dose (for the Q12W group).

Figure 16. Study design of RHBA



Abbreviations: IP = investigational product; LV = date of last treatment period visit; LY = ixekizumab (LY2439821); n = number of patients; Pbo = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous; sPGA = static Physician's Global Assessment; V = study visit; W = study week.

a All patients received SC doses of IP (ixekizumab [Q2W or Q4W], placebo, or etanercept [twice weekly]) starting at Week 0 (Visit 2) up to Week 12.
b All patients will receive 2 SC doses of IP (ixekizumab or placebo) at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 60 (Visit 19). Study visits will occur at least Q4W during Period 3.
c Study visits will occur at least Q12W during Period 4. Treatment (ixekizumab and placebo) will remain blinded to investigators, study site personnel, and patients until all patients reach Week 60 (Visit 19) or have discontinued from the study (moved into Period 5).
d All patients receiving investigational product must enter into Period 5 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed.
e Responders to ixekizumab at Week 12 (Visit 7; responders are defined as achieving an sPGA score of 0 or 1) were randomly assigned at a 1:1:1 ratio to ixekizumab (Q4W, Q12W), or to placebo.
f Patients who experience loss of treatment efficacy (relapse) during Period 3 will remain on ixekizumab 80 mg Q4W in order to maintain the blind.
g Patients who experience loss of treatment efficacy (relapse) during Period 3 will be switched to ixekizumab 80 mg Q4W.
h Non-responders to ixekizumab at Week 12 (Visit 7; non-responders are defined as having an sPGA score >1) will receive ixekizumab 80 mg Q4W.
i Responders to placebo or etanercept at Week 12 (Visit 7) will receive 2 injections of placebo at Week 12 followed by placebo Q4W until relapse.
j Non-responders to placebo at Week 12 (Visit 7) will receive 2 injections of ixekizumab (starting dose) at Week 12 followed by ixekizumab 80 mg Q4W.
k Non-responders to etanercept at Week 12 (Visit 7) will receive 2 injections of placebo at Week 12 followed by ixekizumab 80 mg Q4W starting at Week 16.
l Relapse occurring after Week 12 (Visit 7) is defined as a loss of response equal to an sPGA score ≥3.

- **Objectives**

The primary objectives were to assess, using a gatekeeping testing strategy, whether ixekizumab 80 mg every 2 weeks (Q2W) or every 4 weeks (Q4W) were:

- Superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis as measured by the proportion of patients with a sPGA (0,1) with at least a 2-point improvement from baseline and the proportion of patients achieving PASI 75 from baseline.
- Non-inferior to etanercept at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis based on sPGA (0,1) and PASI 75
- Superior to etanercept at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis based on sPGA (0,1) and PASI 75

- **Outcomes / endpoints**

Primary efficacy end-points and analyses

– Proportion of Patients with sPGA (0,1) and at least a 2-Point Improvement from Baseline at Week 12 compared with Placebo

– Proportion of Patients Achieving PASI 75 at Week 12 compared with Placebo

– Proportion of Patients with sPGA (0 or 1) at Week 12, non-inferiority vs. Etanercept

This non-inferiority analysis was conducted only if the ixekizumab dose was significantly better than placebo, and etanercept was significantly better than placebo.

– Proportion of Patients with PASI 75 at Week 12, non-inferiority vs. Etanercept

This non-inferiority analysis was conducted only if the ixekizumab dose was significantly better than placebo, and etanercept was significantly better than placebo.

– Proportion of Patients with sPGA (0 or 1) at Week 12, superiority vs. Etanercept

– Proportion of Patients with PASI 75 at Week 12, superiority vs. Etanercept

Major Secondary Efficacy Analyses

- Proportion of Patients with sPGA (0) (remission) at Week 12 Compared with Placebo
- Proportion of Patients with PASI 90 at Week 12 Compared with Placebo
- Proportion of Patients with PASI 100 (remission) at Week 12 Compared with Placebo
- Proportion of Patients with sPGA of 0 at Week 12 Superiority to Etanercept
- Proportion of Patients Maintaining sPGA (0,1) from Week 12 to Week 60 vs. Placebo

Similarly to study RHAZ, other secondary efficacy measures used were the NAPSI, PSSI and PPASI. Several Health Outcomes Measures were also assessed (e.g. the Itch NRS, DLQI).

- **Sample size**

The total planned sample size for the study was 1224 patients randomized at a 2:2:2:1 ratio to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, etanercept, and placebo, respectively (350:350:350:175 patients per treatment group, respectively). In order to account for multiple testing for the 2 ixekizumab groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. This study has >93% power to test the superiority of each ixekizumab dose regimen to etanercept and >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0,1) and for PASI 75 at Week 12 (Visit 7).

The sample size of 350 patients in each ixekizumab dosage regimen and etanercept provided >90% power to achieve non-inferiority. The power calculation was based on the following assumptions:

• Retention rate of 70% for the co-primary endpoints, sPGA (0,1) and PASI 75

• 56% for sPGA (0,1) and 53% for PASI 75 for each ixekizumab dosage regimen (assumes that each ixekizumab dosage regimen has the same response rates as etanercept)

• 56% for sPGA (0,1) and 53% for PASI 75 for etanercept

• 10% for sPGA (0,1) and PASI 75 for the placebo group

• 2-sided, alpha = 0.025.

With a retention rate of 70% and an observed sPGA (0,1) difference between etanercept and placebo of 46% (etanercept = 56%, PPBO = 10%), the non-inferiority margin was estimated to be approximately 13.8%. With a retention rate of 70% and an observed PASI 75 difference between etanercept and placebo of 43% (etanercept = 53%, PPBO = 10%), the non-inferiority margin was estimated to be approximately 12.9%.

- **Randomisation**

At Week 0 (Visit 2), patients who met all enrollment criteria were randomized at a 2:2:2:1 ratio to double-blind treatment groups (ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, etanercept, or placebo) as determined by a computer-generated random sequence using an IVRS. The IVRS was used to assign double-blind IP to each patient. Patients were stratified by center.

At Week 12 (Visit 7), patients who entered the blinded Maintenance Dosing Period were classified as a responder or non-responder. Patients who received ixekizumab during the Induction Period and were responders were re-randomized at a 1:1:1 ratio using the IVRS to ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, or placebo to match ixekizumab. Patients were stratified by weight (<100 kg or ≥100 kg) and by ixekizumab induction dosing regimen (80 mg Q2W or 80 mg Q4W).

Patients who received placebo during the Induction Period and who were responders were assigned using the IVRS to continue to receive placebo until relapse (defined as a loss of response equal to an sPGA score ≥3) occurred. Patients who received etanercept during the Induction Period and who were responders were assigned to receive placebo until relapse occurred.

Non-responders who were assigned to any treatment group during the Induction Dosing Period were assigned using the IVRS to receive treatment with ixekizumab 80 mg Q4W (etanercept non-responders received the first dose of ixekizumab at Week 16).

- **Blinding (masking)**

This was a double-blind study.

- **Statistical methods**

Main efficacy population and gatekeeping strategy were identical with those of study RHAZ. Analyses of categorical efficacy endpoints, including the co-primary and a number of the major secondary endpoints, were, based on a Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre. For the categorical efficacy analysis, patients who did not meet clinical response criteria or had missing data at Week 12 were considered non-responders.

For the assessment of non-inferiority, each ixekizumab dose regimen compared to etanercept, the primary analysis was based on the ITT but were to be supported by an analysis based on the PPS. The analyses for assessing non-inferiority were to be conducted only if the ixekizumab dose was significantly better than placebo, and etanercept was significantly better than placebo. Using the retention rate approach non-inferiority was to be claimed if the lower bound of the 2-sided 97.5% CI of the ratio of the differences in the co-primary endpoints at Week 12 was shown to be greater than 0.70. In the retention rate approach, the proportion of etanercept's effect versus placebo that is retained by ixekizumab (retention rate) is assessed. A retention rate threshold of 0.70 was used in this study. Non-inferiority testing of each ixekizumab dose compared to etanercept was carried out by a test of the null hypothesis as follows:

$$H_0 \quad \frac{P_{LY} - P_{PBO}}{P_{etan} - P_{PBO}} \leq 70\%$$

The primary analyses for all continuous efficacy endpoints were performed using a mixed effect repeated measures (MMRM) model. In Study RHBA, the MMRM model included treatment, pooled center, baseline value, visit, and the interaction of treatment-by-visit as fixed factors. For sensitivity purposes, treatment comparisons for continuous outcomes variables were also performed based on an analysis of covariance (ANCOVA). In this study, the model included treatment, pooled centre, and baseline value. As with study RHAZ, missing data were imputed using a modified baseline observation carried forward (mBOCF) approach and by using last observation carried forward (LOCF).

A Maintenance Dosing Period Primary Population was defined also in Study RHBA (same definition as in RHAZ). Due to the database lock occurring after the last patient enrolled completed the Week 36 visit of the Maintenance Dosing Period, efficacy responses over the Maintenance Dosing Period from Week 12 to Week 60 was assessed using an Efficacy Evaluable patient subset of the Maintenance Dosing Period Primary Population. This subset comprised patients who had completed Week 60, discontinued prior to Week 60, or relapsed prior to Week 60 at the time of the 36-week interim database lock. Presentation of results for sPGA and PASI measures for the Maintenance Dosing Period were by individual dose and pooled dose. For all other efficacy and health outcomes measures, presentation of data was only by pooled dose. Treatment comparisons of categorical efficacy endpoints were analyzed

using a Fisher's exact test. Treatment comparisons for continuous efficacy variables were made using MMRM and ANCOVA models. Time to relapse, that is a loss of response (defined as a sPGA ≥3), through Week 60 for the Maintenance Dosing Period Primary Population – Efficacy Evaluable Patients were summarized using Kaplan-Meier estimates.

The SAP was approved on 18 Jun 2012 and amended on 21 Dec 2012 and 13 May 2014. No changes to the conduct of the study or the planned analyses were made after the time of the first unblinding of Lilly personnel to study data on 24 May 2014 (Week 12 interim database lock). The reporting database was validated and subsequently locked on 01 Oct 2014 for an interim analysis of data collected up to the last patient visit at Week 36 (Visit 13) of the Maintenance Dosing Period.

Results

- **Participant flow**

Patient disposition in Study RHBA during the blinded induction and maintenance dosing periods are illustrated in **Figures 17** and **18** respectively.

Figure 17. Patient disposition from study treatment during the blinded induction dosing period of study RHBA

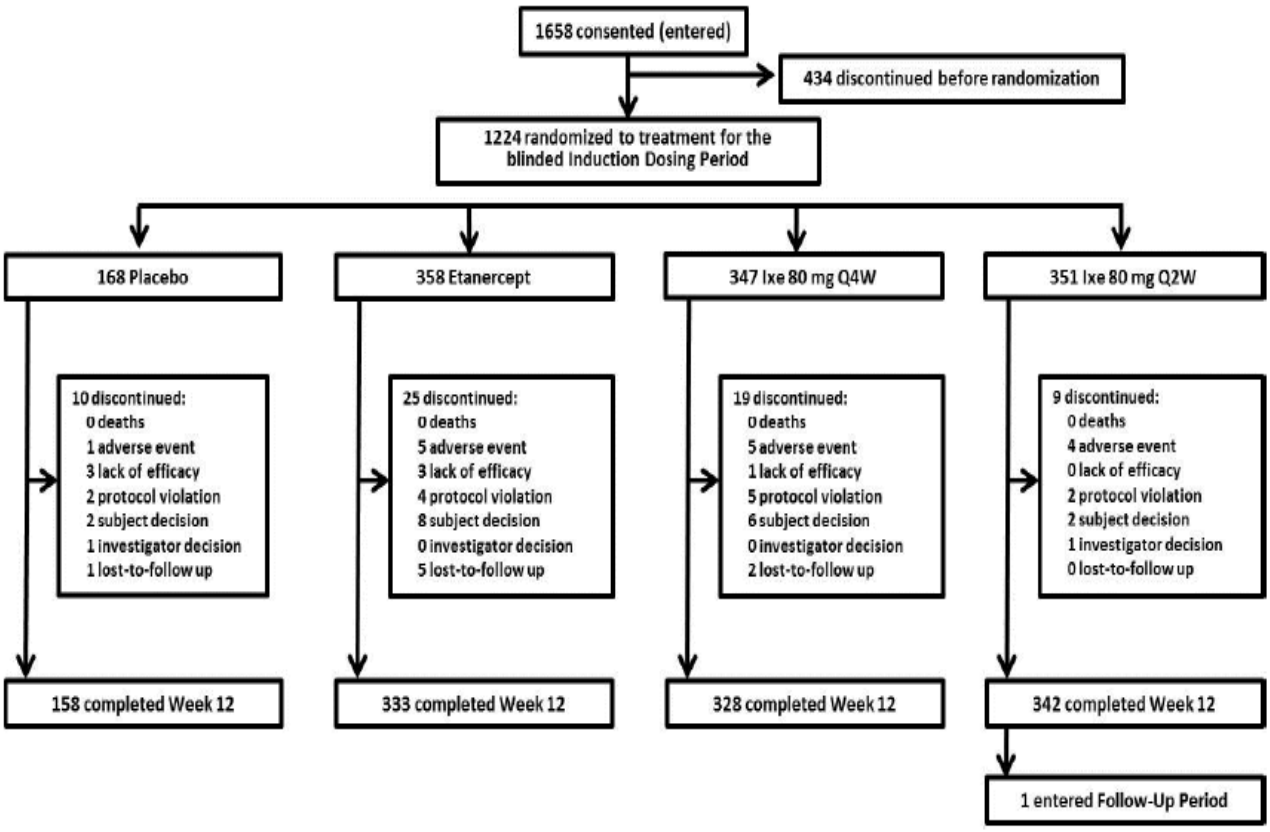
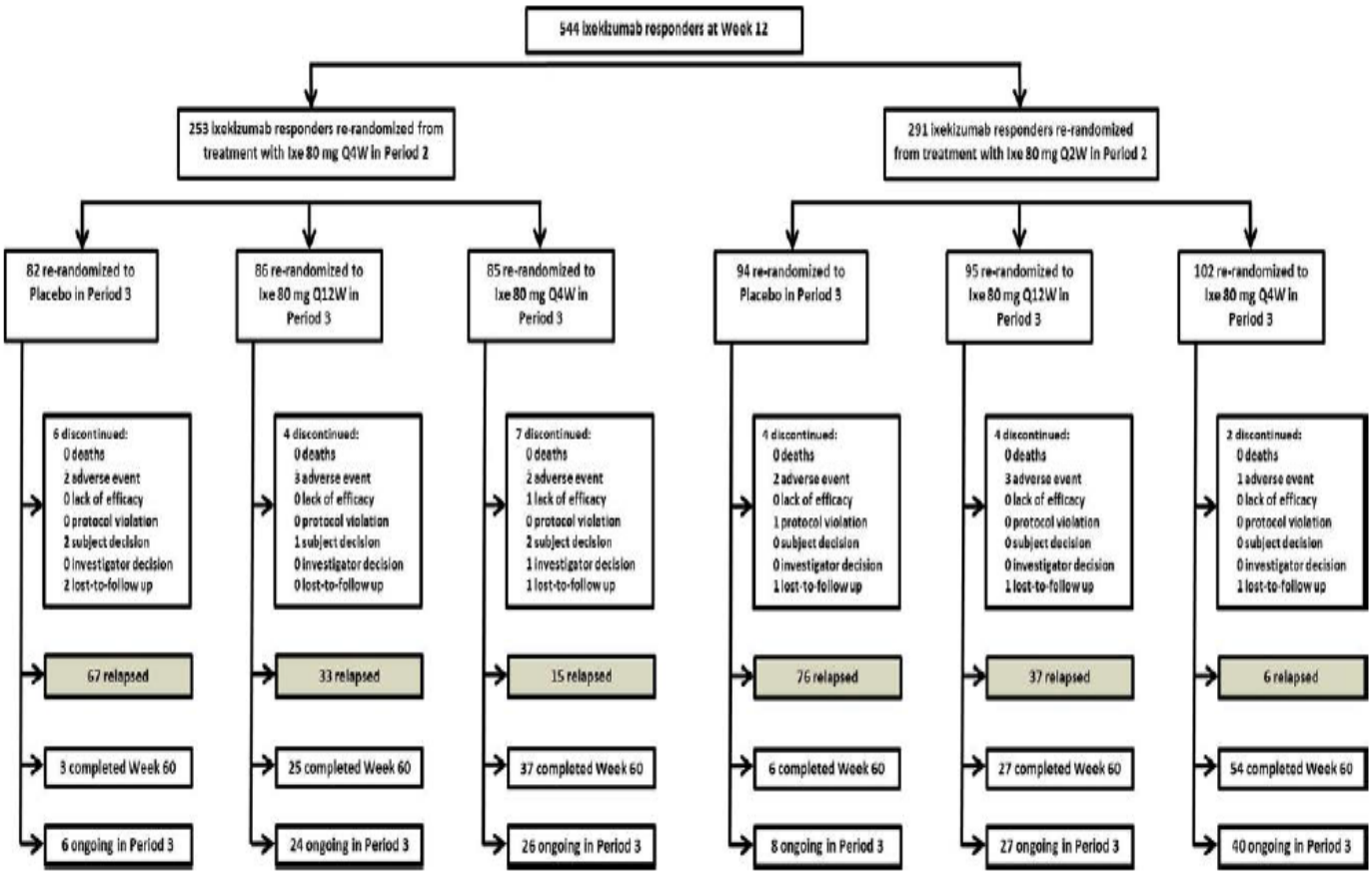


Figure 18. Patient disposition from study treatment during the blinded maintenance dosing Period of study RHBA



- **Recruitment**

Study RHBA was initiated on 30 May 2012 (first patient enrolled/assigned to therapy). The study report included in the MAA presents an interim analysis of data collected through 01 October 2014 (Database lock), including all data up to the last patient visit at Week 36 (Visit 13) of the Maintenance Dosing Period.

- **Conduct of the study**

The protocol for this study was approved on 18 October 2011 and was amended on 15 March 2012 and 31 October 2012. The revisions concerned addition of monthly urine pregnancy testing, change of entry criteria to exclude patients positive for hepatitis B surface antigen or anti-hepatitis B core antibody, revised hepatic safety monitoring, revised exclusion and discontinuation criteria to exclude patients who had or developed a contraindication to etanercept, per the local label, and revised statistical analyses (many of these made after feedback from the FDA).

Protocol deviations

A total of 27.5% of patients had a major protocol deviation during the Induction Dosing Period; the most common protocol deviation was for missing data (10.8% of patients, most commonly missing ECGs). Other common deviations were failure to meet study inclusion criteria (e.g. due to improper informed consent, 7%), met study exclusion criteria but was entered into the study (5%), due to non-compliance with study medication or double-dosing (6.4%) or took incorrect study medication (5%).

For the Maintenance Dosing Period Primary Population, 21% of patients had major protocol deviations.

Compliance

During the Induction Dosing Period, approximately 94% of patients (range across treatment arms 92%-95%) were overall compliant with treatment. During the Maintenance Dosing Period, approximately 94% of patients (range 92%-95%) in the Maintenance Dosing Period Primary Population were compliant with treatment at the time of the database lock. No statistically significant differences were observed between the treatment groups in either population.

- **Baseline data**

Table 25. Patient Demographics and Baseline Characteristic, Study RHBA. ITT Population

	RHBA (N=1224)
Age (Years)	
Mean (SD)	45.0 (13.04)
Gender, n (%)	
Male	821 (67.1)
Female	403 (32.9)
Race, n (%)	
American Indian or Alaska Native	6 (0.5)
Asian	37 (3.0)
Black or African American	39 (3.2)
Native Hawaiian or Other Pacific Islander	3 (0.2)
White	1125 (92.6)
Multiple	5 (0.4)
Geographic Region, n (%)	
Asia	0
North America	657 (53.7)
Europe[a]	516 (42.2)
Central America/South America	0
Australia	51 (4.2)
Weight Category, n (%)	
<100 kg	826 (67.7)
≥100 kg	394 (32.3)
Previous Systemic Therapy, n (%)	
Never Used	438 (35.8)
Nonbiologic Only	498 (40.7)
Biologic Only	109 (8.9)
Biologic and Nonbiologic	179 (14.6)
Previous Nonbiologic Systemic Therapy, n (%)	
Used 1 Therapy	335 (27.4)
Used 2 Therapies	179 (14.6)
Used ≥3 Therapies	163 (13.3)
Previous Nonbiologic Systemic Therapy: Inadequate Response, Intolerance, or Contraindication	
Used <3 Therapies	1137 (92.9)
Used ≥3 Therapies	87 (7.1)
Previous Biologic Therapy, n (%)	
Used 1 Therapy	198 (16.2)
Used 2 Therapies	58 (4.7)
Used ≥3 Therapies	32 (2.6)
Previous Biologic Agent, n (%)	
Tumor Necrosis Factor (TNF)-α Inhibitor (infliximab, etanercept, adalimumab, golimumab)	139 (11.4)
Interleukin (IL) 12/23 Inhibitor (ustekinumab)	102 (8.3)
Other (efalizumab, alefacept, or other)	112 (9.2)
Previous Phototherapy Therapy, n (%)	
Never Used	654 (53.4)
Ever Used	570 (46.6)
Duration of Psoriasis Symptoms in Years	
Mean (SD)	18.7 (12.46)
Baseline static Physician Global Assessment (sPGA), n (%)	
Number of Patients with sPGA = 3	616 (50.3)
Number of Patients with sPGA = 4,5	608 (49.7)
Baseline Psoriasis Area and Severity Index (PASI) Score	
Mean (SD)	19.6 (7.22)

Baseline Itch Numeric Rating Scale (NRS) Score	
Mean (SD)	6.6 (2.55)
Baseline Itch NRS Score, n(%)	
<4	187 (15.3)
≥4	1037 (84.7)
Baseline Dermatology Life Quality Index (DLQI) Score	
Mean (SD)	12.3 (6.91)
Baseline Nail Psoriasis Severity Index (NAPSI) Total Score	
Mean (SD)	26.9 (20.19)

Abbreviations: ITT = intent-to-treat; N = number of patients; n = percentage of patients; SD = standard deviation.

[a] Europe's geographic region includes patients from European Union (EU) member states (1576 patients, 95.3% across all treatment arms [including etanercept], in Austria, France, Netherlands, Spain, United Kingdom, Germany, Italy, Denmark, Poland, Romania, Czech Republic, Hungary, and Bulgaria), and from Russia (77 patients, 4.7% across all treatment arms [including etanercept]), which were combined due to the small number of Russian patients and the preponderance of investigative sites in the west of Russia.

- **Numbers analysed**

Table 26. Study Analysis Populations - Period 2 Induction Dosing, Study RHBA

Period Population and Status	PBO n (%)	ETN n (%)	IXE80Q4W n (%)	IXE80Q2W n (%)	Total n (%)
Randomized Patients	168	358	347	351	1224
Intent to Treat (ITT)	168	358	347	351	1224
Completed Week 12 (% Relative to ITT)	158 (94.0%)	333 (93.0%)	328 (94.5%)	342 (97.4%)	1161 (94.9%)
Per Protocol Set (PPS) (% relative to ITT)	133 (79.2%)	295 (82.4%)	292 (84.1%)	291 (82.9%)	1011 (82.6%)
Completed Week 12 (% Relative to Above Row)	133 (100.0%)	286 (96.9%)	281 (96.2%)	290 (99.7%)	990 (97.9%)
Safety (% Relative to ITT)	167 (99.4%)	357 (99.7%)	347 (100.0%)	350 (99.7%)	1221 (99.8%)
Completed Week 12 (% Relative to Above Row)	158 (94.6%)	333 (93.3%)	328 (94.5%)	342 (97.7%)	1161 (95.1%)

Notes: PBO = Placebo; ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W.

Table 27. Study Analysis Populations - Period 3 Maintenance Dosing, Study RHBA

	PBO		ETN		IXE80Q4W				IXE80Q2W				
	Resp	Non-Resp	Resp	Non-Resp	Resp	Resp	Resp	Non-Resp	Resp	Resp	Resp	Non-Resp	
Period Population and Status	PBO	IXE80 Q4W	PBO	IXE80 Q4W	PBO	IXE80 Q12W	IXE80 Q4W	IXE80 Q4W	PBO	IXE80 Q12W	IXE80 Q4W	IXE80 Q4W	Total
Maintenance Dosing Period Primary Population					82	86	85		94	95	102		544
Maintenance Dosing Period Secondary Population	3	155	132	200				75				49	614

Notes: PBO = Placebo; ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q12W = Ixekizumab 80 mg Q12W; Resp = responder; Non-Resp = non-responder.

Column header: line 1 - treatment during induction dosing period; line 2 - response status at Week 12 as recorded in interactive voice response system (IVRS); line 3 - assigned treatment for maintenance dosing period.

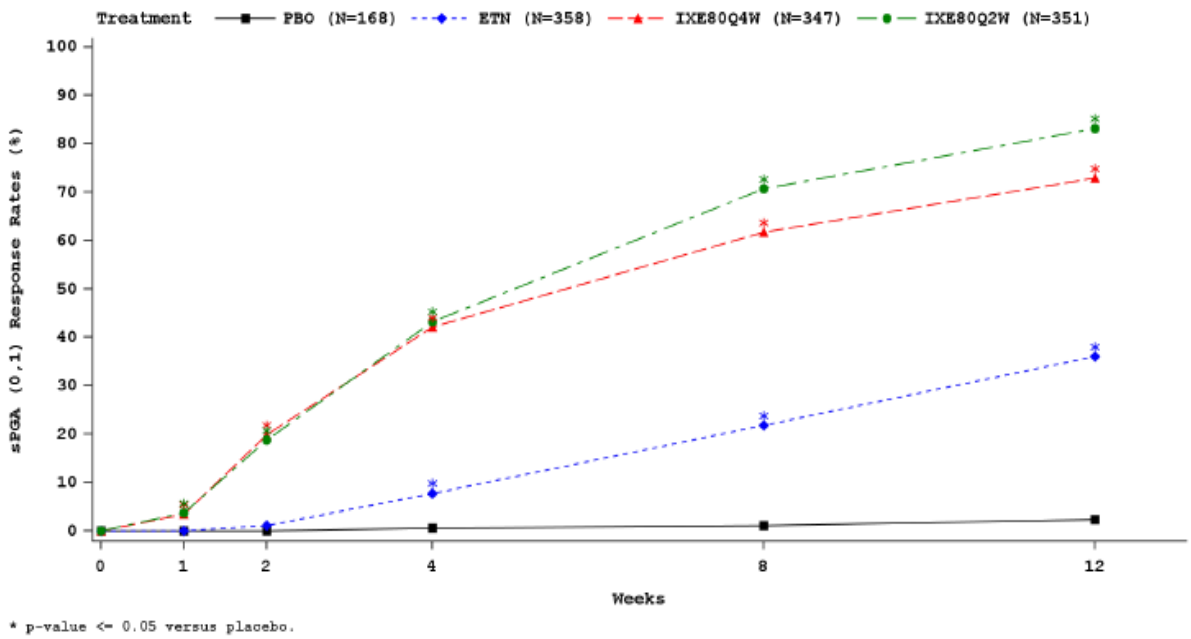
- **Outcomes and estimation**

sPGA (0,1)

After 12 weeks of treatment, 83.2% and 72.9% of patients from the 80 mg Q2W and 80 mg Q4W groups, respectively, achieved sPGA (0,1) compared to 2.4% from the placebo group (p<0.001 for both comparisons). The response rates for sPGA (0,1) over time are shown in **Figure 19**.

For the comparison to the active comparator etanercept, ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W were shown to be non-inferior to etanercept, in the percentages of patients who achieved sPGA (0,1) at Week 12, regardless of method used (fixed-margin approach for the ITT population or retention rate approach). For the fixed-margin approach, the lower bounds of the 97.5% CI for the difference in percentages of responders on 80 mg Q2W minus etanercept and 80 mg Q4W minus etanercept were 39.9% and 29.1%, respectively.

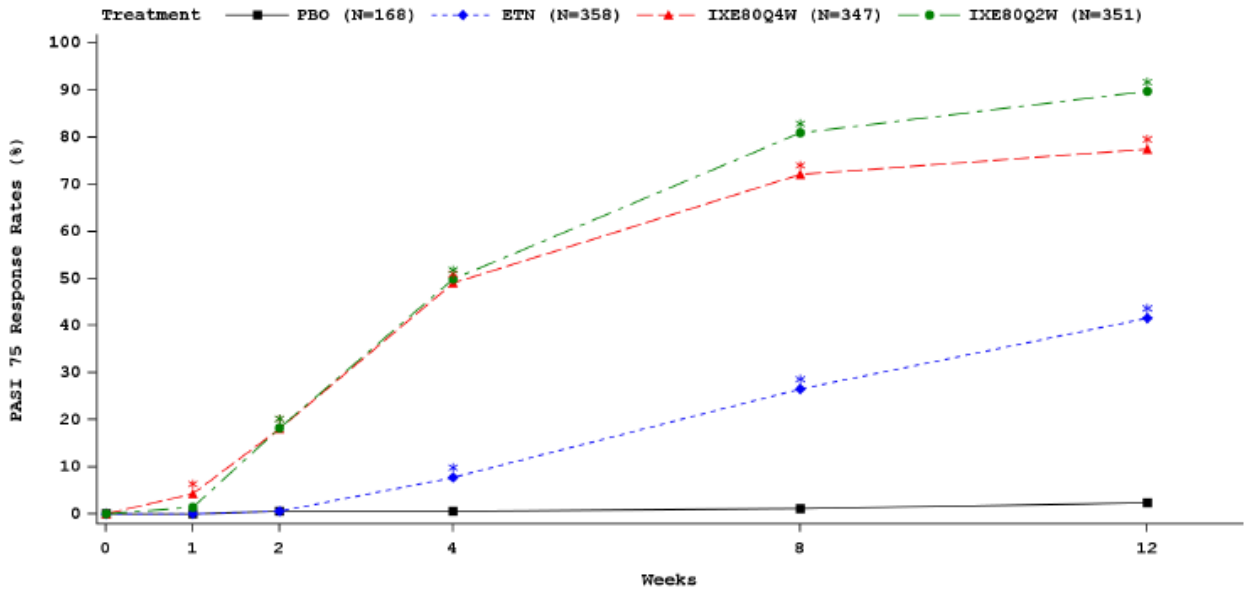
Figure 19. sPGA (0,1), response rates at each postbaseline visit in the Intent-to-Treat Population during the Induction Dosing Period, study RHBA



PASI 75

After 12 weeks of treatment, 89.7% and 77.5% of patients from the ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W treatment groups, respectively, achieved PASI 75 compared to 2.4% from the placebo group (p<0.001 for both comparisons).

For the comparison to etanercept, ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W were also shown to be non-inferior to etanercept, for the percentages of patients who achieved PASI 75 at Week 12, irrespective of method used. Using the fixed-margin approach, the lower bounds of the 97.5% CI for the difference in percentages of responders on 80 mg Q2W minus etanercept and 80 mg Q4W minus etanercept were 41.3% and 28.2%, respectively. The response rates for PASI 75 over time are shown below. **Figure 20.** PASI 75, response rates at each post-baseline visit (NRI) in the Intent-to-Treat Population during the Induction Dosing Period, study RHBA



* p-value <= 0.05 versus placebo.

Gated secondary efficacy end-points

sPGA (0) at Week 12

After 12 weeks of treatment, 41.9% and 32.3% of patients from the 80 mg Q2W and 80 mg Q4W treatment groups, respectively, achieved sPGA (0) compared to 0.6% from the placebo group ($p<0.001$ for both comparisons). For etanercept, 5.9% achieved sPGA (0) ($p<0.001$ for comparison vs. both ixekizumab doses).

PASI 90 at Week 12

After 12 weeks of treatment, 70.7% and 59.7% of patients from the 80 mg Q2W and 80 mg Q4W treatment groups, respectively, achieved PASI 90 compared to 0.6% from the placebo group ($p<0.001$ for both comparisons). For etanercept, 18.7% achieved PASI 90 ($p<0.001$ for both comparisons).

PASI 100 at Week 12

After 12 weeks of treatment, 40.5% and 30.8% of patients from the 80 mg Q2W and 80 mg Q4W treatment groups, respectively, achieved PASI 100 compared to 0.6% from the placebo group ($p<0.001$ for both comparisons). For etanercept, 5.3% achieved PASI 100 ($p<0.001$ for both comparisons).

Maintenance of sPGA (0,1) at Week 60

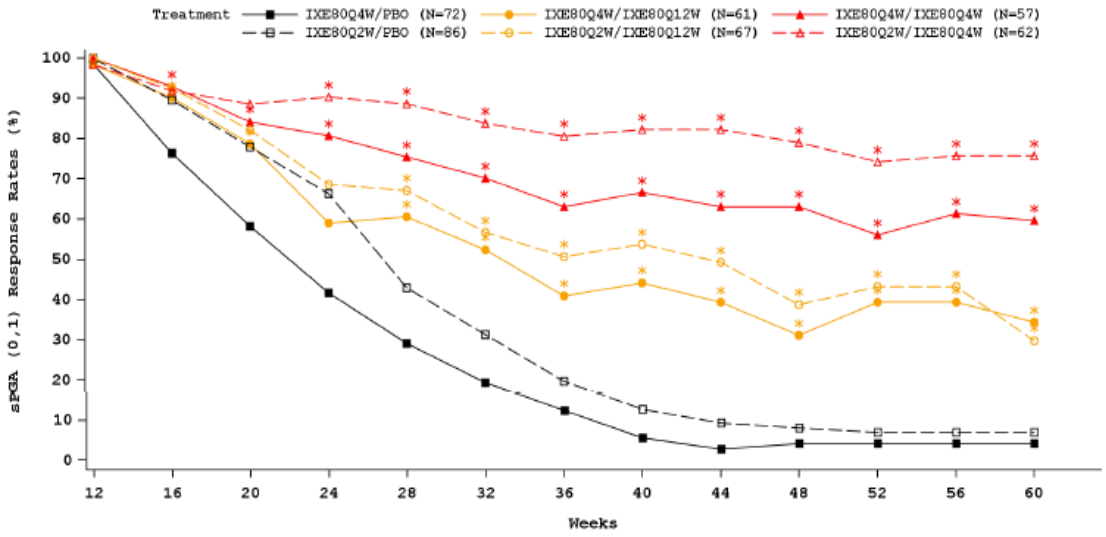
The 'Efficacy evaluable' patients (405 patients in total, out of 544 patients who were re-randomized) is a subset of the Maintenance Dosing Period Primary Population, defined as patients who have completed Week 60, discontinued prior to Week 60, or relapsed prior to Week 60 at the time of the 36-week interim database lock.

The percentages of patients from the ixekizumab 80 mg Q4W maintenance treatment groups (75.8% [Q2W/Q4W] and 59.6% [Q4W/Q4W]) that maintained sPGA (0,1) were statistically significant compared to the respective placebo groups (7.0% [Q2W/PBO] and 4.2% [Q4W/PBO]) at Week 60 ($p<.001$ for both comparisons).

The percentages of patients from the ixekizumab 80 mg Q12W maintenance groups (29.9% [Q2W/Q12W] and 34.4% [Q4W/Q12W]) that maintained sPGA (0,1) were statistically significant

compared to the respective placebo groups (7.0% [Q2W/PBO] and 4.2% [Q4W/PBO]) at Week 60 (p<.001 for both comparisons). These results are summarised in **Figure 21**.

Figure 21. sPGA (0,1), response rates at each post-baseline visit in the Maintenance Dosing Period Primary Population – Efficacy Evaluable Patients, Study RHBA

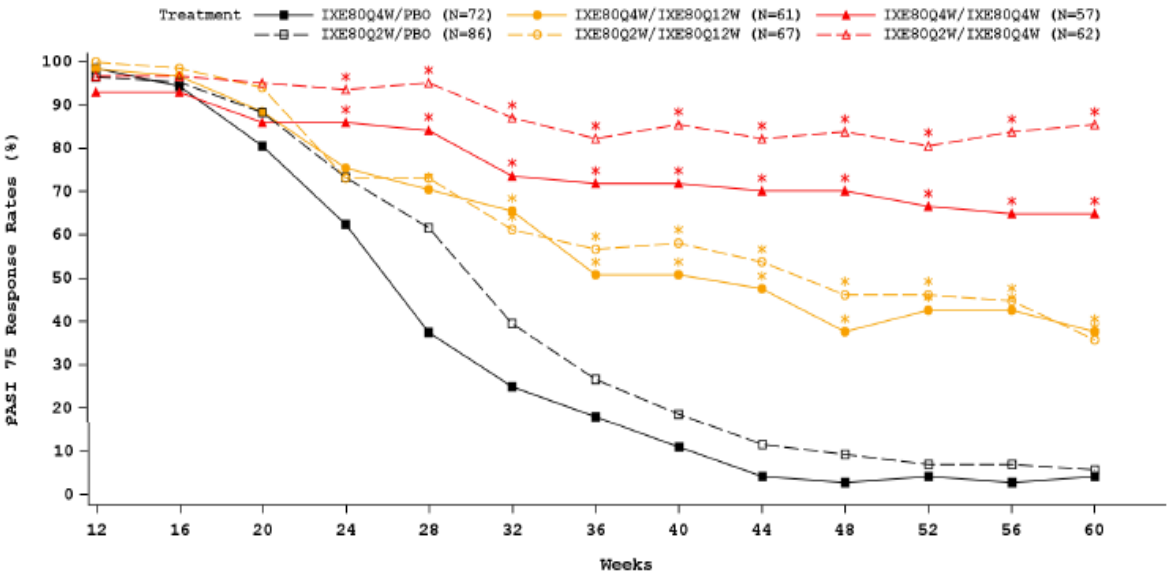


* p-value <= 0.05 versus placebo.

For patients identified as *non-responders* to placebo or to etanercept at Week 12 (Maintenance Dosing Period Secondary Population), 81.3% and 73.0% of patients, respectively, were able to achieve sPGA (0,1) after 12 weeks of treatment with ixekizumab 80 mg Q4W in the Maintenance Dosing Period.

PASI 75 during maintenance period

Figure 22. PASI 75, response rates at each post-baseline visit for the Maintenance Dosing Period Primary Population - Efficacy Evaluable Patients, Study RHBA



* p-value <= 0.05 versus placebo.

RHBC: A 12-Week Multicenter, Randomized, Double-Blind, Placebo- Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients with Moderate to Severe Plaque Psoriasis with a Long-Term Extension Period

Methods

- **Study participants**

The inclusion and exclusion criteria were very similar to those in studies RHAZ and RHBA. Similar to study RHBA, patients with prior etanercept use were excluded from this study.

- **Treatments**

This study consisted of 4 periods; a **Screening Period** (Period 1) lasting from 7 to 30 days prior to Period 2, a Blinded **Induction Dosing Period** (Period 2) from Week 0 (baseline) up to Week 12, a **Long-Term Extension Period** (Period 3) from Week 12 up to Week 264 and a **Post-Treatment Follow-Up Period** (Period 4) from last treatment period visit or Early Termination Visit (ETV) up to a minimum of 12 weeks following that visit.

Treatment at Week 12 remained blinded until all patients completed Week 12 or had discontinued from the study treatment (moved into the Post-Treatment Follow-Up Period), after which it will be open-label through Week 264. The Long-Term Extension Period is ongoing. Available safety data from this period up to the database lock date were provided in the study report.

At Week 0 (Visit 2), patients who meet all criteria for enrolment were randomized at a 2:2:2:1 ratio to the following double-blind **Induction** Dosing Period treatments (Week 0 up to Week 12):

- **80 mg ixekizumab Q2W:** A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10). Placebo for etanercept (1 SC injection) given twice weekly starting at Week 0 up to Week 12.
- **80 mg ixekizumab Q4W:** A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q4W (Weeks 4 and 8). Placebo for ixekizumab given as 1 SC injection at Weeks 2, 6, and 10 and Placebo for etanercept (1 SC injection) given twice weekly starting at Week 0 up to Week 12.
- **Placebo:** Placebo for ixekizumab (Week 0) given as 2 SC injections followed by placebo for ixekizumab Q2W (Weeks 2, 4, 6, 8, and 10). Placebo for etanercept (1 SC injection) given twice weekly (every 3-4 days) starting at Week 0 up to Week 12.
- **50 mg etanercept twice weekly:** Etanercept 50 mg (1 SC injection) given twice weekly (every 3-4 days) starting at Week 0 and up to Week 12. Placebo for ixekizumab given as 2 SC injections (Week 0) followed by placebo for ixekizumab Q2W given as 1 SC injection (Weeks 2, 4, 6, 8, and 10)

During the **Long-Term Extension** Period (Period 3; Weeks 12 to 264), the treatment was **80 mg ixekizumab Q4W**:

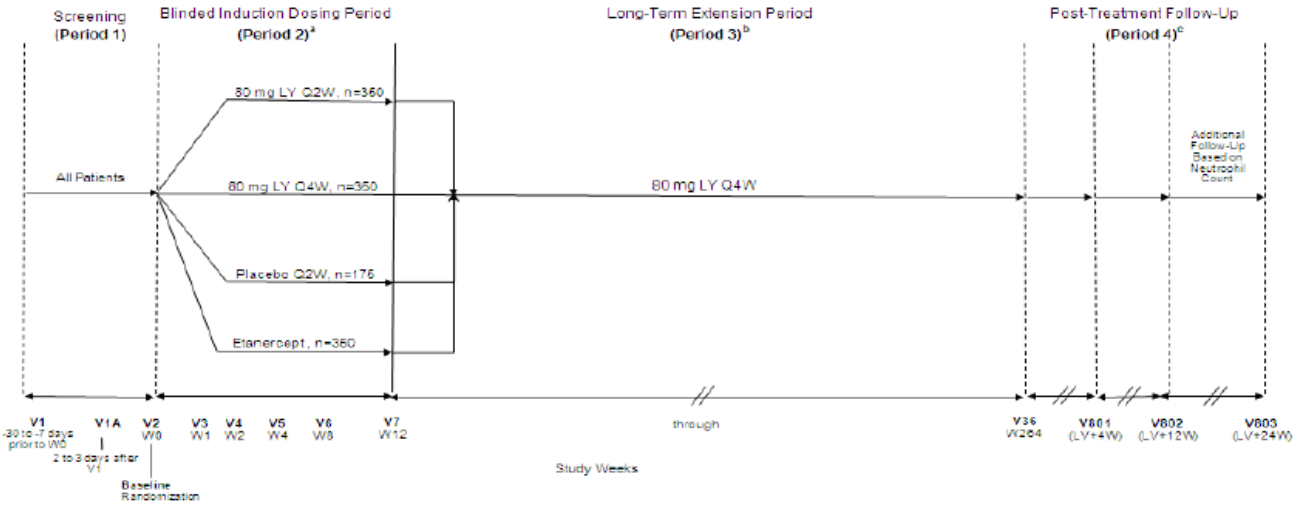
– For patients randomized to 80 mg Q2W or Q4W at Week 0, a dose of 80 mg was given as 1 SC injection + a placebo injection at Week 12; 80 mg ixekizumab will be given as 1 SC injection Q4W thereafter.

– For patients randomized to etanercept at Week 0, placebo will be given as 2 SC injections at Week 12; 80 mg ixekizumab will be given as 1 SC injection Q4W thereafter. Thus, patients

randomized to etanercept at Week 0 were not given a starting dose of 160 mg ixekizumab at any time during the study.

– For patients randomized to placebo at Week 0, a starting dose of 160 mg of ixekizumab will be given as 2 SC injections at Week 12; 80 mg ixekizumab will be given as 1 SC injection Q4W thereafter.

Figure 23. Illustration of study design for study RHBC (not to scale)



Abbreviations: LV = date of last visit; LY = ixekizumab (LY2439821); n = number of patients; Pbo = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week.

[a] *All patients received SC doses of investigational product (ixekizumab [Q2W or Q4W], placebo, or etanercept [twice weekly]) starting at Week 0 (Visit 2) up to Week 12*

[b] *All patients received 2 SC doses of investigational product (ixekizumab or placebo) at Week 12 (Visit 7) and 1 SC dose of ixekizumab Q4W from Week 16 (Visit 8) through Week 264 (Visit 36). Treatment at Week 12 remained blinded until all patients completed Week 12 (Visit 7) or discontinued from the study treatment (moved into Period 4).*

[c] *All patients receiving investigational product must enter into Period 4 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed.*

- **Objectives**

The primary objectives of this study were similar to those in Study RHBA, i.e. primarily to assess whether 80 mg ixekizumab Q2W or Q4W were superior to placebo at Week 12, non-inferior to etanercept at Week 12, and lastly, superior to etanercept at Week 12, in the treatment of moderate-to-severe plaque psoriasis based on sPGA (0,1) and PASI 75 vs. baseline.

- **Outcomes / endpoints**

Primary efficacy end-points and analyses

– Proportion of patients with an sPGA (0,1) at Week 12 compared with placebo

– Proportion of patients with PASI 75 at Week 12 compared with placebo

– Proportion of patients with an sPGA (0,1) at Week 12, non-inferiority to etanercept

– Proportion of patients with PASI 75 at Week 12, non-inferiority to etanercept

– Proportion of patients with an sPGA (0,1) at Week 12, superiority to etanercept

– Proportion of patients with PASI 75 at Week 12, superiority to etanercept

Secondary efficacy end-points

The following order of statistical testing was performed for secondary end-points, using a gatekeeping testing strategy:

– Proportion of patients achieving an sPGA (0) at Week 12 compared with placebo
– Proportion of patients with PASI 90 at Week 12 compared with placebo
– Proportion of patients with PASI 100 at Week 12 compared with placebo
– Proportion of patients achieving an sPGA (0) at Week 12, superiority to etanercept
– Proportion of patients with PASI 90 at Week 12, superiority to etanercept
– Proportion of patients with PASI 100 at Week 12, superiority to etanercept
– Change from baseline in Itch NRS at Week 12 compared with placebo
– Change from baseline in DLQI at Week 12 compared with placebo
– Change from baseline in NAPSI (for fingernails) at Week 12 compared with placebo

Health Outcome/Quality-of-Life Measures

A number of different health outcome measures were assessed in this study, e.g. Itch NRS, DLQI, QIDS-SR16, WPAI-PSO, SF-36, patient's global assessment of disease severity.

- **Sample size**

For the primary comparisons in the Induction Dosing Period; superiority versus placebo and, non-inferiority versus etanercept, the same assumptions as in Study RHBA were made. Hence, the total sample size planned for the study was 1225 patients randomized at a 2:2:2:1 ratio to 80 mg ixekizumab Q2W, 80 mg ixekizumab Q4W, etanercept, and placebo, respectively (350:350:350:175 patients per treatment group, respectively).

- **Randomisation**

At Week 0 (Visit 2), patients who met all criteria for enrolment at Visits 1/1A and 2 were randomized at a 2:2:2:1 ratio to double-blind treatment groups; 80 mg ixekizumab Q2W, 80 mg ixekizumab Q4W, etanercept, or placebo, as determined by a computer-generated random sequence using an interactive voice response system (IVRS). The IVRS was used to assign double-blind investigational product to each patient. Patients were stratified by center.

There was no re-randomisation in this study. After the induction dosing period, patients were to enter the Long-Term Extension Period and, received 80 mg ixekizumab Q4W.

- **Blinding (masking)**

This was a double blind study.

- **Statistical methods**

Methods were very similar to those used in study RHBA.

The SAP was approved on 21 December 2012 and amended on 12 May 2014 (Amendment 1) prior to the unblinding of the study team. No changes to the conduct of the study or the planned analyses were

made after the time of the first unblinding of Lilly personnel to study data. The reporting database was validated, locked, and unblinded for analysis on 14 July 2014.

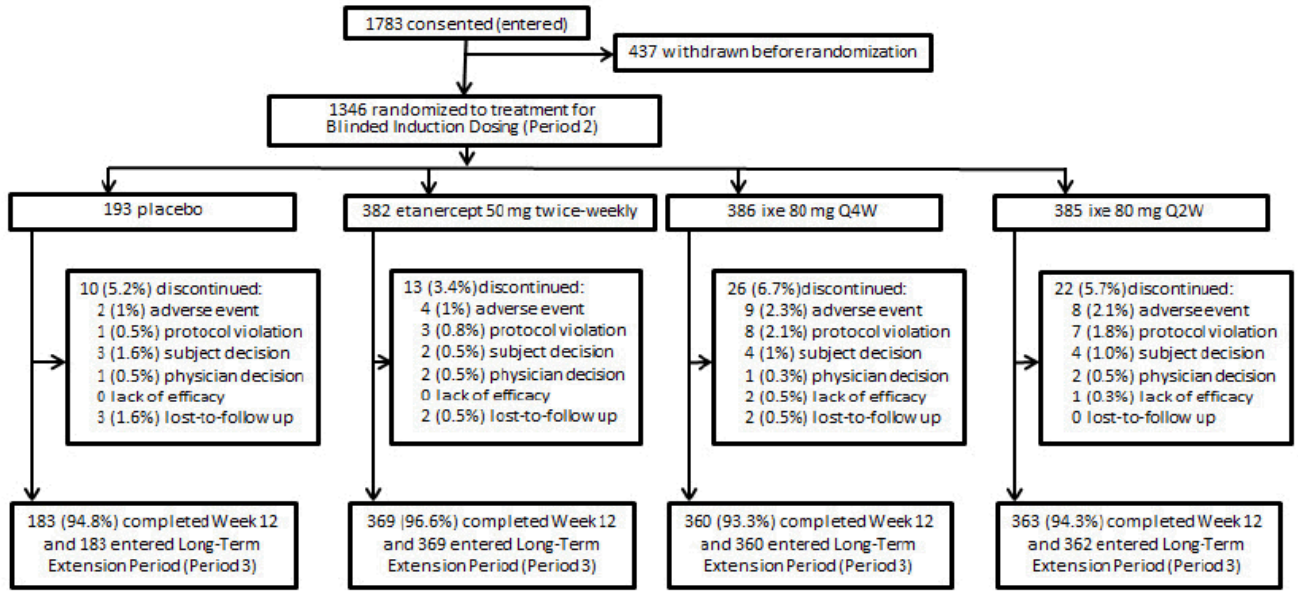
Results

- **Participant flow**

During the blinded Induction Dosing Period, 5.3% of patients discontinued study treatment; the most common reasons (>1% in all patients) for discontinuation being adverse event (1.7%), protocol violation (1.4%), and patient decision (1.0%).

At the time of data lock for this report, 8.7% of patients had discontinued from the overall study. The most common reasons were adverse event (2.4%), subject decision (2.2%) and lack of efficacy (1.1%).

Figure 24. Patient disposition for Screening, blinded Induction Dosing Period, and Long-Term Extension Period commencement, study RHBC.



Note:

- One of the patients in IXE80Q4W treatment group discontinued study treatment due to a pre-existing condition (hypertension). This patient is included in this figure, but not included in the adverse event analysis tables.
- One additional patient in IXE80Q2W treatment group discontinued study treatment due to an adverse event (osteomyelitis) after completing the induction dosing period (Week 12) and was not entered or dosed in the long term extension period. This patient/event is not included in this figure, but is included in the adverse event analysis tables.

- **Recruitment**

Study RHBC was initiated on 11 August 2012 (first patient enrolled/assigned to therapy). The last patient visit prior to database lock was 22 May 2014 (database lock date 14 July 2014).

- **Conduct of the study**

Prior to the date the first patient enrolled (screened) in the study (27 July 2012), the protocol was amended to incorporate a number of changes in the conduct of the study and planned analyses. These were similar to revisions made for study RHBA described above.

After the commencement of the study, but prior to the first unblinding of company personnel to study data (14 July 2014), the protocol was amended to incorporate the additional changes in the conduct of

the study and planned analyses (e.g. revised entry criteria for previous HBV infection and revised statistical analyses, e.g. with respect to the non-inferiority analysis plan and re-ordering of testing so that sPGA (0,1) was tested before PASI 75.

After commencement of the study, but prior to the first unblinding of company personnel to study data, the SAP was amended to incorporate additional changes in the planned analyses (amendment 1 approved on 12 May 2014), e.g. the Major Secondary Objective of ixekizumab superiority to placebo at Week 12 with regards to Itch NRS was revised to an analysis of the proportion of patients achieving a ≥4 point reduction from baseline, amongst those patients who had baseline Itch NRS ≥4, analyses of treatment-emergent ADA effects on efficacy were added and Crohn's disease and Ulcerative Colitis were added to the Adverse Events of Special Interest.

Protocol deviations

A total of 23.5% of patients had a major protocol deviation during the Induction Dosing Period; the most common protocol deviation was for missing data (11% of patients, most commonly missing ECGs). Other common deviations were failure to meet study inclusion criteria (e.g. due to improper informed consent, 2%), took incorrect study medication (4%), met study exclusion criteria but was entered into the study (4%), or due to non-compliance with study medication or double-dosing (6%).

Compliance

Overall compliance in the Induction Dosing Period was 94.1% (range across treatment arms 91%-95%) with no significant differences seen between the treatment arms.

- **Baseline data**

Table 28. Patient Demographics and Baseline Characteristics from study RHBC. ITT Population

	RHBC (N=1346)
Age (Years)	
Mean (SD)	45.8 (13.07)
Gender, n (%)	
Male	918 (68.2)
Female	428 (31.8)
Race, n (%)	
American Indian or Alaska Native	10 (0.7)
Asian	41 (3.0)
Black or African American	32 (2.4)
Native Hawaiian or Other Pacific Islander	6 (0.4)
White	1248 (92.7)
Multiple	9 (0.7)
Geographic Region, n (%)	
Asia	0
North America	655 (48.7)
Europe[a]	589 (43.8)
Central America/South America	102 (7.6)
Australia	0
Weight Category, n (%)	
<100 kg	943 (70.4)
≥100 kg	396 (29.6)
Previous Systemic Therapy, n (%)	
Never Used	580 (43.1)
Nonbiologic Only	557 (41.4)
Biologic Only	90 (6.7)
Biologic and Nonbiologic	119 (8.8)

Previous Nonbiologic Systemic Therapy, n (%)	
Used 1 Therapy	368 (27.3)
Used 2 Therapies	168 (12.5)
Used ≥3 Therapies	140 (10.4)
Previous Nonbiologic Systemic Therapy: Inadequate Response, Intolerance, or Contraindication	
Used <3 Therapies	1254 (93.4)
Used ≥3 Therapies	88 (6.6)
Previous Biologic Therapy, n (%)	
Used 1 Therapy	153 (11.4)
Used 2 Therapies	41 (3.0)
Used ≥3 Therapies	15 (1.1)
Previous Biologic Agent, n (%)	
Tumor Necrosis Factor (TNF)-α Inhibitor (infliximab, etanercept, adalimumab, golimumab)	95 (7.1)
Interleukin (IL) 12/23 Inhibitor (ustekinumab)	74 (5.5)
Other (efalizumab, alefacept, or other)	86 (6.4)
Previous Phototherapy Therapy, n (%)	
Never Used	824 (61.2)
Ever Used	522 (38.8)
Duration of Psoriasis Symptoms in Years	
Mean (SD)	18.1 (12.20)
Baseline static Physician Global Assessment (sPGA), n (%)	
Number of Patients with sPGA = 3	695 (51.7)
Number of Patients with sPGA = 4,5	648 (48.3)
Baseline Psoriasis Area and Severity Index (PASI) Score	
Mean (SD)	20.9 (8.19)

	RHBC (N=1346)
Baseline Itch Numeric Rating Scale (NRS) Score	
Mean (SD)	6.3 (2.61)
Baseline Itch NRS Score, n(%)	
<4	243 (18.1)
≥4	1103 (81.9)
Baseline Dermatology Life Quality Index (DLQI) Score	
Mean (SD)	12.0 (6.93)
Baseline Nail Psoriasis Severity Index (NAPSI) Total Score	
Mean (SD)	25.8 (19.99)

Abbreviations: ITT = intent-to-treat; N = number of patients; n = percentage of patients; SD = standard deviation.

[a] Europe's geographic region includes patients from European Union (EU) member states (1576 patients, 95.3% across all treatment arms [including etanercept], in Austria, France, Netherlands, Spain, United Kingdom, Germany, Italy, Denmark, Poland, Romania, Czech Republic, Hungary, and Bulgaria), and from Russia (77 patients, 4.7% across all treatment arms [including etanercept]), which were combined due to the small number of Russian patients and the preponderance of investigative sites in the west of Russia.

- **Numbers analysed**

Table 29. Study Analysis Populations - Period 2 Induction Dosing

Period Population and Status	PBO n (%)	ETN n (%)	IXE80Q4W n (%)	IXE80Q2W n (%)	Total n (%)
Randomized Patients	193	382	386	385	1346
Intent to Treat (ITT)	193	382	386	385	1346
Completed Week 12 (% Relative to ITT)	183 (94.8%)	369 (96.6%)	360 (93.3%)	363 (94.3%)	1275 (94.7%)
Per Protocol Set (PPS) (% relative to ITT)	165 (85.5%)	339 (88.7%)	338 (87.6%)	338 (87.8%)	1180 (87.7%)
Completed Week 12 (% Relative to PPS)	163 (98.8%)	335 (98.8%)	333 (98.5%)	332 (98.2%)	1163 (98.6%)
Safety (% Relative to ITT)	193 (100.0%)	382 (100.0%)	382 (99.0%)	384 (99.7%)	1341 (99.6%)
Completed Week 12 (% Relative to Safety)	183 (94.8%)	369 (96.6%)	360 (94.2%)	363 (94.5%)	1275 (95.1%)

Notes: PBO = Placebo; ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W.

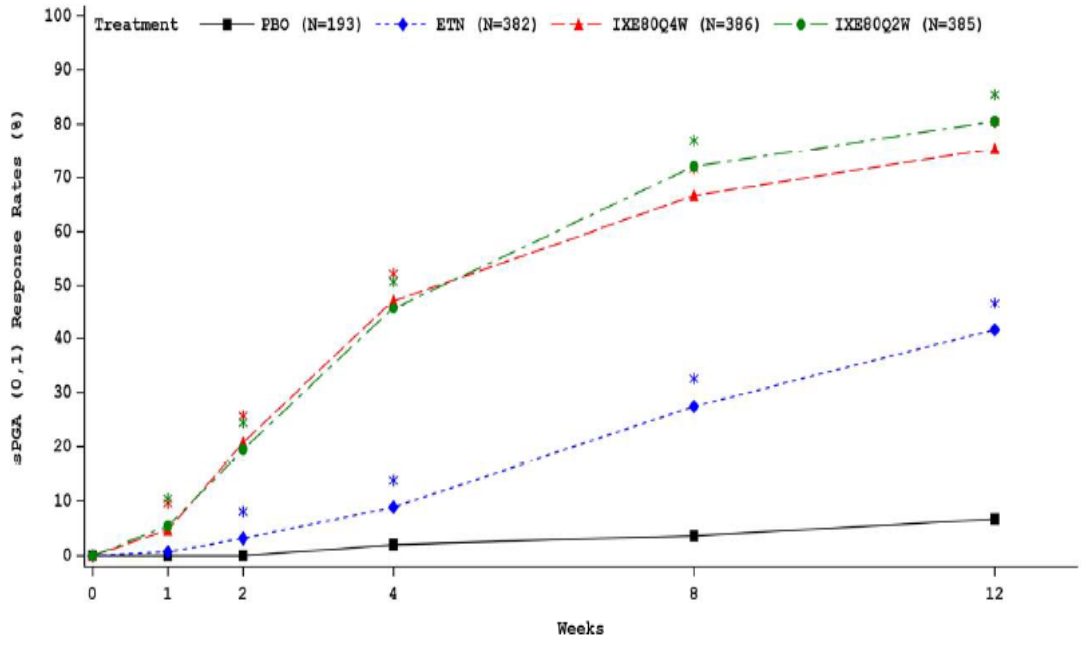
- **Outcomes and estimation**

sPGA (0,1)

The response rate for sPGA (0,1) at Week 12 was 75.4% for ixekizumab 80 mg Q4W and 80.5% for ixekizumab 80 mg Q2W compared with the placebo response rate of 6.7% ($p<0.001$ for both comparisons).

The sPGA (0,1) response rate for etanercept was 41.6%. For the comparison vs. etanercept, efficacy of ixekizumab 80 mg Q4W and Q2W met non-inferiority criteria (according to the fixed-margin approach) in terms of the proportion of patients achieving a sPGA (0,1) at 12 weeks of treatment, because the lower bound of the 97.5% CI for the difference in proportion of responders in sPGA (0,1) between ixekizumab dose group and etanercept group was 26.3% for Q4W and 31.7% for Q2W, respectively, which were each greater than the pre-specified non-inferiority margin of -12.0%. Analysis of non-inferiority using the retention rate approach was consistent with the results using the fixed-margin approach. The time course for sPGA (0,1) response is shown in **Figure 25**.

Figure 25. sPGA (0,1), response rates at each post baseline visit (NRI) in the intent-to-treat population during the Induction Dosing Period.



* p-value <= 0.05 versus placebo.

PASI 75

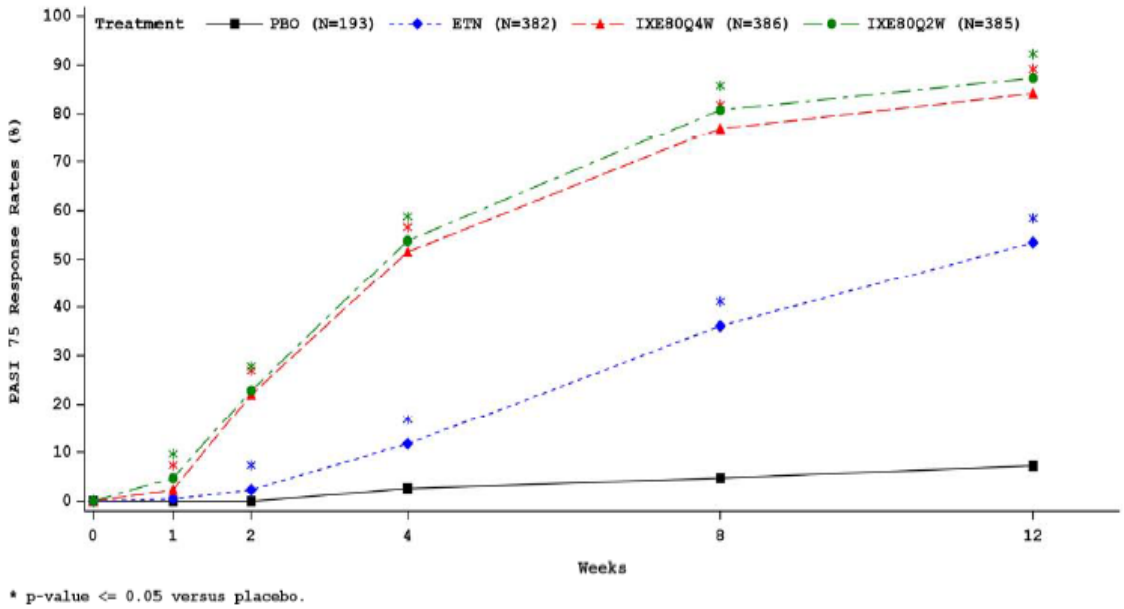
The response rate for PASI 75 at Week 12, was 84.2% for ixekizumab 80 mg Q4W, 87.3% for ixekizumab Q2W, and 7.3% of placebo patients, respectively ($p<0.001$ vs. placebo for both comparisons).

The PASI 75 response rate for etanercept was 53.4%. At 12 weeks of treatment, efficacy of ixekizumab 80 mg Q4W and Q2W met non-inferiority criteria (according to the fixed-margin approach) to the active comparator, etanercept, in terms of the proportion of patients achieving a PASI 75 because the lower bound of the 97.5% CI for the difference in the proportion of US patients meeting PASI 75 between ixekizumab dose group and etanercept group was 23.7% for Q4W and 27.0% for Q2W, respectively, which were each greater than the pre-specified non-inferiority margin of -12.0%. Analysis of non-inferiority using the retention rate approach was consistent with the results using the fixed-margin approach.

Superiority of ixekizumab 80 mg Q4W and Q2W efficacy compared to etanercept with respect to PASI 75 at week 12 was also demonstrated, regardless of statistical method used.

The time course for PASI 75 response is shown in **Figure 26**.

Figure 26. PASI 75, response rates at each post-baseline visit for the intent-to-treat population during the Induction Dosing Period (NRI)



The primary efficacy analyses were repeated using the Per Protocol Set. The results were consistent with the primary analyses. Results for sPGA(0,1) and PASI 75 at Week 12 using the pMI method analyses of the time courses of sPGA (0,1) and PASI 75 response rates using categorical MMRM were consistent with the NRI method. By-center analyses of sPGA (0,1) and PASI 75 showed no significant treatment-by-center effect for either measure.

Gated secondary efficacy end-points

sPGA (0) at Week 12

Ixekizumab 80 mg Q4W and Q2W were significantly superior to placebo for the achievement of sPGA (0); the response rate for ixekizumab was 36.0% and 40.3%, respectively versus the placebo response rate of 0%. The response rate for etanercept was 8.6% and superiority was shown for both ixekizumab doses ($p<0.001$).

PASI 90 at Week 12

Ixekizumab 80 mg Q4W and Q2W were significantly superior to placebo for the achievement of PASI 90; the response rate for ixekizumab was 65.3% and 68.1%, respectively, versus the placebo response rate of 3.1%. The response rate for etanercept was 25.7% and superiority was shown for both ixekizumab doses ($p<0.001$).

PASI 100 at Week 12

Ixekizumab 80 mg Q4W and Q2W had a significantly higher PASI 100 response rate compared with placebo; the response rate for ixekizumab was 35.0% and 37.7%, respectively, versus the placebo response rate of 0%. The response rate for etanercept was 7.3% and superiority was shown for both ixekizumab doses ($p<0.001$).

Itch NRS at Week 12

Among patients who had baseline Itch NRS ≥4 point, ixekizumab 80 mg Q4W and Q2W had a significantly higher itch responder rate (defined as a ≥4 point reduction in Itch NRS) compared with placebo. At Week 12, the Itch NRS responder rates were 79.9% and 82.5%, respectively, versus the placebo response rate of 20.9%. The response rate for etanercept was 64.1%.

DLQI at Week 12

At baseline, mean (SD) DLQI total score (on the 30-point DLQI) for patients randomized to all treatment groups was 12.0 (6.9) and was similar across groups. At Week 12, ixekizumab 80 mg Q4W and Q2W DLQI total score mean change from baseline (MMRM) were significantly greater (-9.6 and -10.2 respectively) versus the placebo of -1.7. The corresponding change in DLQI score for etanercept was -8.0.

NAPSI at Week 12

For patients who reported nail involvement at baseline, patients treated with ixekizumab 80 mg Q4W and 80 mg Q2W had significantly greater improvement in fingernail involvement than patients receiving placebo. At Week 12, the mean change from baseline on the NAPSI was -10.0 for the 80 mg Q4W treatment group and -10.4 for 80 mg Q2W, compared with 1.6 for patients treated with placebo and -6.4 for patients treated with etanercept.

Ancillary analyses

Sub-group analyses

Pre-specified subgroups were examined to determine if there were differential effects in rates of achievement of sPGA (0,1), sPGA (0), PASI 75, PASI 90, or PASI 100 at Week 12 (Induction Dosing Period) and Week 60 (Maintenance Dosing Period), using the appropriate integrated analysis set. Subgroup variables included patient demographics (age, sex, race, ethnicity, weight, geographic region); disease-related (previous psoriasis therapy type and frequency, baseline disease severity, age

of psoriasis onset, and concomitant topical therapy); and disease location (nails, scalp). There were no major differences in responder rates based on age, gender, race or region (data not shown).

Weight and BMI

Table 30. sPGA (0,1) and PASI 75 Percentage of Patients Meeting Response Criteria at Week 12 (NRI) Primary Psoriasis Placebo-Controlled Integrated Analysis Set, Selected Subgroups ITT Population – RHAZ, RHBA, and RHBC Induction Dosing Period (Weight and BMI)

Subgroup	Endpoint	p-value (Interaction)[a]	Placebo N=792 n (%)	80 mg Q4W N=1165 n (%)	80 mg Q2W N=1169 n (%)	All Ixekizumab N=2334 n (%)
Weight						
<100 kg	*Patients in*		*538 (67.9)*	*791 (67.9)*	*819 (70.1)*	*1610 (69.0)*
≥100 kg	*Subgroup*		*251 (31.7)*	*368 (31.6)*	*349 (29.9)*	*717 (30.7)*
<100 kg	**sPGA (0,1)**	0.793	26 (4.8)	625 (79.0)[b]	692 (84.5)[b,e]	1317 (81.8)
≥100 kg			5 (2.0)	248 (67.4)[b]	264 (75.6)[b,e]	512 (71.4)
<100 kg	**PASI 75**	0.448	27 (5.0)	677 (85.6)[b]	738 (90.1)[b,e]	1415 (87.9)
≥100 kg			8 (3.2)	273 (74.2)[b]	299 (85.7)[b,c]	572 (79.8)
<80 kg	*Patients in*		*258 (32.6)*	*354 (30.4)*	*394 (33.7)*	*748 (32.0)*
≥80 to <100 kg	*Subgroup*		*280 (35.4)*	*437 (37.5)*	*425 (36.4)*	*862 (36.9)*
≥100 kg			*251 (31.7)*	*368 (31.6)*	*349 (29.9)*	*717 (30.7)*
<80 kg	**sPGA (0,1)**	0.924	14 (5.4)	281 (79.4)[b]	338 (85.8)[b,e]	619 (82.8)
≥80 to <100 kg			12 (4.3)	344 (78.7)[b]	354 (83.3)[b]	698 (81.0)
≥100 kg			5 (2.0)	248 (67.4)[b]	264 (75.6)[b,e]	512 (71.4)
<80 kg	**PASI 75**	0.616	11 (4.3)	303 (85.6)[b]	358 (90.9)[b,e]	661 (88.4)
≥80 to <100 kg			16 (5.7)	374 (85.6)[b]	380 (89.4)[b]	754 (87.5)
≥100 kg			8 (3.2)	273 (74.2)[b]	299 (85.7)[b,c]	572 (79.8)
<90 kg	*Patients in*		*422 (53.3)*	*583 (50.0)*	*622 (53.2)*	*1205 (51.6)*
≥90 kg	*Subgroup*		*367 (46.3)*	*576 (49.4)*	*546 (46.7)*	*1122 (48.1)*
<90 kg	**sPGA (0,1)**	0.517	23 (5.5)	463 (79.4)[b]	531 (85.4)[b,e]	994 (82.5)
≥90 kg			8 (2.2)	410 (71.2)[b]	425 (77.8)[b,e]	835 (74.4)
<90 kg	**PASI 75**	0.845	21 (5.0)	499 (85.6)[b]	565 (90.8)[b,e]	1064 (88.3)
≥90 kg			14 (3.8)	451 (78.3)[b]	472 (86.4)[b,c]	923 (82.3)
Body Mass Index						
<18.5 kg/m^2	*Patients in*		*10 (1.3)*	*7 (0.6)*	*7 (0.6)*	*14 (0.6)*
≥18.5 to 25 kg/m^2	*Subgroup*		*164 (20.7)*	*229 (19.7)*	*245 (21.0)*	*474 (20.3)*
≥25 to <30 kg/m^2			*259 (32.7)*	*388 (33.3)*	*400 (34.2)*	*788 (33.8)*
≥30 to <40 kg/m^2			*271 (34.2)*	*414 (35.5)*	*399 (34.1)*	*813 (34.8)*
>40 kg/m^2			*84 (10.6)*	*117 (10.0)*	*116 (9.9)*	*233 (10.0)*
<18.5 kg/m^2	**sPGA (0,1)**	0.917	1 (10.0)	5 (71.4)[d]	5 (71.4)[d]	10 (71.4)
≥18.5 to 25 kg/m^2			8 (4.9)	192 (83.8)[b]	211 (86.1)[b]	403 (85.0)
≥25 to <30 kg/m^2			11 (4.2)	309 (79.6)[b]	343 (85.8)[b,e]	652 (82.7)
≥30 to <40 kg/m^2			9 (3.3)	296 (71.5)[b]	320 (80.2)[b,e]	616 (75.8)
>40 kg/m^2			2 (2.4)	69 (59.0)[b]	76 (65.5)[b]	145 (62.2)
<18.5 kg/m^2	**PASI 75**	0.283	1 (10.0)	6 (85.7)[b]	5 (71.4)[c]	11 (78.6)
≥18.5 to 25 kg/m^2			9 (5.5)	203 (88.6)[b]	222 (90.6)[b]	425 (89.7)
≥25 to <30 kg/m^2			9 (3.5)	332 (85.6)[b]	367 (91.8)[b,e]	699 (88.7)
≥30 to <40 kg/m^2			11 (4.1)	323 (78.0)[b]	345 (86.5)[b,e]	668 (82.2)
>40 kg/m^2			5 (6.0)	84 (71.8)[b]	97 (83.6)[b,e]	181 (77.7)

a A logistic regression analysis with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors, and the treatment-by-subgroup interaction is tested at the 10% significance level.

b p<.001 versus PBO; c p<.001 versus 80 mg Q4W

d p≤05 versus PBO; e p≤05 versus 80 mg Q4W

Immunogenicity, impact on efficacy

Induction Dosing Period

The incidence of treatment-emergent ADA (TE-ADA) positive patients was 11% (256 of 2293), with 9% (103 of 1150) in the 80 mg Q2W and 13% (153 of 1143) in the 80 mg Q4W groups, compared with 0.5% (4 of 781) for placebo-treated patients. Among these evaluable ixekizumab-treated patients, the incidence of confirmed neutralizing antibody (NAb)-positive patients was 1.0% (24 of 2293) with fewer NAb-positive patients in the 80 mg Q2W (n=5) than in the 80 mg Q4W (n=19) groups.

Of the ixekizumab-treated TE-ADA positive patients, 61% had low ADA titer (<1:160). All of the NAb-positive patients had moderate-to-high ADA titer (≥1:160). However, 83% (213 of 256) of the TE-ADA positive patients had inconclusive NAb status due to serum concentrations of ixekizumab exceeding the drug tolerance threshold of the NAb assay in the samples tested.

Efficacy results:

In the Induction Dosing Period, among TE-ADA positive patients treated with either ixekizumab dosing regimen (80 mg Q2W or 80 mg Q4W), 66% achieved an sPGA (0,1) at Week 12. This response was lower than the 81% of TE-ADA negative patients who achieved an sPGA (0,1), however, lower response was not uniformly observed in all TE-ADA positive patients. TE-ADA positive patients with low ADA titer had sPGA (0,1) response rates similar to patients who were TE-ADA negative:

- sPGA (0,1) achieved for 80 mg Q2W: 79% (low ADA titer) versus 84% (TE-ADA negative)
- sPGA (0,1) achieved for 80 mg Q4W: 75% (low ADA titer) versus 79% (TE-ADA negative)

Maintenance Dosing Period

The incidence of immunogenicity ranged from 14% to 17% during the Maintenance Dosing Period in those who received ixekizumab (80 mg Q2W or Q4W) or placebo in the Induction Dosing Period and subsequently maintained on 80 mg Q4W up to Week 60. More frequent dosing (Q4W versus Q12W) was associated with lower incidence of immunogenicity during the Maintenance Dosing Period. Patients with low ADA titer represented the majority of the TE-ADA positive patients, and their efficacy response rates were comparable to TE-ADA negative patients. There was greater variability in the efficacy responses among the moderate-to-high ADA titer patients, however, these individuals comprised a minority of the overall TE-ADA positive patients. Efficacy responses were generally lower in the NAb-positive patients, but this subgroup represented a small proportion of the ixekizumab-treated patients during the Maintenance Dosing Period. Despite the elevated proportion of TE-ADA positive patients with inconclusive NAb-positive results, these patients exhibited similar efficacy responses to the TE-ADA negative patients.

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).

Summary of Efficacy for Pivotal Trial I1F-MC-RHAZ

Title: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period and a Long-Term Extension Period to Evaluate the Efficacy and Safety of LY2439821 in Patients with Moderate-to-Severe Plaque Psoriasis		
Study identifier	I1F-MC-RHAZ	
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study	
	Duration of Main phase:	12 weeks (Induction period)
	Duration of Extension phase:	48 weeks (Maintenance period); 204 weeks (Long-term extension period)
Hypothesis	Superiority	
Treatment groups	Ixekizumab Q2W	Ixekizumab 80 mg Q2W. Duration 12 weeks (Induction). Number randomized 433.
	Ixekizumab Q4W	Ixekizumab 80 mg Q4W. Duration 12 weeks (Induction), 48 weeks (Maintenance). Number randomized 432.
	Ixekizumab Q12W	Ixekizumab 80 mg Q12W. Duration 48 weeks (Maintenance).
	Placebo	Placebo. Duration 12 weeks (Induction), 48 weeks (Maintenance). Number randomized 431.
Database lock	07 Aug 2014 (Last patient visit prior to database lock: 24 June 2014)	

Results and Analysis				
Analysis Description	**Co-Primary Analysis**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	433	432	431
	sPGA (0,1)	354/433 (81.8%)	330/432 (76.4%)	14/431 (3.2%)
	PASI 75	386/433 (89.1%)	357/432 (82.6%)	17/431 (3.9%)
Effect estimate per comparison	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Logistic regression analysis, odds ratio	146.51	
		95% CI	81.02, 264.92	
		P-value	p<.001	
	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Logistic regression analysis, odds ratio	102.89	

		95% CI	57.52, 184.04
		P-value	p<.001
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		Logistic regression analysis, odds ratio	223.94
		95% CI	125.05, 401.03
		P-value	p<.001
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		Logistic regression analysis, odds ratio	125.54
		95% CI	72.26, 218.10
		P-value	p<.001

Results and Analysis				
Analysis Description	**Key Secondary Analysis: sPGA (0) at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	433	432	431
	sPGA (0)	160/433 (37.0%)	149/432 (34.5%)	0

Effect estimate per comparison	sPGA (0) at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo
		Logistic regression analysis, odds ratio	N/A
		95% CI	N/A
		P-value	N/A
	sPGA (0) at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		Logistic regression analysis, odds ratio	N/A
		95% CI	N/A
		P-value	N/A

Results and Analysis	
Analysis Description	**Key Secondary Analysis: PASI 90 at Week 12**

Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	433	432	431
	PASI 90	307/433 (70.9%)	279/432 (64.6%)	2/431 (0.5%)
Effect estimate per comparison	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Logistic regression analysis, odds ratio	562.34	
		95% CI	137.80, 2294.78	
		P-value	p<.001	
	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Logistic regression analysis, odds ratio	411.70	
		95% CI	101.09, 1676.63	
		P-value	p<.001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: PASI 100 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	433	432	431
	PASI 100	153/433 (35.3%)	145/433 (33.6%)	0
Effect estimate per comparison	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Logistic regression analysis, odds ratio	N/A	
		95% CI	N/A	
		P-value	N/A	
	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Logistic regression analysis, odds ratio	N/A	
		95% CI	N/A	
		P-value	N/A	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Maintenance of sPGA (0,1) at Week 60**			
Analysis population and time point description	Maintenance Dosing Period Primary Population 60 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab/Ixekizu-mab 80 mg Q4W	Ixekizumab/ Ixekizu-mab 80 mg Q12W	Ixekizumab/Placebo
	Number of subjects	229	227	226
	sPGA (0,1)	167/229 (72.9%)	85/227 (37.4%)	17/226 (7.5%)
Effect estimate per comparison	sPGA (0,1) at Week 60	Comparison groups	Ixekizumab/Ixekizumab 80 mg Q4W vs. Ixekizumab/Placebo	
		Logistic regression analysis, odds ratio	35.84	
		95% CI	20.01, 64.20	
		P-value	p<.001	
	sPGA (0,1) at Week 60	Comparison groups	Ixekizumab/Ixekizumab 80 mg Q12W vs. Ixekizumab/Placebo	
		Logistic regression analysis, odds ratio	7.57	
		95% CI	4.30, 13.34	
		P-value	p<.001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Itch NRS ≥4 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	391	379	374
	Itch NRS ≥4	336/391 (85.9%)	305/379 (80.5%)	58/374 (15.5%)
Effect estimate per comparison	Itch NRS ≥4 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Logistic regression analysis, odds ratio	34.39	
		95% CI	22.97, 51.49	
		P-value	p<.001	
	Itch NRS ≥4 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	

		Logistic regression analysis, odds ratio	22.90	
		95% CI	15.65, 33.51	
		P-value	p<.001	
Results and Analysis				
Analysis Description	**Key Secondary Analysis: DLQI score at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	414	407	403
	DLQI Score: LSM (SE)	-11.1 (0.26)	-10.7 (0.27)	-1.0 (0.27)
Effect estimate per comparison	DLQI score at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-10.1 (0.33)	
		95% CI	-10.7, -9.4	
		P-value	p<.001	
	DLQI score at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-9.7 (0.33)	
		95% CI	-10.4, -9.1	
		P-value	p<.001	
Results and Analysis				
Analysis Description	**Key Secondary Analysis: NAPSI score at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	275	266	267
	NAPSI Score: LSM (SE)	-7.24 (0.657)	-7.19 (0.671)	2.17 (0.672)
Effect estimate per comparison	NAPSI score at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-9.41 (0.917)	
		95% CI	-11.20, -7.61	

		P-value	p<.001
	NAPSI score at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	-9.36 (0.922)
		95% CI	-11.17, -7.55
		P-value	p<.001

Abbreviations: CI = confidence interval; DLQI = Dermatology Life Quality Index; ITT = intent-to-treat; LSM = least squares mean; N/A = not applicable; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SE = standard error; sPGA = static Physician Global Assessment; vs. = versus.

Summary of Efficacy for Pivotal Trial I1F-MC-RHBA

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis		
Study identifier	I1F-MC-RHBA	
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study	
	Duration of Main phase: Duration of Extension phase:	12 weeks (Induction period) 48 weeks (Maintenance period); 204 weeks (Long-term extension period)
Hypothesis	Superiority to placebo; non-inferiority/superiority to etanercept	
Treatment groups	Ixekizumab Q2W	Ixekizumab 80 mg Q2W. Duration 12 weeks (Induction). Number randomized 351.
	Ixekizumab Q4W	Ixekizumab 80 mg Q4W. Duration 12 weeks (Induction), 48 weeks (Maintenance). Number randomized 347.
	Ixekizumab Q12W	Ixekizumab 80 mg Q12W. Duration 48 weeks (Maintenance).
	Placebo	Placebo. Duration 12 weeks (Induction), 48 weeks (Maintenance). Number randomized 168.
	Etanercept twice weekly	Etanercept 50 mg twice weekly. Duration 12 weeks (Induction). Number randomized 358.
Database lock	01 Oct 2014 (Last patient completed Week 36: 11 Sept 2014)	

Results and Analysis				
Analysis Description	**Co-Primary Analysis: Superiority to placebo**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo

estimate variability	Number of subjects	351	347	168
	sPGA (0,1)	292/351 (83.2%)	253/347 (72.9%)	4/168 (2.4%)
	PASI 75	315/351 (89.7%)	269/347 (77.5%)	4/168 (2.4%)
Effect estimate per comparison	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	80.8	
		Confidence level (2-sided): 97.5%	75.6, 86.0	
		P-value	p<.0001	
	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	70.5	
		Confidence level (2-sided): 97.5%	64.6, 76.5	
		P-value	p<.0001	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	87.4	
		Confidence level (2-sided): 97.5%	82.9, 91.8	
		P-value	p<.0001	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	75.1	
		Confidence level (2-sided): 97.5%	69.5, 80.8	
		P-value	p<.0001	

Results and Analysis				
Analysis Description	**Co-Primary Analysis: Non-inferiority to etanercept**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept 50 mg twice weekly
	Number of subjects	351	347	358
	sPGA (0,1)	292/351 (83.2%)	253/347 (72.9%)	129/358 (36.0%)
	PASI 75	315/351 (89.7%)	269/347 (77.5%)	149/358 (41.6%)
Effect estimate per	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept	

comparison		Retention Rate: (IXE-PBO)/(ETN-PBO)	2.40
		Confidence level (2-sided): 97.5%	2.03, 2.94
		Non-inferiority retention rate threshold is 0.70	
	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	2.10
		Confidence level (2-sided): 97.5%	1.75, 2.58
		Non-inferiority retention rate threshold is 0.70	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	2.23
		Confidence level (2-sided): 97.5%	1.92, 2.65
		Non-inferiority retention rate threshold is 0.70	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.91
		Confidence level (2-sided): 97.5%	1.64, 2.29
		Non-inferiority retention rate threshold is 0.70	

Results and Analysis				
Analysis Description	**Co-Primary Analysis: Superiority to etanercept**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept 50 mg twice weekly
	Number of subjects	351	347	358
	sPGA (0,1)	292/351 (83.2%)	253/347 (72.9%)	129/358 (36.0%)
	PASI 75	315/351 (89.7%)	269/347 (77.5%)	149/358 (41.6%)
Effect estimate per comparison	Co-Primary endpoint: sPGA (0,1)	Comparison groups		Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)		2.40
		Confidence level (2-sided): 97.5%		2.03, 2.94
		Superiority retention rate threshold is 1.00		

	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	2.10
		Confidence level (2-sided): 97.5%	1.75, 2.58
		Superiority retention rate threshold is 1.00	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	2.23
		Confidence level (2-sided): 97.5%	1.92, 2.65
		Superiority retention rate threshold is 1.00	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.91
		Confidence level (2-sided): 97.5%	1.64, 2.29
		Superiority retention rate threshold is 1.00	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: sPGA (0) at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	351	347	168
	sPGA (0)	147/351 (41.9%)	112/347 (32.3%)	1/168 (0.6%)
Effect estimate per comparison	sPGA (0) at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	41.3	
		Confidence level (2-sided): 97.5%	35.2, 47.3	
		P-value	p<.0001	
	sPGA (0) at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	31.7	
		Confidence level (2-sided): 97.5%	25.9, 37.5	
		P-value	p<.0001	
Results and Analysis				

Analysis Description	**Key Secondary Analysis: Superiority to placebo: PASI 90 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	351	347	168
	PASI 90	248/351 (70.7%)	207/347 (59.7%)	1/168 (0.6%)
Effect estimate per comparison	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	70.1	
		Confidence level (2-sided): 97.5%	64.5, 75.7	
		P-value	p<.0001	
	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	59.1	
		Confidence level (2-sided): 97.5%	53.0, 65.1	
		P-value	p<.0001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: PASI 100 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	351	347	168
	PASI 100	142/351 (40.5%)	107/347 (30.8%)	1/168 (0.6%)
Effect estimate per comparison	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	39.9	
		Confidence level (2-sided): 97.5%	33.8, 45.9	
		P-value	p<.0001	
	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	30.2	

		Confidence level (2-sided): 97.5%		24.5, 36.0
		P-value		p<.0001
Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to etanercept: sPGA (0) at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept 50 mg twice weekly
	Number of subjects	351	347	358
	sPGA (0)	147/351 (41.9%)	112/347 (32.3%)	21/358 (5.9%)
Effect estimate per comparison	sPGA (0) at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)		36.0
		Confidence level (2-sided): 97.5%		29.5, 42.5
		P-value		p<.0001
	sPGA (0) at Week 12	Comparison groups		Ixekizumab 80 mg Q4W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)		26.4
		Confidence level (2-sided): 97.5%		20.1, 32.7
		P-value		p<.0001
Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to etanercept: PASI 90 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept
	Number of subjects	351	347	358
	PASI 90	248/351 (70.7%)	207/347 (59.7%)	67/358 (18.7%)
Effect estimate per comparison	PASI 90 at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)		51.9
		Confidence level (2-sided): 97.5%		44.8, 59.1

		P-value	p<.0001
	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	40.9
		Confidence level (2-sided): 97.5%	33.4, 48.4
		P-value	p<.0001

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to etanercept: PASI 100 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept
	Number of subjects	351	347	358
	PASI 100	142/351 (40.5%)	107/347 (30.8%)	19/358 (5.3%)
Effect estimate per comparison	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	35.1	
		Confidence level (2-sided): 97.5%	28.7, 41.6	
		P-value	p<.0001	
	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	25.5	
		Confidence level (2-sided): 97.5%	19.4, 31.7	
		P-value	p<.0001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority of placebo: Maintenance of sPGA (0,1) at Week 60**			
Analysis population and time point description	Maintenance Dosing Period Primary Population 60 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab/80 mg Ixekizumab Q4W	Ixekizumab/80 mg Ixekizumab Q12W	Ixekizumab/Placebo
	Number of subjects	119	128	158
	sPGA (0,1)	81/119 (68.1%)	41/128 (32.0%)	9/158 (5.7%)

Effect estimate per comparison	sPGA (0,1) at Week 60	Comparison groups	Ixekizumab/80 mg Ixekizumab Q4W vs. Ixekizumab/Placebo
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	62.4
		Confidence level (2-sided): 95%	53.2, 71.5
		P-value	p<.001
	sPGA (0,1) at Week 60	Comparison groups	Ixekizumab/80 mg Ixekizumab Q12W vs. Ixekizumab/Placebo
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	26.3
		Confidence level (2-sided): 95%	17.5, 35.2
		P-value	p<.001

Abbreviations: ETN = etanercept; ITT = intent-to-treat; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; sPGA = static Physician Global Assessment; vs. = versus.

Summary of Efficacy for Pivotal Trial I1F-MC-RHBC

Title: A 12-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients with Moderate to Severe Plaque Psoriasis with a Long-Term Extension Period		
Study identifier	I1F-MC-RHBC	
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study	
	Duration of Main phase: Duration of Extension phase:	12 weeks (Induction period) 252 weeks (Long-term extension period)
Hypothesis	Superiority to placebo; non-inferiority/superiority to etanercept	
Treatment groups	Ixekizumab Q2W	Ixekizumab 80 mg Q2W. Duration 12 weeks (Induction). Number randomized 385.
	Ixekizumab Q4W	Ixekizumab 80 mg Q4W. Duration 12 weeks (Induction). Number randomized 386.
	Placebo	Placebo. Duration 12 weeks (Induction). Number randomized 193.
	Etanercept twice weekly	Etanercept 50 mg twice weekly. Duration 12 weeks (Induction). Number randomized 382.
Database lock	14 Jul 2014 (Last patient visit prior to database lock: 22 May 2014)	

Results and Analysis	
Analysis Description	**Co-Primary Analysis: Superiority to placebo**
Analysis population and time point description	ITT Population 12 weeks

Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	385	386	193
	sPGA (0,1)	310/385 (80.5%)	291/386 (75.4%)	13/193 (6.7%)
	PASI 75	336/385 (87.3%)	325/386 (84.2%)	14/193 (7.3%)
Effect estimate per comparison	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	73.8	
		Confidence level (2-sided): 97.5%	67.7, 79.9	
		P-value	p<.0001	
	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	68.7	
		Confidence level (2-sided): 97.5%	62.3, 75.0	
		P-value	p<.0001	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	80.0	
		Confidence level (2-sided): 97.5%	74.4, 85.7	
		P-value	p<.0001	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	76.9	
		Confidence level (2-sided): 97.5%	71.0, 82.8	
		P-value	p<.0001	

Results and Analysis				
Analysis Description	**Co-Primary Analysis: Non-inferiority to etanercept**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept 50 mg twice weekly
	Number of subjects	385	386	382
	sPGA (0,1)	310/385 (80.5%)	291/386 (75.4%)	159/382 (41.6%)
	PASI 75	336/385 (87.3%)	325/386 (84.2%)	204/382 (53.4%)

Effect estimate per comparison	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	2.11
		Confidence level (2-sided): 97.5%	1.79, 2.59
		Non-inferiority retention rate threshold is 0.70	
	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.97
		Confidence level (2-sided): 97.5%	1.66, 2.41
		Non-inferiority retention rate threshold is 0.70	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.73
		Confidence level (2-sided): 97.5%	1.52, 2.01
		Non-inferiority retention rate threshold is 0.70	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.67
		Confidence level (2-sided): 97.5%	1.46, 1.94
		Non-inferiority retention rate threshold is 0.70	

Results and Analysis				
Analysis Description	**Co-Primary Analysis: Superiority to etanercept**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept 50 mg twice weekly
	Number of subjects	385	386	382
	sPGA (0,1)	310/385 (80.5%)	291/386 (75.4%)	159/382 (41.6%)
	PASI 75	336/385 (87.3%)	325/386 (84.2%)	204/382 (53.4%)
Effect estimate per comparison	Co-Primary endpoint: sPGA (0,1)	Comparison groups		Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)		2.11
		Confidence level (2-sided): 97.5%		1.79, 2.59
		Superiority retention rate threshold is 1.00		

	Co-Primary endpoint: sPGA (0,1)	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.97
		Confidence level (2-sided): 97.5%	1.66, 2.41
		Superiority retention rate threshold is 1.00	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.73
		Confidence level (2-sided): 97.5%	1.52, 2.01
		Superiority retention rate threshold is 1.00	
	Co-Primary endpoint: PASI 75	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept
		Retention Rate: (IXE-PBO)/(ETN-PBO)	1.67
		Confidence level (2-sided): 97.5%	1.46, 1.94
		Superiority retention rate threshold is 1.00	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: sPGA (0) at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	385	386	193
	sPGA (0)	155/385 (40.3%)	139/386 (36.0%)	0
Effect estimate per comparison	sPGA (0) at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	40.3	
		Confidence level (2-sided): 97.5%	34.7, 45.9	
		P-value	p<.0001	
	sPGA (0) at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	36.0	
		Confidence level (2-sided): 97.5%	30.5, 41.5	
		P-value	p<.0001	
Results and Analysis				

Analysis Description	**Key Secondary Analysis: Superiority to placebo: PASI 90 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	385	386	193
	PASI 90	262/385 (68.1%)	252/386 (65.3%)	6/193 (3.1%)
Effect estimate per comparison	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	64.9	
		Confidence level (2-sided): 97.5%	58.9, 71.0	
		P-value	p<.0001	
	PASI 90 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	62.2	
		Confidence level (2-sided): 97.5%	56.1, 68.3	
		P-value	p<.0001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: PASI 100 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	385	386	193
	PASI 100	145/385 (37.7%)	135/386 (35.0%)	0
Effect estimate per comparison	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	37.7	
		Confidence level (2-sided): 97.5%	32.1, 43.2	
		P-value	p<.0001	
	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	35.0	
		Confidence level (2-sided): 97.5%	29.5, 40.4	

		P-value		p<.0001
Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to etanercept: sPGA (0) at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept 50 mg twice weekly
	Number of subjects	385	386	382
	sPGA (0)	155/385 (40.3%)	139/386 (36.0%)	33/382 (8.6%)
Effect estimate per comparison	sPGA (0) at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)		31.6
		Confidence level (2-sided): 97.5%		25.2, 38.1
		P-value		p<.0001
	sPGA (0) at Week 12	Comparison groups		Ixekizumab 80 mg Q4W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)		27.4
		Confidence level (2-sided): 97.5%		21.0, 33.7
		P-value		p<.0001
Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to etanercept: PASI 90 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept
	Number of subjects	385	386	382
	PASI 90	262/385 (68.1%)	252/386 (65.3%)	98/382 (25.7%)
Effect estimate per comparison	PASI 90 at Week 12	Comparison groups		Ixekizumab 80 mg Q2W vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)		42.4
		Confidence level (2-sided): 97.5%		35.1, 49.7
		P-value		p<.0001
	PASI 90 at Week 12	Comparison groups		Ixekizumab 80 mg Q4W vs. Etanercept

		Cochran-Mantel-Haenszel risk difference, Estimate (%)	39.6
		Confidence level (2-sided): 97.5%	32.2, 47.0
		P-value	p<.0001

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to etanercept: PASI 100 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Etanercept
	Number of subjects	385	386	382
	PASI 100	145/385 (37.7%)	135/386 (35.0%)	28/382 (7.3%)
Effect estimate per comparison	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Etanercept	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	30.3	
		Confidence level (2-sided): 97.5%	24.0, 36.6	
		P-value	p<.0001	
	PASI 100 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Etanercept	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	27.6	
		Confidence level (2-sided): 97.5%	21.4, 33.9	
		P-value	p<.0001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: Itch NRS ≥4 at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	320	313	158
	Itch NRS ≥4	264/320 (82.5%)	250/313 (79.9%)	33/158 (20.9%)
Effect estimate per comparison	Itch NRS ≥4 at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	61.6	
		Confidence level (2-sided): 97.5%	52.9, 70.3	

		P-value	p<.0001
	Itch NRS ≥4 at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	59.0
		Confidence level (2-sided): 97.5%	50.1, 67.8
		P-value	p<.0001

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: DLQI score at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	363	363	182
	DLQI Score: LSM (SE)	-10.2 (0.23)	-9.6 (0.23)	-1.7 (0.32)
Effect estimate per comparison	DLQI score at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-8.4 (0.39)	
		95% CI	-9.2, -7.7	
		P-value	p<.001	
	DLQI score at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo	
		LSM Difference (SE)	-7.9 (0.40)	
		95% CI	-8.7, -7.1	
		P-value	p<.001	

Results and Analysis				
Analysis Description	**Key Secondary Analysis: Superiority to placebo: NAPSI score at Week 12**			
Analysis population and time point description	ITT Population 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Placebo
	Number of subjects	221	218	112
	NAPSI Score: LSM (SE)	-10.41 (0.782)	-9.98 (0.784)	1.64 (1.099)
Effect estimate per comparison	NAPSI score at Week 12	Comparison groups	Ixekizumab 80 mg Q2W vs. Placebo	
		LSM Difference (SE)	-12.05 (1.346)	

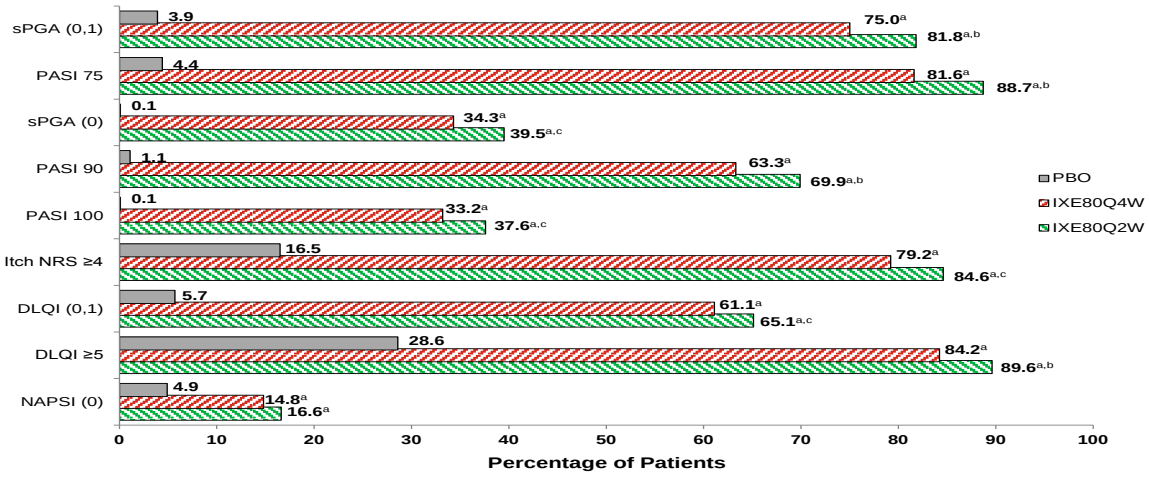
		95% CI	-14.69, -9.41
		P-value	p<.001
	NAPSI score at Week 12	Comparison groups	Ixekizumab 80 mg Q4W vs. Placebo
		LSM Difference (SE)	-11.62 (1.348)
		95% CI	-14.26, -8.97
		P-value	p<.001

Abbreviations: DLQI = Dermatology Life Quality Index; ETN = etanercept; ITT = intent-to-treat; IXE = ixekizumab; LSM = least squares mean; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error; sPGA = static Physician Global Assessment; vs. = versus.

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

Integrated results for the primary end-points as well as major, secondary end-points in the three studies are shown in **Figure 27**.

Figure 27. sPGA, PASI, Itch NRS, DLQI, NAPSI percentage of patients meeting response criteria at Week 12 (NRI) Primary Psoriasis Placebo-Controlled Integrated Analysis Set ITT Population – Studies RHAZ, RHBA, and RHBC Induction Dosing Period.



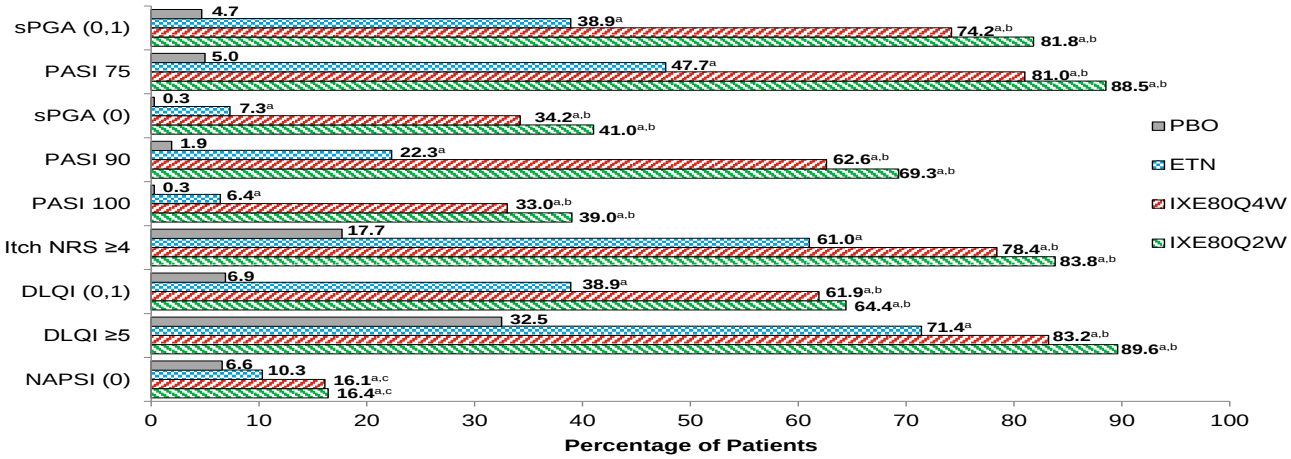
[a] p<.001 versus placebo

[b] p<.001 versus ixekizumab 80 mg Q4W

[c] p≤.05 versus ixekizumab 80 mg Q4W

Similarly, integrated results for studies RHBA and RHBC (including the active comparator etanercept) for the primary end-points and major, secondary end-points are shown in Figure **28**.

Figure 28. sPGA, PASI, Itch NRS, DLQI, and NAPSI, percentage of patients meeting response criteria at Week 12 Psoriasis Placebo- and Active-Controlled Integrated Analysis Set ITT Population – Studies RHBA and RHBC Induction Dosing Period

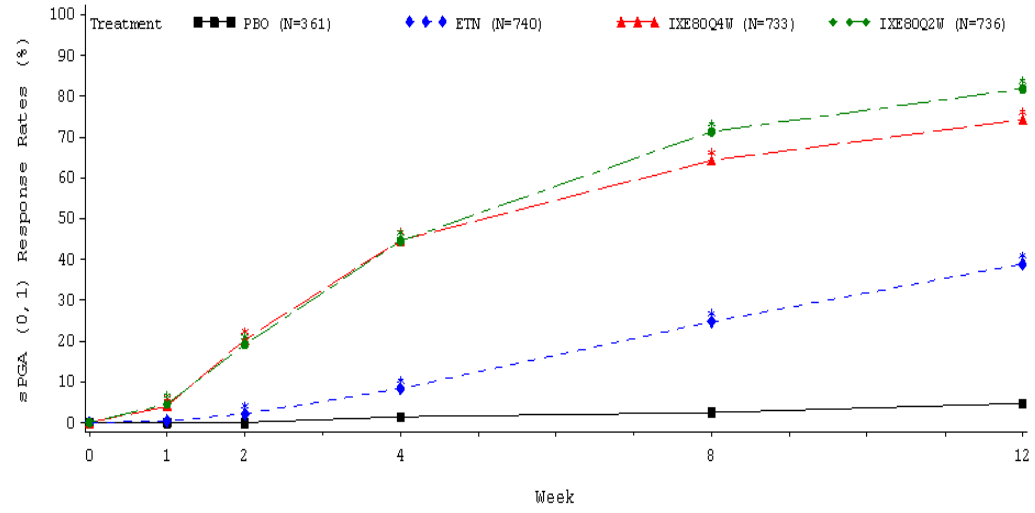


a p<.001 versus placebo; b p<.001 versus etanercept; c p≤.05 versus etanercept

Onset of Response

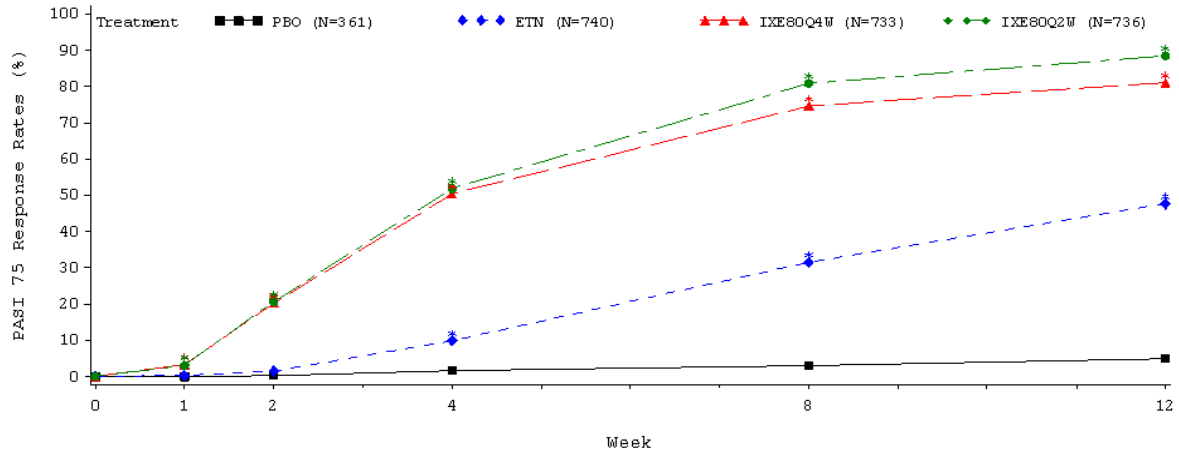
Integrated results for studies RHBA and RHBC for the primary end-points sPGA (0,1) and PASI 75 over time (Induction period), including the comparison with etanercept, are shown in **Figures 29** and **30**.

Figure 29. sPGA (0,1) response rates at each postbaseline visit (NRI) Primary Psoriasis Placebo- and Active-Controlled Integrated Analysis Set ITT Population – Studies RHBA and RHBC Induction Dosing Period



Notes: PBO = Placebo; ETN= Etanercept; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; N = number of patients in the analysis population; NRI = non-responder imputation; sPGA = static physician global assessment.
* p-value <= 0.05 versus placebo.

Figure 30. PASI 75 response rates at each postbaseline visit (NRI) Primary Psoriasis Placebo- and Active-Controlled Integrated Analysis Set ITT Population – Studies RHBA and RHBC Induction Dosing Period

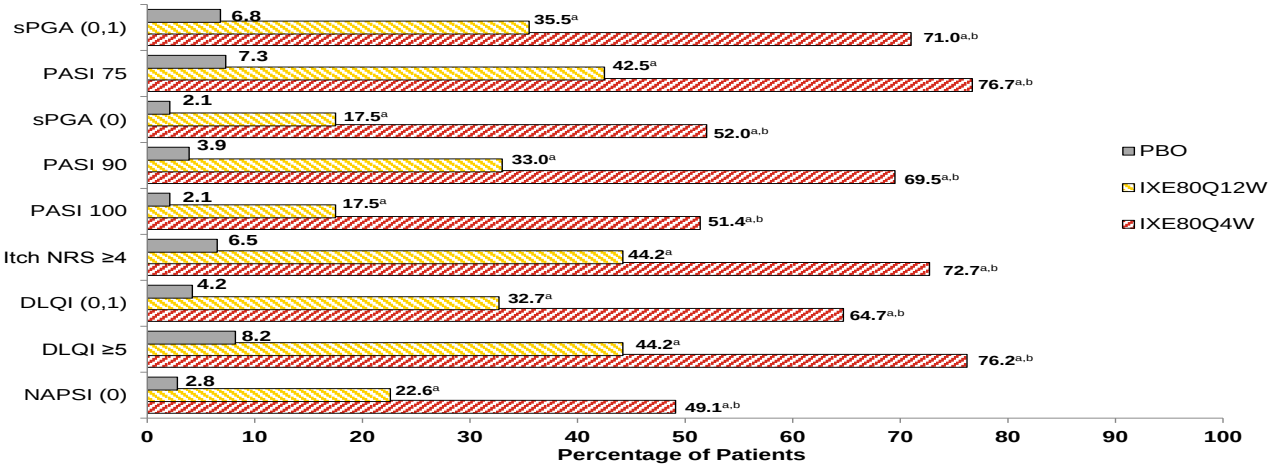


Notes: PBO = Placebo; ETN= Etanercept; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; N = number of patients in the analysis population; NRI = non-responder imputation; PASI = psoriasis area and severity index.
* p-value <= 0.05 versus placebo.

sPGA (0,1) and PASI 75 response rates in the Primary Psoriasis Placebo-Controlled Integrated Analysis Set during the Induction Dosing Period also showed a significant difference for patients treated with either ixekizumab regimen compared with placebo from Week 1 (data not shown).

Results for the maintenance *integrated* analysis set are shown in **Figure 31**. Superiority (p<0.001 for all comparisons) of both ixekizumab dose regimens (80 mg Q12W and 80 mg Q4W) was confirmed in the maintenance of drug effect, as measured by efficacy response rates at Week 60.

Figure 31. sPGA, PASI, Itch NRS, DLQI, and NAPSI response rate at Week 60, Psoriasis Maintenance Integrated Analysis Set. Maintenance Dosing Period efficacy Evaluable Population – RHAZ and RHBA

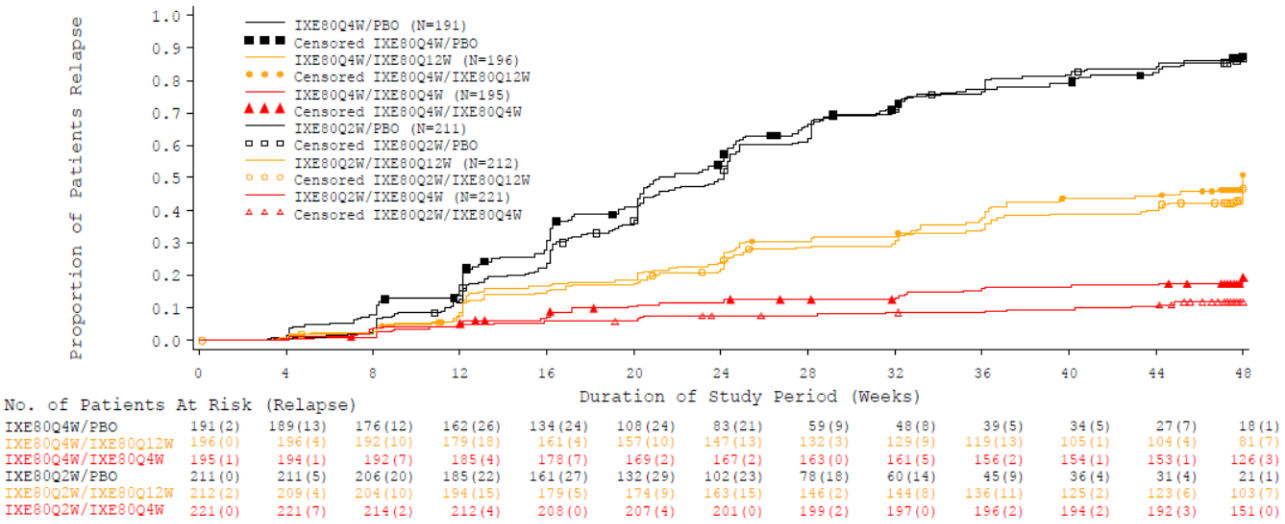


[a] p<.001 versus placebo; [b] p<.001 versus ixekizumab 80 mg Q12W

Relapse following treatment withdrawal

Relapse during the Maintenance Dosing Period was defined as reaching a sPGA ≥ 3 (moderate) and results are shown in **Figure 32**.

Figure 32. Kaplan-Meier plot of time to relapse (sPGA ≥3) Maintenance Dosing Period by individual dose. Psoriasis Maintenance Integrated Analysis Set, Studies RHAZ and RHBA) (Primary Population—Efficacy Evaluable Patients)



No. of Patients At Risk (Relapse)

IXE80Q4W/PBO	191(2)	189(13)	176(12)	162(26)	134(24)	108(24)	83(21)	59(9)	48(8)	39(5)	34(5)	27(7)	18(1)
IXE80Q4W/IXE80Q12W	196(0)	196(4)	192(10)	179(18)	161(4)	157(10)	147(13)	132(3)	129(9)	119(13)	105(1)	104(4)	81(7)
IXE80Q4W/IXE80Q4W	195(1)	194(1)	192(7)	185(4)	178(7)	169(2)	167(2)	163(0)	161(5)	156(2)	154(1)	153(1)	126(3)
IXE80Q2W/PBO	211(0)	211(5)	206(20)	185(22)	161(27)	132(29)	102(23)	78(18)	60(14)	45(9)	36(4)	31(4)	21(1)
IXE80Q2W/IXE80Q12W	212(2)	209(4)	204(10)	194(15)	179(5)	174(9)	163(15)	146(2)	144(8)	136(11)	125(2)	123(6)	103(7)
IXE80Q2W/IXE80Q4W	221(0)	221(7)	214(2)	212(4)	208(0)	207(4)	201(0)	199(2)	197(0)	196(2)	194(2)	192(3)	151(0)

Notes: PBO = Placebo; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q12W = Ixekizumab 80 mg Q12W; N = number of patients in the analysis population;sPGA = static physician global assessment.

Supportive studies

RHAT

Study RHAT was an open-label, long-term study evaluating ixekizumab 80 mg Q2W in Japanese patients with moderate-to-severe psoriasis (including plaque, erythrodermic, and pustular forms) during a 12-week Induction Dosing Period. The primary endpoints were assessed at Week 12. Following the Induction Dosing Period, patients are treated with ixekizumab 80 mg Q4W for an additional 40 weeks. The study included a Drug-Free (withdrawal) Period and a Re-treatment Period (192 weeks), both of which are still in progress. At the time of the study report, all patients in RHAT had completed Week 52 or had discontinued the study.

RHBL

Study RHBL was an open-label,12-week study of ixekizumab 80 mg Q2W in patients with moderate-to-severe plaque psoriasis (comparing 2 delivery devices, a prefilled syringe and an autoinjector), followed by a 40-week Optional Safety Extension Period (80 mg Q4W, prefilled syringe). Efficacy endpoints were secondary objectives of Study RHBL. The primary objective was the effect of drug-delivery device on ixekizumab PK following 160-mg starting dose. At the time of the study report, all patients in RHBL had completed Week 12 and entered into the ongoing Optional Safety Extension Period or had discontinued the study.

The efficacy results from both supportive studies are presented in **Table 31**.

Table 31. Summary of sPGA and PASI Response Rates (%) Studies RHAT and RHBL

Study/Time Point/No. Pts	sPGA (0,1)	PASI 75	PASI 90	sPGA (0)	PASI 100
RHAT Week 12 N=78	89.7	98.7	83.3	35.9	32.1
RHAT Week 52 N=78	83.3	92.3	80.8	52.6	48.7
RHBL Week 12[a] N=204	77.0	83.3	69.6	47.1	45.1

Abbreviations: N = number of patients; No. = number; PASI = Psoriasis Area and Severity Index; Pts = patients; sPGA = static Physician Global Assessment
[a]*Pooled data from autoinjector group and prefilled syringe group*

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of ixekizumab in plaque psoriasis is primarily supported by data from one phase 2 dose finding study and three pivotal phase 3 studies, followed by long-term extension studies.

Standard efficacy variables for plaque psoriasis were used to assess efficacy of ixekizumab in the phase II and III studies, in accordance with published guidelines, e.g. CHMP/EWP/2454/02, 2004. Both physicians reported psoriasis efficacy evaluations (PASI and sPGA) and patient reported psoriasis efficacy evaluations were used (e.g. DLQI, Itch NRS).

PASI is a common, well-accepted score for assessment of plaque psoriasis severity. For global assessment of psoriasis by the physician, the static Physician Global Assessment (sPGA) was used. In the CHMP psoriasis guideline, use of a global assessment scale is recommended as a co-primary end-point, in addition to PASI.

The Itch NRS scale for assessment of itch severity in psoriasis was developed and rated by the applicant. The Applicant determined that a 4-point decrease in this scale indicated a clinically meaningful itch response.

The phase II study RHAJ was performed with four different doses of ixekizumab (10, 25, 75 and 150 mg) administered at 2-week intervals initially and thereafter every 4 weeks. The dose levels were selected based on clinical effects and tolerability from an interim analysis of PK/PD data from a Phase 1 Study in patients with psoriasis vulgaris. A maintenance dose of 80 mg every 4 weeks (Q4W) was implemented in an amendment. The study had an adequate design (randomised, double-blind, placebo-controlled, parallel-group), was performed in a relevant population and had end-points corresponding to those used in the phase 3 studies (e.g. PASI 75 assessed at week 12).

The pivotal trials in support of the efficacy and safety of ixekizumab were multicentre phase 3 studies placebo-controlled, randomised, double-blind, with a parallel group design (Studies RHAZ, RHBA and RHBC). The two latter were also active-controlled with the approved TNF-α antagonist biologic etanercept (Enbrel) as comparator. These studies were designed to demonstrate the safety and efficacy of two ixekizumab induction regimens (80 mg every 2 or 4 weeks; Q2W or Q4W) after 12 weeks of therapy. Studies RHAZ and RHBA also investigated maintenance dosing regimens of ixekizumab 80 mg administered every 4 or 12 weeks (Q4W or Q12W) or placebo up to week 60 using a randomised withdrawal design. The treatments and study design were considered adequate.

The study population was relevant and consisted of male and female patients with moderate to severe chronic plaque-type psoriasis. The list of prohibited medications and respective wash-out periods were also deemed adequate by the CHMP. In studies RHBA and RHBC, previous exposure to etanercept was not allowed, which was endorsed by the CHMP. Previous use of other biologics targeting TNF α was allowed after a washout period.

In studies RHBA and RHBC, etanercept was included as active comparator. This choice was made since etanercept is a biologic agent used for the treatment of plaque psoriasis for a long time with an acceptable safety profile and with the same mode of administration as ixekizumab (SC injection). The posology of etanercept in the study was in accordance with the labelling for Enbrel, and the dosage used was the highest recommended for Enbrel.

The CHMP noted that the Applicant had applied for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and requested further justification as to why Taltz should be indicated prior to treatment with phototherapy. In their response the applicant clarified that it was not intended to recommend Taltz treatment prior to phototherapy in the general psoriasis patient population and therefore agreed to modify the initially proposed indication as follows: "treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy".

The respective primary objectives of the three studies were the same, i.e. to demonstrate the superiority of ixekizumab in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and sPGA (0,1) response (co-primary endpoints) at Week 12, compared to placebo. In studies RHBA and RHBC, comparisons with etanercept were also among the primary objectives (non-inferiority and superiority comparisons of ixekizumab vs. etanercept).

In study RHAZ, patients were stratified by geographic regions, previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥3 conventional systemic therapies), and weight (<100 kg or ≥100 kg). In studies RHBA and RHBC, patients were only stratified by centre. In both studies RHAZ and RHBA, patients were stratified by weight (<100 kg or ≥ 100 kg) and ixekizumab induction dose regimen (80 mg Q2W or Q4W) at re-randomisation in the maintenance phase.

All the pivotal phase III studies were double-blind and steps taken to achieve and maintain blinding were considered appropriate. Statistical considerations regarding planned analyses and the methods used were also considered appropriate. In all the studies the primary analysis set was the intent-to-treat (ITT) population including all patients who were randomized.

Efficacy data and additional analyses

In the phase 2 study RHAJ, the 25 mg, 75 mg, and 150 mg ixekizumab dose groups all showed a statistically significant higher rate of PASI 75 response at Week 12 (approximately 80% for all doses) compared with placebo (8%). A similar pattern was observed for the sPGA (0,1). For other end-points, a separation of the three highest doses was observed for some of them, e.g. for PASI 90 and sPGA(0) response.

The dosing regimens for the phase 3 studies were selected based on PK/PD modelling of Phase 2 data. The induction dosing regimens of 80 mg Q4W and 80 mg Q2W were predicted to provide cumulative exposure and sPGA and PASI responses comparable to the ixekizumab 75 mg and 150 mg Q4W dosing regimens, respectively, used in Study RHAJ. The 160 mg starting dose was selected to allow for steady state to be achieved earlier and thus enable a more rapid onset of clinical response.

For the maintenance dose, it was anticipated that less frequent dosing would be needed to maintain response during long-term therapy. As a result, the 80 mg Q4W dose was chosen to determine if the response achieved through 12 weeks would be maintained with long-term dosing. To determine whether even less frequent dosing would maintain response, an 80 mg Q12W dose was also evaluated. These two dosing regimens were expected to result in distinct exposures allowing for adequate comparison of two dosing frequencies for maintenance therapy. The applicant´s reasoning behind the choice of induction and maintenance dosing regimens to be studied in phase 3 was endorsed by the CHMP.

Baseline demographic characteristics were overall well-balanced across study groups, with the majority of patients being male (about two thirds), White/Caucasian (>90%) and below 65 years of age (>90%). Thus, few patients aged ≥ 65 years were included (6-7%) and very few above 75 years

(about 1%). The mean body weight was slightly above 90 kg, and mean BMI was about to 30 kg/m^2. Almost 80% of the study population had a BMI of 25 kg/m^2 or above, i.e. were overweight or obese.

Concerning baseline disease characteristics, data were also largely comparable across treatment groups for the pooled patient population. Approximately equal proportions of the patients had moderate psoriasis (sPGA 3) and severe psoriasis (sPGA 4 or 5). The mean baseline PASI score was approximately 20.

More than 60% of the patients were previously exposed to systemic psoriasis therapy and about 26% had previous exposure to systemic biologic therapy, including also patients who had previously failed biologics. In studies RHBA and RHBC that included the active comparator etanercept, previous exposure to etanercept was not allowed. The numbers who had previous exposure to biologic systemic psoriasis therapy was lower compared to the other studies, but balanced across study arms within these studies. Approximately 43% of all patients had previously used phototherapy.

No important issues were raised related to protocol amendments or compliance with study medication. Protocol deviations categorized as major were reported rather frequently, e.g. by 27.5% of patients in study RHBA and 23.5% in study RHBC while the figure was somewhat lower in study RHAZ (14%). The majority of these deviations were related to missing data (most commonly missing ECGs). Other common deviations were related to study inclusion or exclusion criteria, non-compliance with study medication, double-dosing or took incorrect study medication. All randomised subjects were included in the ITT population.

Induction treatment efficacy results

All three phase 3 studies met their co-primary end-points, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response and sPGA (0,1) response at week 12. This was observed for both ixekizumab doses, however, higher response rates were observed for the 80 mg Q2W vs. the 80 mg Q4W induction dose regimen. Based on the integrated data, PASI 75 response was 89% for the Q2W regimen, 82% for the Q4W regimen vs. approximately 4% for placebo and 48% for etanercept. Corresponding figures for sPGA (0,1) response were 82, 75%, 4% and 39%, respectively.

Secondary end-points were also met, e.g. PASI 90, PASI 100 and sPGA (0) response vs. placebo at week 12. In studies RHAB and RHBC, both ixekizumab doses were superior to etanercept with respect to both PASI 75, sPGA (0,1), sPGA (0), PASI 100 and PASI 90 and also for other end-points.

For both the co-primary and the major secondary end-points, the response rates were higher for the 80 mg Q2W vs. the Q4W induction dose regimen. The differences were not large, though, being in the range 4-7% across different comparisons.

Maintenance treatment efficacy results

Studies RHAZ and RHAB evaluated withdrawal of treatment with two different ixekizumab maintenance dosing regimens in ixekizumab responders. The effect of ixekizumab was maintained up to week 60 in studies RHAZ and RHAB.

Relapse during the maintenance dosing period was defined as reaching an sPGA ≥3 (moderate). In the Psoriasis Maintenance Integrated Analysis Set, relapse was experienced by 84% of patients treated with placebo, 50% in the 80 mg Q12W group and 17% in the 80 mg Q4W group. The median time to relapse was 164 days for patients treated with placebo, i.e. about 5 months.

The PASI 75 response rate at week 60 was approximately 77% for the 80 mg Q4W dose regimen and 43% for the 80 mg Q12W dose regimen (integrated analysis of the Maintenance Dosing Period efficacy Evaluable Population – RHAZ and RHBA). Corresponding sPGA (0,1) response rates at week 60 were

71% for ixekizumab Q4W and 36% for ixekizumab Q12W. Thus, the differences between the two maintenance dose regimens (Q4W vs. Q12W) were marked, with differences in response rates generally being in the range 30-40%.

It seemed as if the group treated with ixekizumab 80 mg Q2W during the induction phase had higher PASI 75 and sPGA (0,1) response rates during the maintenance phase, compared with those who received the Q4W induction regimen. This was more apparent in study RHBA than in study RHAZ, with about 17-19% higher response rates for most end-points in the Q2W/Q4W group compared with the Q4W/Q4W group. Thus, in this study, the more intense induction dose regimen appeared to result in higher response rates after a long period. This difference was even more marked when the final results up to week 60 were submitted for study RHBA.

The same pattern was observed for other end-points, such as Itch NRS response rates, DLQI and NAPSI. For the Itch NRS, more than 70% of patients on the Q4W maintenance dose regimen had a ≥ 4 point improvement. More than 60% of patients on the Q4W maintenance dose regimen reached a DLQI of 0 or 1, corresponding to no or little impact of their condition on quality of life. For the patients with nail psoriasis, almost 50% reached clearance of their fingernails (NAPSI = 0) at Week 60 with the Q4W maintenance dose regimen.

Only responders to ixekizumab were re-randomised after the induction phase in studies RHAZ and RHBA whereas all non-responders to ixekizumab, placebo or etanercept were assigned to treatment with ixekizumab 80 mg Q4W during the maintenance phase.

In patients who did not respond to the recommended dose of ixekizumab 80 mg Q2W at Week 12, 26% achieved an sPGA (0,1) and 52% achieved a PASI 75 response at Week 60. Thus, some patients who don´t respond initially may respond with continued ixekizumab treatment. However, only 26% in this group reached an sPGA (0,1).

Results from the updated Psoriasis Maintenance Integrated Analysis Set indicated that 33% achieved an sPGA (0,1) and 56% achieved a PASI 75 response at Week 60 among those patients who did not respond to Q2W by Week 12. A total of 14% of patients who did not respond to Q2W by Week 12, were able to achieve complete clearance (PASI 100 or sPGA 0) after 60 weeks of treatment.

It may be difficult to identify patients beforehand regarding future response to psoriasis treatments based on clinical or bio-markers, although patients with severe, widespread psoriasis resistant to previous treatment are likely to be more treatment resistant. Since the median time to a clinical response was between 16 and 24 weeks for those patients that had not responded after the induction dosing period, it was suggested to propose a time-range rather than a single time point after which treatment should be discontinued. This is reflected in the SmPC, which states that consideration should be given to discontinuing treatment in patients who have shown no response after 16-20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.

Of the patients who were etanercept non-responders during the induction phase in study RHBA, 73% achieved sPGA (0,1) and 83.5% met PASI 75 response after treatment with ixekizumab 80 mg Q4W for 12 weeks. This suggests that non-response to etanercept does not prevent patients from achieving a clinically meaningful response with ixekizumab treatment. This was endorsed by the CHMP and described in section 5.1 of the SmPC.

Sub-group analyses

Adequate sub-group analyses were performed. There were no major differences in responder rates based on age, gender, race or region.

Body weight seems to be one factor influencing the response, with overall 5-10% lower response rates in the group weighing above 90 kg or 100 kg in comparison with those below these cut-off values. It can be noted that the phase 3 study population is generally overweight or obese with almost 80% of the total population having a BMI of 25 kg/m^2 or higher. In particular, the sub-group with a BMI > 40 kg/m^2 (making up about 10% of the total population) had 10-20% lower PASI 75 and sPGA (0,1) response compared with patients with normal BMI. The proposed posology for ixekizumab is not differentiated based on body weight. However, even if there is a tendency to lower response rates in obese patients, ixekizumab was superior to placebo for all comparisons and the response rates for PASI 75 and sPGA (0,1) are regarded as clinically relevant also for these patients. It may well be that obese or extremely obese patients are more likely to respond poorly to ixekizumab, even if there are several factors that may influence whether a patient is a responder or a non-responder.

The Q2W/Q4W posology is considered to produce clinically relevant responses also for patients >100 kg. On the other hand, patients weighing less than 60 kg showed the highest response rates for the induction period in the Q4W group. Patients in this category showed 7% to 11% higher response rates with the Q4W Induction Dose regimen for the efficacy endpoints (NRI). However, as this was a fairly small group it could represent a chance finding. Therefore, no further actions (e.g. posology changes) were deemed necessary for this weight category.

Substantial numbers of subjects had received previous systemic therapy for their psoriasis condition, e.g. >60% had used previous systemic therapies, and 25-30% of the study population had used previous biologic therapy. No major differences in sPGA (0,1) and PASI 75 response rates were observed between previous users vs. non-users, however, the responses rates tended to be lower in those patients who had used several different biologics previously. For previous non-biologic systemic therapy, the analysis was focused on those who have had inadequate response, intolerance or contraindication to less than three or more than three previous therapies. No major differences were observed although those with previous experience of less than three non-biologics had somewhat higher sPGA (0,1) and PASI 75 response rates. Thus, no major differences were observed across sub-groups, even if the response rates were generally somewhat lower in the groups with previous failure to other therapies.

The impact of immunogenicity on efficacy was also assessed. The incidence of immunogenicity during the Induction Period was in the range 9 to 13%, with more frequent administration of ixekizumab associated with lower rates of immunogenicity. The subgroup of TE-ADA positive patients with NAb-positive status tended to have low response or were non-responders, suggesting a relationship between the presence of NAb and efficacy response. The number of NAb-positive patients was approximately 1% in the induction phase.

During the maintenance period, the incidence of immunogenicity ranged from 14% to 17% in those who received ixekizumab or placebo in the induction period and subsequently maintained on 80 mg Q4W up to Week 60. As observed in the induction period, more frequent dosing (Q4W versus Q12W) was associated with lower incidence of immunogenicity during the Maintenance Dosing Period. Similar to the induction period, patients with low ADA titer represented the majority of the TE-ADA positive patients, and their efficacy response rates were comparable to TE-ADA negative patients. Efficacy responses were generally lower in the NAb-positive patients.

It appeared that patients with moderate-to-high ADA titers and NAb positive patients tended to have poor response to ixekizumab. Both during the induction and maintenance dosing periods, the most frequent dose regimens had the lowest incidences of immunogenicity.

The CHMP requested that the issue of immunogenicity in patients receiving ixekizumab is followed up in the ongoing extensions of Studies RHAZ, RHBA and RHBC in order to describe the development of antibodies and neutralising antibodies to ixekizumab treatment but also to fully describe the effect of antibody titre on ixekizumab pharmacokinetics and investigate the effect of neutralising antibodies on clinical efficacy. Annual reports from these studies will be provided in the PSURs as described in the RMP.

2.5.4. Conclusions on the clinical efficacy

Ixekizumab has demonstrated clearly statistically significant effects vs. placebo and all three phase 3 studies met their co-primary end-points to demonstrate superiority vs. placebo with respect to PASI 75 response and sPGA (0,1) response at week 12. Secondary end-points were also met, e.g. PASI 90, PASI 100 and sPGA (0) response vs. placebo. The response rates are regarded high, e.g. almost 90% of patients treated with ixekizumab 80 mg Q2W reached PASI 75. Around 40% also reach the more stringent sPGA(0) and PASI 100 at week 12, which is highly clinically relevant.

Both ixekizumab induction dose regimens were superior to etanercept with respect to both PASI 75, sPGA (0,1), PASI 90, PASI 100 and sPGA (0). Etanercept is considered an acceptable comparator, although its efficacy in plaque psoriasis is generally considered to be in the lower range when compared with other biologics approved in this indication.

The 80 mg Q2W regimen generally showed 4-7 % higher response rates for most end-points compared with the 80 mg Q4W regimen. Therefore, and despite this modest difference, the Q2W induction regimen was considered to translate in better results in the real-life setting.

The Q4W regimen is considered appropriate as the maintenance dose regimen due to differences in response rates of 30-40% for the two maintenance dose regimens studied, i.e. 80 mg Q4W vs. 80 mg Q12W.

Regarding immunogenicity, the CHMP agreed that the percentage of patients developing Nabs was low (about 1%) based on the results from the pivotal phase 3 studies. However, the Applicant was requested to follow-up all patients to follow-up the presence of neutralising antibodies and clinical response to more fully understand the consequence of development of neutralising antibodies, in the extension phases of the phase 3 studies as detailed in the RMP.

In conclusion, ixekizumab has demonstrated statistically significant and clinically relevant effects vs. placebo and etanercept in all three phase 3 studies, for induction and maintenance treatment of plaque psoriasis.

2.6. Clinical safety

Patient exposure

A total of 4736 patients have been studied in 11 clinical trials of psoriasis and rheumatoid arthritis. In the 7 studies of psoriasis, 4204 patients were treated with ixekizumab. For patients with moderate-to-severe psoriasis, exposure to ixekizumab at any dose/dose includes 4729.7 patients-years, with over 2190 patients with psoriasis treated with any dose/dose regimen for at least 1 year. There are three pivotal studies in plaque psoriasis. These studies were pooled to evaluate the safety in comparison to placebo and to etanercept 50 mg x2 /week with treatment of ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W for 12 weeks. During the maintenance period all patients on active treatment received only ixekizumab either 80 mg Q4W or 80 mg Q12W for up to 48 weeks.

The safety of ixekizumab was assessed using 5 integrated datasets that were pooled on the basis of the patient population and the design of the individual studies.

These five databases were:

- The 'Primary Psoriasis Placebo-Controlled Integrated Analysis Set' (N=3119, for the safety population, defined as all randomised patients who received at least 1 dose of their assigned study treatment) enabled comparisons between ixekizumab and placebo, and between ixekizumab induction doses, based on the 3 pivotal studies.
- The 'Psoriasis Placebo- and Active-Controlled Integrated Analysis Set' (N=2562, for the safety population, defined as all randomised patients who received at least 1 dose of their assigned study treatment) was created from the 2 active comparator studies.
- The Maintenance Dosing Period Primary Population of the 'Psoriasis Maintenance Integrated Analysis Set' (N=1226) was used to assess the safety of ixekizumab 80 mg Q4W and 80 mg Q12 during the 48-week long-term treatment period, the effect of treatment withdrawal (placebo), and any carry-over effects of the induction regimens on safety outcomes observed for the maintenance treatment regimen (Q2W/Q4W compared to Q4W/Q4W).
- All Psoriasis Ixekizumab Exposures Integrated Analysis Set' (N=4204). Of the 7 psoriasis studies included in this analysis set, the three pivotal Phase 3 studies and one Phase 2 study offered patients the opportunity to participate in long-term extension studies for up to a total treatment period of 5 years and are included in this analysis set.
- All Rheumatoid Arthritis (RA) Ixekizumab Exposures Analysis Set' (N=532).

Adverse events were summarised in frequencies (unadjusted incidence) and in exposure-adjusted incidence rates (per 100 patient-years) for both the Induction and Maintenance Dosing Periods. Unadjusted rates of adverse events were the primary means to assess AEs from the Induction Dosing Period (12 weeks) and exposure -adjusted rates were the focus of Maintenance Dosing Period (48 weeks) evaluations.

Patient exposure in each of the five different safety data for ixekizumab is summarized in the table below.

Table 32. Exposure to ixekizumab by integrated analysis set for pooled studies

Analysis Set	Primary Ps Placebo-Controlled (12 Weeks)			Ps Placebo- and Active-Controlled (12 Weeks)			Ps Maintenance (48 Weeks)			All Ps IXE Exposures				
Studies Included	RHAZ, RHBA, RHBC			RHBA, RHBC			RHAZ, RHBA			RHAZ, RHBA, RHBC, RHAT, RHBL, RHAJ, RHAG				
Treatment Group	IXE 80 Q4W	IXE 80 Q2W	Total IXE	IXE 80 Q4W	IXE 80 Q2W	Total IXE	IXE 80 Q12W	IXE 80 Q4W	Total IXE	IXE 80 Q4W[a]	IXE 80 Q4W/ Q4W[b]	IXE 80 Q2W/ Q4W[c]	IXE 80 Q2W or Q4W[d]	IXE (All Doses Pooled)
N	1161	1167	2328	729	734	1463	408	416	824	3798	729	1010	4030	4204
Days, n														
≥84	1019	1027	2046	655	656	1311								
≥90							349	392	741	3493	712	974	3569	3972
≥183							275	364	639	2964	684	944	3151	3536
≥365							0	1	1	1574	391	578	1845	2190
≥548										695	189	193	809	1070
≥730										147	64	67	202	378
Patient-years[e]	265.9	268.6	534.5	167.6	168.9	336.5	269.5	326.7	596.2	3616.4	836.7	1094.7	3950.9	4729.7

Abbreviations: IXE = ixekizumab; IXE 80 Q2W = ixekizumab 80 mg every 2 weeks; IXE 80 Q4W = ixekizumab 80 mg every 4 weeks; IXE 80 Q12W = ixekizumab 80 mg every 12 weeks; IXE 80 Q2W/Q4W = patients who started 80 mg Q2W and switched to 80 mg Q4W; IXE 80 Q4W/Q4W = patients who started 80 mg Q4W and remained on 80 mg Q4W; N = number of patients in the treatment group; n = number of patients in the specified category; Ps = psoriasis.

[a] Data from patients who received at least one dose of ixekizumab 80 mg Q4W in studies: RHAT, RHAZ, RHBA, RHBC and RHBL

[b] Data from patients who received 80 mg Q4W/Q4W treatment in studies: RHAZ, RHBA and RHBC

[c] Data from patients who received 80 mg Q2W/Q4W treatment in studies: RHAT, RHAZ, RHBA, RHBC and RHBL

[d] Data from patients who started 80 mg Q2W or Q4W and either switched or remained on 80 mg Q4W in studies: RHAT, RHAZ, RHBA, RHBC and RHBL

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

Note: Grey shading indicates that a value was not calculated or not applicable.

Since submission of the initial marketing authorization application (MAA) for ixekizumab the integrated safety database has been updated with a data lock of 09 April 2015. The updated database now includes 60-week data from Studies I1F-MC-RHBA (UNCOVER-2) and I1F-MC-RHBC (UNCOVER-3). In the induction period, 2328 patients were treated with ixekizumab and 791 patients were treated with placebo. The mean duration of study drug exposure for the total ixekizumab group was 83.9 days and for placebo group was 83.1 days. The median duration of treatment was 85 days for both the total ixekizumab and placebo groups.

Adverse events

The safety population is defined as all randomised patients who received at least 1 dose of their assigned study treatment. A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or before the date of the last visit within the treatment period. A common AE is an event occurring in ≥1% of patients.

Table 33. Summary of adverse events, induction dosing period. Psoriasis safety population, primary psoriasis placebo controlled integrated analysis set (Studies RHAZ, RHBA and RHBC)

	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)
TEAEs	370 (46.8%)	683 (58.8%)[a]	681 (58.4%)[a]	1364 (58.6%)[a]
Mild	200 (25.3%)	374 (32.2%)	389 (33.3%)	763 (32.8%)
Moderate	142 (18.0%)	268 (23.1%)	256 (21.9%)	524 (22.5%)
Severe	28 (3.5%)	41 (3.5%)	36 (3.1%)	77 (3.3%)
Death	0	0	0	0
SAEs	12 (1.5%)	26 (2.2%)	20 (1.7%)	46 (2.0%)
TEAE possibly related to study drug	103 (13.0%)	285 (24.5%)[a]	347 (29.7%)[a,b]	632 (27.1%)[a]
Discontinuation from study drug due to AE (including death)	9 (1.1%)	24 (2.1%)	25 (2.1%)	49 (2.1%)

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

[a] Statistically significant compared with placebo.

[b] Statistically significant compared with ixekizumab 80 mg Q4W.

Table 34. Summary of adverse events, induction dosing period. Psoriasis safety population, primary psoriasis placebo and active controlled integrated analysis set (Studies RHBA and RHBC)

	Placebo N=360 n (%)	80 mg Q4W N=729 n (%)	80 mg Q2W N=734 n (%)	Total IXE N=1463 n (%)	ETN N=739 n (%)
TEAEs	160 (44.4%)	419 (57.5%)[a]	424 (57.8%)[a]	843 (57.6%)[a]	399 (54.0%)[a]
Mild	96 (26.7%)	227 (31.1%)	225 (30.7%)	452 (30.9%)	226 (30.6%)
Moderate	54 (15.0%)	168 (23.0%)	177 (24.1%)	345 (23.6%)	136 (18.4%)
Severe	10 (2.8%)	24 (3.3%)	22 (3.0%)	46 (3.1%)[b]	36 (4.9%)
Missing	0	0	0	0	1 (0.1%)
Deaths	0	0	0	0	0
SAEs	7 (1.9%)	14 (1.9%)	14 (1.9%)	28 (1.9%)	14 (1.9%)
TEAEs possibly related to study drug	54 (15.0%)	174 (23.9%)[a]	220 (30.0%)[a,b]	394 (26.9%)[a]	176 (23.8%)[a]
Discontinuation from study drug due to AE (including death)	3 (0.8%)	14 (1.9%)	15 (2.0%)	29 (2.0%)	9 (1.2%)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; AE = adverse event; ETN = etanercept; IXE = ixekizumab; N = number of patients in a treatment group; n = number of patients with at least one event in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Statistically significant compared with placebo.

[b] Statistically significant compared with etanercept.

Unadjusted incidence was used as the primary means to assess AEs from the induction period because the treatment duration was the same (12 weeks) in each study and the rates of early discontinuation were low and similar across treatments.

Summary of adverse events during the induction period of the pooled placebo and active control studies showed for all TEAEs in percentage of the different groups 44, 57.5, 57.8 and 54 for placebo, ixekizumab 80mg Q4W, ixekizumab 80mg Q2W and etanercept respectively. Common adverse events were nasopharyngitis, upper respiratory tract infection, injection site reactions and headache. There were higher rates of any TEAEs in the pooled ixekizumab groups than in the placebo group, but numerically only slightly higher than in the etanercept group (57.6 % vs 54%) and there seemed to be no dose dependent pattern between the two different ixekizumab dosing schedules. If looking specifically at mild, moderate and severe TEAEs, a similar rate of mild TEAEs was found between total ixekizumab and etanercept, for moderate TEAEs a higher rate of 23.6% for ixekizumab vs 18.4% for etanercept was detected but on the other hand a significantly higher rate of severe TEAEs for

etanercept 4.9 % compared with pooled ixekizumab 3.1 %. However, if looking specifically at the lower dosing schedule of ixekizumab -80 mg Q4W- this difference is less and not significant.

Long term safety data

The maintenance study periods were longer (additionally 48 weeks), and duration of exposure varied markedly across treatments. Therefore, exposure-adjusted rates were the focus of maintenance period evaluations.

Table 35. Summary of exposure adjusted adverse events, maintenance dosing period. Maintenance dosing period primary population, Psoriasis Maintenance integrated analysis set (Studies RHAZ and RHBA)

	Placebo N=402 n (IR)	80 mg Q12W N=408 n (IR)	80 mg Q4W N=416 n (IR)	Total IXE N=824 n (IR)
Total patient-years	184.1	269.5	326.7	596.2
TEAEs	231 (125.5)	294 (109.1)	320 (97.9)[a]	614 (103.0)[a]
Mild	105 (57.0)	122 (45.3)	131 (40.1)	253 (42.4)
Moderate	105 (57.0)	148 (54.9)	157 (48.1)	305 (51.2)
Severe	21 (11.4)	24 (8.9)	32 (9.8)	56 (9.4)
Death	0	0	2 (0.6)	2 (0.3)
SAEs	15 (8.1)	23 (8.5)	25 (7.7)	48 (8.1)
TEAEs possibly related to study drug	81 (44.0)	87 (32.3)[a]	129 (39.5)	216 (36.2)
Discontinuation from study drug due to AE (including death)	8 (4.3)	9 (3.3)	12 (3.7)	21 (3.5)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; 80 mg Q12W = ixekizumab 80 mg every 12 weeks; AE = adverse event; IR = incidence rate per 100 patient-years; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with at least one event in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Statistically significant compared with placebo.

Serious adverse event / deaths / other significant events

Adverse events pre-specified as being of special interest (AESIs) are listed in **Table 36**. These AESIs were selected based on standard drug registration topics (for example, hepatic), safety findings from the Phase 1 and Phase 2 ixekizumab programs, potential risks associated with biologic immunomodulators (as noted in product labels and published literature), and comorbidities and risk factors prevalent in the psoriasis population (for example, MACE, inflammatory bowel disease [IBD]).

Table 36. Unadjusted incidence if treatment-emergent adverse events of special interest across integrated analysis set

Analysis Set	Primary Psoriasis Placebo-Controlled				Psoriasis Placebo- and Active-Controlled					Psoriasis Maintenance			
Treatment Group	PBO	IXE 80 Q4W	IXE 80 Q2W	Total IXE	PBO	ETN	IXE 80 Q4W	IXE 80 Q2W	Total IXE	PBO	IXE 80 Q12W	IXE 80 Q4W	Total IXE
N	791	1161	1167	2328	360	739	729	734	1463	402	408	416	824
Infection - %	22.9	27.4 [c]	27.0[c]	27.2[c]	20.6	21.5	26.2[c, d]	25.9[d]	26.0[c, d]	35.6	48.3[a]	**56.0[a, e]**	52.2[a]
Cytopenias –SOC - %	1.0	1.0	1.0	1.0	0.6	1.5	1.2	1.1	1.2	1.0	1.0	2.4	1.7
Cytopenias –SMQ - %	0.4	0.5	0.8	0.6	0.3	1.5	0.7	1.0	0.8	0.7	0.5	1.2	0.8
Allergic/hypersensitivities-%	2.1	4.0[c]	3.5	3.7[c]	1.9	2.6	3.7	3.7	3.7	3.0	4.4	7.2[c]	5.8[c]
Anaphylaxis - %	0.3	0.3	0.3	0.3	0	0.3	0.3	0.3	0.3	0	0.2	0	0.1
Criterion 1* - %	0	0	0	0	0	0	0	0	0	0	0	0	0
Criterion 2** - %	0.3	0.3	0.3	0.3	0	0.3	0.3	0.3	0.3	0	0.2	0	0.1
Non-anaphylaxis - %	1.9	3.6[c]	3.2	3.4[c]	1.9	2.4	3.4	3.4	3.4	3.0	4.2	7.2[c]	5.7[c]
Injection site reactions - %	3.3	12.9[a]	**16.8[a, b]**	14.9[a]	3.6	16.4[a]	13.3[a]	17.3[a]	15.3[a]	2.0	5.1[c]	**8.9[a, e]**	7.0[a]
Cerebro-CV events - %	0.1	0.9 [c]	0.3	0.6	0.3	0.3	0.8	0.4	0.6	0.5	1.0	1.0	1.0
ATTC (MACE) - %	0.1	0.2	0	0.1	0.3	0.1	0.1	0	0.1	0.2	0	0.7	0.4
Malignancies- %	0.3	0.3	0.3	0.3	0	0.1	0	0.4	0.2	0.2	1.0	0.2	0.6
Hepatic - %	0.9	1.2	1.5	1.4	0.3	2.2[c]	1.0	1.9[c]	1.4	2.2	2.7	4.3	3.5
Depression - %	0.6	0.4	0.3	0.4	0.6	0.8	0.4	0.4	0.4	0.5	1.0	0.7	0.8
Crohn's disease- %	0	0.1	0.1	0.1	0	0	0	0.1	0.1	0.7	0	0	0 [c]
Ulcerative colitis- %	0	0	0.2	0.1	0	0	0	0.1	0.1	0	0.2	0.2	0.2
Interstitial lung disease - %	0.1	0	0.1	0.0	0	0	0	0.1	0.1	0	0	0	0
PCP - %	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: Allergic = allergic reactions; ATTC = Antithrombotic Trialists' Collaboration events; CV= cardiovascular; MACE = major adverse cerebro-cardiovascular event; PCP = pneumocystis pneumonia; SMQ = standardised MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] p<.001 versus placebo [b] **p<.05 IXEQ2W vs IXEQ4W** [c] p<.05 versus placebo [d] p<.05 versus ETN [e] **p<.05 IXEQ4W vs IXEQ12**

* Criterion 1: TEAEs based on selected MedDRA preferred terms from the anaphylactic reaction SMQ.

**Criterion 2: TEAEs from 2 or more 4 categories of AEs as described by Sampson et al. (2006).

Notes: Displayed incidences are not exposure-adjusted. Gray shading indicates there was no statistically significant difference between groups. Bold indicates a statistically significant difference for comparisons between ixekizumab regimens (IXEQ2W vs IXEQ4W or IXEQ4W vs IXEQ12W).

Infections

Infection-related TEAEs were more frequent in each ixekizumab treatment group than placebo. Significant differences compared to placebo in the primary placebo controlled trials were detected for both 80 mg Q2W and 80 mg Q4W during the induction period (22,9 vs 27.0 and 27.4 respectively) with no difference between the two induction doses. The incidence of patients with at least 1 infection-related TEAE was also greater in each ixekizumab treatment group compared with etanercept. Certain mild or moderate opportunistic infections, particularly Candida infections, were more frequent with ixekizumab than placebo. Most of the infection-related TEAEs were mild or moderate in severity, did not lead to early discontinuation from study treatment, and were from 1 to 2 weeks in duration. The most frequent infection-related TEAEs were nasopharyngitis and upper respiratory tract infection; oral candidiasis, conjunctivitis, and tinea infections are also associated with ixekizumab treatment.

The outcome of the infection-related TEAEs being more frequent in each ixekizumab treatment group than placebo is in line with similar findings of immune-modulating biological medicinal products presently on the market to be associated with a potentially increased risk of infections.

In the Maintenance Dosing Period, the unadjusted incidence of infections within the treatment-emergent adverse events of special interest across integrated analysis set demonstrated a significant difference compared to placebo and between the 80 mg Q12W group and 80 mg Q4W group with 35.6, 48.3 and 56.0 respectively. However, the exposure-adjusted incidence rates (per 100 patient-years) of infectious TEAEs across all integrated analysis sets did not significantly differ between these groups.

Across all psoriasis studies (4204 ixekizumab-treated patients), serious infections reported by 2 or more patients were cellulitis (n=14), appendicitis (n=4), bronchopneumonia (n=3), diverticulitis (n=3), erysipelas (n=3), pneumonia (n=3), and urinary tract infection (n=3).

In the pivotal Phase 3 studies, the incidence of infection-related SAEs did not differ significantly between the ixekizumab dosing groups and placebo.

Further data provided by the Applicant showed that all infections combined had the same median duration for ixekizumab and placebo treated patients. However, it was noted that this was largely due to the higher duration of urinary tract infection in the placebo group. All other infections were of longer duration in the Taltz group, as may be expected based on the mechanism of action of ixekizumab.

Candida infections

The incidence of Candida infections was numerically greater with ixekizumab compared with placebo in the Induction Dosing Period. The incidence of infections identified by the preferred term 'oral candidiasis' was significantly greater with ixekizumab 80 mg Q2W compared to placebo, and the difference for 80 mg Q2W versus 80 mg Q4W approached significance. The exposure-adjusted incidence rate of Candida infections in the maintenance 80 mg Q4W group was numerically greater compared with the rate for the induction Q4W group (4.9 versus 2.6, respectively). There was a trend for a greater incidence with ixekizumab treatment than placebo, especially with ixekizumab 80 mg Q4W than with Q12W.Candida events in the largest psoriasis analysis set were reported by 3.0% of ixekizumab-treated patients with psoriasis (128/4204).

None were serious, and none led to discontinuation of study treatment. Most were mild or moderate in severity, were single events (not recurrent), and were adequately managed with anti-fungal medications.

Opportunistic infections and viral hepatitis:

Apart from the Candida infections rates of opportunistic infections did not differ significantly between the total ixekizumab treatment group and placebo. Rates of herpes simplex, herpes zoster, and staphylococcal infections also did not significantly differ between the total ixekizumab group and placebo. Furthermore, across the 4 psoriasis integrated analysis sets, no cases of viral hepatitis, confirmed active or reactivated tuberculosis, or invasive fungal infections occurred in ixekizumab-treated patients. One patient in the total ixekizumab treatment group had a TEAE related to TB compared to 0 patients in the placebo group but this patient was enrolled prior to treatment for latent TB and the event therefore inappropriately classified as a TEAE.

There were 102 patients enrolled in the ixekizumab psoriasis clinical studies with either a previous history of treated TB or a positive tuberculin purified protein derivative skin test (PPD) and/or a positive QuantiFERON®-TB Gold test (QFT) at screening. There were no TEAEs of hepatitis B infection in the All Psoriasis Ixekizumab Exposure Integrated Analysis Set analysis set.

Vaccination

Results of one study with two inactive vaccines have been submitted. The conclusions from assessment of this study are that overall, results are not considered adequate to fully convince that study drug does not interfere in the immune response to these vaccines.

Hypersensitivity

The percentage of patients who experienced a TEAE of allergic reactions/hypersensitivities of any type (localized to injection site or non-localized) was also summarized by 3 categories: anaphylaxis, non-anaphylaxis, and injection site reactions. Injection site reactions are presented separately under the heading "Injection site reactions".

Eight patients (0.3%) in the total ixekizumab treatment group had at least 1 potential anaphylaxis event as defined by Sampson search criteria compared to 2 patients (0.3%) in the placebo group. Among the 8 ixekizumab-treated patients, the maximum severity of the event for 6 patients was mild and for 2 patients was moderate. For 5 of these patients the symptoms occurred on the same day as the ixekizumab injection. Only 1 patient had a single event typically associated with hypersensitivity reactions (generalized pruritus). The events identified in this search for potential cases of anaphylaxis were not considered to indicate an anaphylactic reaction in any of these 5 patients. The other 3 ixekizumab-treated patients did not have events on the same day as drug injection and are not considered to meet criteria for anaphylaxis. A total of 0.5% of ixekizumab-treated patients (n=20) had at least 1 potential anaphylaxis event as defined by Sampson Criterion 2. However, apart from the 5 patients in in the Primary Placebo-Controlled Analysis Set noted above, none of these patients had potential anaphylaxis events on the same day as dosing with ixekizumab. Two patients had at least 1 anaphylaxis event based on specific MedDRA PTs. The events occurred after the first dose of ixekizumab, but approximately 2 weeks later.

The applicant compiled all present individual data of TE-ADA for all patients with reported “potential anaphylaxis” including the two patients who developed an SAE identified as a potential anaphylaxis event based on specific MedDRA PTs. Of these 15 cases were TE-ADA negative and 7 cases were TE-ADA positive patients. The applicant concluded that from a safety perspective with the presented available data, no association has been established between anaphylaxis reactions and immunogenicity and that the incidence of potential anaphylaxis events in patients who were TE-ADA+ at any time was 0.2% (7/4209). Although there was a gap in time from exposure and development of event of 10 to 14 days after the dose of ixekizumab both patients developed high titre ADAs after the events.

Non-anaphylactic hypersensitivity reaction excluding injection site reactions

Table 37. Overview of non-anaphylaxis events reported in ≥ 2 patients in the total ixekizumab treatment group-Primary placebo-controlled integrated analysis set

Preferred Term	PBO (N=791) n (%)	IXE80Q4W (N=1161) n (%)	IXE80Q2W (N=1167) n (%)	Total IXE (N=2328) n (%)
Patients with >=1 Nonanaphylaxis Event	15 (1.9%)	42 (3.6%)	37 (3.2%)	79 (3.4%)
Urticaria	0	6 (0.5%)	9 (0.8%)	15 (0.6%)
Dermatitis	1 (0.1%)	6 (0.5%)	6 (0.5%)	12 (0.5%)
Dermatitis contact	1 (0.1%)	4 (0.3%)	6 (0.5%)	10 (0.4%)
Eczema	0	3 (0.3%)	3 (0.3%)	6 (0.3%)
Rhinitis allergic	2 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.3%)
Rash	2 (0.3%)	3 (0.3%)	2 (0.2%)	5 (0.2%)
Drug hypersensitivity	2 (0.3%)	3 (0.3%)	1 (0.1%)	4 (0.2%)
Hypersensitivity	0	4 (0.3%)	0	4 (0.2%)
Angioedema	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Rash pruritic	0	2 (0.2%)	0	2 (0.1%)
Rash pustular	0	2 (0.2%)	0	2 (0.1%)

Abbreviations: IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q2W = ixekizumab 80 mg Q2W; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients with at least 1 TEAE in the specified category; PBO = Placebo; TEAE = treatment-emergent adverse event.

Urticaria was more frequently reported in the IXE treated patients in all analysed datasets. From the data presented above “Dermatitis” and “Contact dermatitis” are consistently numerically increased in frequency in the above table and in all other datasets. These types of events will continue to be monitored by the applicant as more data become available.

Injection site reactions

Injection site reactions are very common following ixekizumab administration. Injection site reactions were significantly more frequent in ixekizumab-treated patients than in placebo-treated patients, but similar in etanercept-treated patients.

Most injection site reactions were mild or moderate in severity and did not lead to treatment discontinuation. The frequency of injection site reactions was significantly higher for Q2W than for Q4W. Q2W involved twice as many active injections. The incidence rates per 100 active injections did not differ between these groups. No association between injection site reactions and treatment-emergent anti-drug antibodies was established.

When evaluating exposure-adjusted rates during the maintenance phase, a significant difference was observed when comparing the ixekizumab 80 mg Q4W treatment group and the total ixekizumab treatment group with placebo but not when comparing the ixekizumab 80 mg Q12W treatment group with placebo.

Cerebro-Cardiovascular Events

Major Adverse Cerebro-Cardiovascular Events (MACE)

The incidence of adjudicated MACEs among ixekizumab-treated patients in the 12 week Induction Dosing Period was low (0.1% to 0.2%) and did not differ significantly between treatment groups (**Table 38**).

Table 38. Exposure-Adjusted Incidence Rate of Adjudicated Major Adverse Cerebro-Cardiovascular Events (ATTC MACE) Across All Integrated Analysis Sets (Incidence per 100 Person-Years)

Analysis Sets for Induction Dosing Regimens									
Analysis Set	**Primary Ps Placebo-Controlled**				**Ps Placebo- and Active-Controlled**				
Treatment Group	**PBO**	**IXE 80 Q4W**	**IXE 80 Q2W**	**Total IXE**	**PBO**	**ETN**	**IXE 80 Q4W**	**IXE 80 Q2W**	**Total IXE**
N	791	1161	1167	2328	360	739	729	734	1463
ATTC MACE	0.6	0.8	0	0.4	1.2	0.6	0.6	0	0.3

Analysis Sets Inclusive of Maintenance or Longer-Term Dosing					
Analysis Set	**Ps Maintenance ***				**All Ps IXE Exposures ****
Treatment Group	**PBO**	**IXE 80 Q12W**	**IXE 80 Q4W**	**Total IXE**	**IXE (All Doses Pooled)**
N	402	408	416	824	4030
ATTC MACE	0.5	0	0.9	0.5	0.7

Abbreviations: ATTC = Antithrombotic Trialists' Collaboration Events; ETN = etanercept; IXE = ixekizumab; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; IXE80Q12W = ixekizumab 80 mg every 12 weeks; MACE = major adverse cerebro-cardiovascular event; N = number of patients in the specified treatment group of the analysis population; Ps = psoriasis.

* *Maintenance Dosing Period Primary Population*

** *The N for the All Psoriasis Ixekizumab Exposures Integrated Analysis Set is based on the studies for which cerebro-cardiovascular events were adjudicated: the Phase 3 studies (RHAZ, RHBA, RHBC, RHBL, and RHAT). Cerebro-cardiovascular events in the Phase 1 study (RHAG) and Phase 2 study (RHAJ) were not adjudicated.*

Note: There were no statistically significant differences between treatment groups in any integrated analysis set.

Malignancies

Among all ixekizumab psoriasis studies (N=4204), 46 patients (1.1%) exposed to ixekizumab developed a malignancy: 23 NMSCs and 23 malignancies excluding NMSC. The incidence of malignancies was balanced during the 12-week Induction Dosing Period of the placebo-controlled

clinical studies: 2 (0.3%) in placebo-treated patients and 6 (0.3%) in ixekizumab-treated patients. This corresponds to an exposure-adjusted incidence rate of 1.1 per 100 patient-years in both the placebo and ixekizumab treatment groups. The incidence rates were also balanced when NMSCs were evaluated separately: 0.6 per 100 patient-years for both NMSCs and malignancies excluding NMSC in placebo and ixekizumab treatment groups, respectively.

Autoimmune Disease, Including Crohn's Disease and Ulcerative Colitis

Several studies demonstrate an increased prevalence of IBD among psoriasis patients than in the general population. In the performed clinical studies, a total of 2 cases of Crohn's disease were reported during the induction period in the ixekizumab treated group and during the maintenance period additional 3 cases in the placebo group. However, apparently these three patients were receiving ixekizumab during the induction period and given the long pharmacodynamics activity of ixekizumab it cannot be excluded that the drug may have contributed to these events.

Neutropenia

Significantly greater reductions in total neutrophils were noted for ixekizumab- and etanercept-treated patients compared to placebo-treated patients (-4.72, -8.42, and 0.03x109/L change from baseline in neutrophils, for total ixekizumab, etanercept, and placebo patients, respectively). A greater number of ixekizumab-treated patients shifted to a higher grade of neutropenia compared to placebo. Patients treated with ixekizumab who reported Grade 3 neutropenia at some time post baseline were uncommon. No clear association with AEs of infection was noted.

The Applicant was requested to re-analyse all patients who developed reduction in neutrophil and / or platelet count below the lower limit of the reference range. In their response the Applicant concluded that the time period with highest risk of developing low neutrophil count is within the first 18 weeks of exposure and the time period with highest risk of developing low platelet count is within the first 6-18 weeks of exposure. The risk for both continues throughout exposure though at a lower level after 18 weeks. The applicant was also requested to present a bar chart of duration of neutropenia and thrombocytopenia (all exposure integrated set / pooled dosage of Taltz v. placebo). By reporting on the populations (as opposed to individuals), it is not apparent that duration of Neutropenia and Thrombocytopenia may be described as either transient (i.e. fluctuate) or persistent. The data suggest that both patterns occur.

There were only 4 patients with single events in the induction period (and no additional patients in the All Psoriasis Ixekizumab Integrated Analysis Set) with bleeding events that preceded or were accompanied by thrombocytopenia of any CTCAE grade. None of these bleeding events were serious or led to study drug discontinuation.

Hepatic events

In the Psoriasis Placebo- and Active-Controlled Integrated Analysis Set, there was a statistically significant difference in the percentage of patients reporting hepatic-related TEAEs compared to placebo, for both the etanercept and the ixekizumab Q2W treatment groups. Few patients experienced a serious hepatic-related AE or discontinued due a hepatic AE.

Depression

Treatment with ixekizumab did not worsen depression when compared to treatment with placebo or etanercept as assessed by QIDS-SR16 total score during the 12-week Induction Dosing Period or up to 60 weeks in the Maintenance Dosing Period (placebo comparison only). The percentage of ixekizumab-

treated patients with depression-related events was similar to background prevalence in the psoriasis population.

Laboratory findings

An overview of significant treatment-emergent abnormally high or low chemistry laboratory values for the Primary Psoriasis Placebo-Controlled Integrated Analysis Set in the Induction Dosing Period is presented in **Table 39.**

Table 39. Table Percentage of Patients with Notable Treatment-Emergent Abnormal High or Low Clinical Laboratory Values—Induction Dosing Period Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)

Laboratory Value	TE High or Low	Placebo N=791 n/Nx (%)	80 mg Q4W N=1161 n/Nx (%)	80 mg Q2W N=1167 n/Nx (%)	Total IXE N=2328 n/Nx (%)
Alkaline phosphatase (U/L)	TE low	0/784	3/1148 (0.3%)	8/1158 (0.7%)[a,d]	11/2306 (0.5%)[a]
Apolipoprotein B (g/L)	TE high	18/657 (2.7%)	50/ 979 (5.1%)[a]	33/998 (3.3%)	83/1977 (4.2%)
Aspartate aminotransferase (U/L)	TE high	67/664 (10.1%)	144/ 974 (14.8%)[a]	148/991 (14.9%)[a]	292/1965 (14.9%)[a]
Bilirubin (µmol/L)	TE high	16/735 (2.2%)	44/1110 (4.0%)[a]	38/1124 (3.4%)	82/2234 (3.7%)
Blood urea nitrogen (mmol/L)	TE high	7/778 (0.9%)	22/1137 (1.9%)[b]	23/1151 (2.0%)[b]	45/2288 (2.0%)[b]
Creatine kinase (U/L)	TE high	33/767 (4.3%)	78/1124 (6.9%)[a]	75/1140 (6.6%)[a]	153/2264 (6.8%)[a]
Glucose (mmol/L)	TE low	7/112 (6.3%)	0/199	8/183 (4.4%)[c]	8/382 (2.1%)
LDL cholesterol (mmol/L)	TE high	0/766	6/1116 (0.5%)[a]	3/1136 (0.3%)	9/2252 (0.4%)
Phosphate (mmol/L)	TE high	13/782 (1.7%)	38/1148 (3.3%)[a,b]	25/1158 (2.2%)	63/2306 (2.7%)
Protein (g/L)	TE high	5/771 (0.6%)	10/1131 (0.9%)	19/1140 (1.7%)[a,b]	29/2271 (1.3%)[b]
Sodium (mmol/L)	TE high	6/785 (0.8%)	11/1149 (1.0%)	20/1159 (1.7%)[b]	31/2308 (1.3%)
Urine nitrite	TE abnormal	3/769 (0.4%)	11/1122 (1.0%)[b]	12/1133 (1.1%)[b]	23/2255 (1.0%)[b]
Urine specific gravity	TE high	0/779	6/1142 (0.5%)[a]	1/1151 (0.1%)	7/2293 (0.3%)

* *A treatment-emergent low result is defined as a change from values greater than or equal to the LLN at baseline, to a value less than the LLN at any time during the treatment period. A treatment-emergent high result is defined as a change from values less than or equal to the ULN at baseline, to a value more than the ULN at any time during the treatment period. ULN/LLN: upper/lower limit normal from large clinical trial population based reference limits (Lilly reference limits).*

[a] *Statistically significant compared with placebo (p<.05) and OR>1.*

[b] *Mantel Haenszel OR >2 versus placebo; the absolute count among LY-treated subjects is at least 4; and incidence >1% for total ixekizumab group.*

[c] *Statistically significant comparison between ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W.*

[d] *OR ≥2 for ixekizumab 80 mg Q2W versus ixekizumab 80 mg Q4W.*

In the Maintenance Dosing Period Primary Population Analysis Set the following were observed:

- Significantly higher proportions of the total ixekizumab group and the ixekizumab 80 mg Q4W group had treatment-emergent low creatinine clearance compared with the placebo group (8.9% total ixekizumab; 9.6% ixekizumab 80 mg Q4W; and 5.6% placebo), although there were no significant mean changes in creatinine clearance from baseline. Only 1 AE of renal

failure was reported from the Maintenance Dosing Period Primary Population (one patient from study RHAZ reported mild renal failure, with the verbatim term “renal insufficiency”; the event was non-serious, the patient recovered while continuing in the study, and the event was likely not drug-related).

- Significantly higher proportions of the total ixekizumab group, the ixekizumab Q4W group, and the ixekizumab 80 mg Q12W group had treatment-emergent high serum phosphate compared with placebo.
- Significantly higher proportions of the ixekizumab 80 mg Q4W group had TE-high creatinine compared with placebo.
- Significantly higher proportions of the total ixekizumab group and the ixekizumab 80-mg Q4W group had TE-high CK compared with that of the placebo group.
- Significantly higher proportions of the total ixekizumab group and the ixekizumab 80 mg Q4W group than the placebo group had abnormally high very low-density lipoprotein (VLDL) cholesterol (20.7% total ixekizumab; 21.6% ixekizumab Q4W, vs 14.1% placebo).
- Significantly higher proportions of the ixekizumab 80 mg Q4W group than the placebo group had TE- high C-reactive protein (12.5% vs 7.6%), and abnormally high immunoglobulin A (IgA) (8.5% vs 4.7%).
- Significantly higher proportion of the total ixekizumab group and ixekizumab 80 mg Q12W group had treatment-emergent abnormal urine nitrite compared with the placebo group (2.2% total ixekizumab; 2.7% ixekizumab 80 mg Q12W; vs 0.3% placebo).

Safety in special populations

No meaningful differences were observed in patient groups <65 and >65 years, ≥75 years, and <75 years regarding the AEs or SAEs (**Table 40**).

Table 40. Overview of adverse events by age category. All Treatment periods. All psoriasis ixekizumab exposure integrated analysis set

	<65 Years	65-74 Years	75-84 Years	>85 Years
Event Category	Pooled IXE (N=3903) n (%)	Pooled IXE (N=265) n (%)	Pooled IXE (N=34) n (%)	Pooled IXE (N=2) n (%)
Total TEAEs	3073 (78.7%)	199 (75.1%)	20 (58.8%)	1 (50.0%)
Serious AEs	264 (6.8%)	37 (14.0%)	2 (5.9%)	0
Fatal	3 (0.1%)	2 (0.8%)	0	0
Hospitalization	236 (6.0%)	31 (11.7%)	1 (2.9%)	0
Life-threatening	9 (0.2%)	3 (1.1%)	0	0
Disability	2 (0.1%)	0	0	0
Other	35 (0.9%)	8 (3.0%)	1 (2.9%)	0
AE leading to drop-out	169 (4.3%)	20 (7.5%)	1 (2.9%)	0
Psychiatric disorders (SOC)	144 (3.7%)	8 (3.0%)	0	0
Nervous system disorders (SOC)	465 (11.9%)	24 (9.1%)	1 (2.9%)	0
Accidents and injuries (SMQ)	475 (12.2%)	19 (7.2%)	2 (5.9%)	0
Cardiac disorders (SOC)	88 (2.3%)	23 (8.7%)	3 (8.8%)	0
Vascular disorders (SOC)	167 (4.3%)	9 (3.4%)	2 (5.9%)	0
Cerebrovascular disorders (SMQ)	0	0	0	0
Infections and infestations (SOC)	2097 (53.7%)	110 (41.5%)	11 (32.4%)	1 (50.0%)
Quality of life decreased (PT)	0	0	0	0
Hypotension, falls, fractures (LSC)	81 (2.1%)	9 (3.4%)	1 (2.9%)	0
Fractures (LSC)	0	0	0	0

Abbreviations: AE = adverse event; IXE = ixekizumab; LSC = Lilly Specified Category; MedDRA = Medical Dictionary for Regulatory Activities; n = patients with ≥1 event; PT = preferred term; SAE = serious adverse event; SMQ = standard MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event.

Pregnancy and lactation

As of 09 April 2015, 58 pregnancies had been reported in association with ixekizumab use, 18 in female study participants exposed to ixekizumab, and 40 in female partners of male study participants exposed to ixekizumab. Of the female study participants' 6 outcome normal , 2 premature, 4 spontaneous and 4 planned abortions, 2 outcome pending.

Immunological events

Immunogenicity

9–17 % of patients treated with ixekizumab (induction and maintenance periods) at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres and not associated with reduced clinical response up to 60 weeks of treatment with the initial analysis (See Clinical Efficacy).

Approximately 1 % of patients treated with ixekizumab had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response. An association between immunogenicity and treatment emergent adverse events has not been established. Of 3678 ixekizumab treated patients 2.0% were detected to have NAb at some point by Week 60. Most cases of NAb positivity developed within the first 6 months of treatment with ixekizumab with the highest number during the first 12 weeks.

Events

Treatment-emergent adverse events and allergic reaction/hypersensitivity events, and injection site reactions were evaluated for potential association development of ADA (TE-ADA+ status). For these analyses, only events that occurred within 14 days before or after TE-ADA+ results were included, for

both transient and persistent periods of TE-ADA+ status. Evaluation included a treatment by TE-ADA status interaction test for possible interaction between these variables. In the Primary Placebo-Controlled Integrated Analysis Set, 34.4% of TE-ADA+ ixekizumab-treated patients had at least 1 TEAE, compared with 58.3% of ixekizumab-treated patients who were TE-ADA-. Corresponding frequencies for SAEs and for discontinuations due to AEs were 3.1% (TE-ADA+) versus 1.8% (TE-ADA-) and 2.0% versus 1.8%, respectively. No interaction was shown between treatment group and TE-ADA status for overall TEAEs, SAEs, or discontinuations due to AEs.

In the Primary Placebo-Controlled Integrated Analysis Set, 3.1% of TE-ADA+ ixekizumab-treated patients had non-anaphylaxis allergic reaction/hypersensitivity events compared with 3.5% of ixekizumab patients who were TE-ADA-. Among the ixekizumab-treated patients who were TE-ADA+, the frequencies of allergic reaction/hypersensitivity events were similar for those with low titre (<1:160) or moderate-to-high titre (>1:160) ADA (3.2% versus 3.0%, respectively). In this same analysis set, 7.4% of TE-ADA+ ixekizumab-treated patients had an injection site reaction versus 13.6% of TE-ADA- ixekizumab patients. The frequency of injection site reactions among ixekizumab-treated patients with low titre TE-ADA+ were slightly higher than for those with moderate-to-high titres (8.3% versus 6.1%, respectively). There was no interaction between treatment group and TE-ADA status for either allergic reaction/hypersensitivity events or injection site reactions.

Safety related to drug-drug interactions and other interactions

No *in vitro* or *in vivo* studies were submitted to investigating the potential effect of other drugs on the PK of ixekizumab.

No study has been performed to evaluate the concurrent use of live or inactive vaccines with ixekizumab.

Discontinuation due to adverse events

About 95% of patients completed the placebo controlled induction period of the pivotal Phase 3 studies, with no significant differences between any of the treatment groups for the overall incidence of early discontinuation. About 5% of patients discontinued treatment early for any reason. A significantly greater percentage of patients in the placebo group discontinued due to a lack of efficacy compared with the ixekizumab groups. The 2 ixekizumab induction dosing regimens were comparable with regard to reasons for early discontinuation from study treatment. The most frequently reported AEs leading to discontinuation were injection site reaction (n=4 [0.2%]), and 6 different AEs all with n=2 (0.1%).

2.6.1. Discussion on clinical safety

A total of 4736 patients have been studied in 11 clinical trials of psoriasis and rheumatoid arthritis. In the 7 studies of psoriasis, 4204 patients were treated with ixekizumab.

Placebo controlled phase III studies in plaque psoriasis were pooled to evaluate the safety in comparison to placebo and to etanercept 50 mg x2 /week with treatment duration up to 12 weeks. For patients with moderate-to-severe psoriasis, exposure to ixekizumab at any dose/dose includes 4729.7 patients-years, with over 2190 patients with psoriasis treated with any dose/dose regimen for at least 1 year in blinded and open label clinical studies.

The integrated safety database had a data lock of 09 April 2015. The database includes 60-week data from Studies RHBA (UNCOVER-2) and RHBC (UNCOVER-3). In the induction period, 2328 patients were treated with ixekizumab and 791 patients were treated with placebo.

If looking strictly at the psoriatic patients exposed to the recommended dosing (160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks), 578 patients received this treatment for one year and 67 for two years. However, in total a considerable number of patients have been exposed to ixekizumab and a sufficient number at the recommended dosage. The safety database is considered sufficient.

Targeting IL-17A raises the potential risks of infection and immune dysfunction as IL-17A is the principal effector of Th17 cells and therefore plays an important role in host defense against extracellular bacteria and fungi at mucosal surfaces. Accordingly, there are reports of increased susceptibility for infections with Candida in individuals who have genetic defects in IL-17 signaling. In addition, IL-17 is reported to have a role in the immune response to cutaneous staphylococcal infections.

Adverse events of ixekizumab were evaluated during 12 weeks clinical trials;" Induction Dosing Period" and during the 48 weeks long-term treatment; "Maintenance Dosing Period".

There were higher rates of any TEAE s in the pooled ixekizumab groups compared to the placebo treated group but numerically only slightly higher than in the etanercept treated group. There was on the other hand a significantly higher rate of severe TEAEs in the etanercept treated group. Overall the adverse events were not dose-related. However, when studying specific adverse events evaluated by the investigators as possibly related to study drug the frequency in the ixekizumab 80 mg Q2W was higher than in ixekizumab 80 mg Q4W.This difference appears to be related to a higher number of injection site reactions and when adjusting the frequency per 100 active injections the incidence rate did not differ between these groups. In addition there was a trend towards more candida infections with ixekizumab 80 mg Q2W versus 80 mg Q4W during the induction phase and for ixekizumab 80 mg Q4W vs ixekizumab Q12W during the maintenance phase.

The most common adverse events following 12 weeks treatment with ixekizumab were nasopharyngitis, upper respiratory tract infection and injection site reactions.

Reactions at the injection site, including erythema, swelling, pruritus and pain, were observed significantly higher than for placebo but similar to etanercept.

There was no significant difference in AEs causing discontinuation between any ixekizumab dose and etanercept during the induction period.

Requested follow-up data showed that the highest hazard rates of adverse events with ixekizumab during the induction period occurred in the first 4 weeks of exposure. The most frequent treatment-emergent adverse events by preferred term (PT) upon exposure to ixekizumab compared to placebo sorted by relative risk during the induction period were injection site erythema and reactions, oropharyngeal pain and nausea and there was a trend for diarrhoea, headache, cough, sinusitis, fatigue and bronchitis to be more commonly experienced with ixekizumab. When referring to SOC level general disorders and administration site conditions, gastrointestinal and nervous system disorders, infections were more common with ixekizumab.

Adverse events of special interest and potential long-term risks

The long term safety of ixekizumab, evaluated following 48 weeks of treatment, was essentially similar to the 12 week induction period, though the exposure-adjusted incidence rate of ixekizumab-treated patients reporting at least 1 TEAE was somewhat lower in the Maintenance Dosing Period than in the Induction Dosing Period. The exposure-adjusted incidence rate of any SAE among ixekizumab treated

patients were similar to placebo in the Maintenance Dosing Period, and were similar to the rate of any SAE among ixekizumab treated patients in the Induction Dosing Period.

Adverse events of special interests evaluated were infections, allergic reaction/hypersensitivity events, injection site reactions, immunogenicity, malignancies, cerebro-cardiovascular events (MACE including QT prolongation), autoimmune disease including Crohn's Disease and Ulcerative Colitis, liver function (hepatic evaluations) neutropenia and depression.

Infections

Infection-related TEAEs were more frequent in each ixekizumab treatment group than placebo group in the primary placebo controlled trials during the induction period (22.9 vs 27.0 and 27.4 respectively for placebo, 80 mg Q2W and 80 mg Q4W) including certain opportunistic infections, mainly candida infections. The most frequent infection-related TEAEs were nasopharyngitis and upper respiratory tract infection; oral candidiasis, conjunctivitis and tinea infections are also associated with ixekizumab treatment. The increased number of infection-related TEAEs was mainly seen during the induction period; in the Maintenance Dosing Period, the exposure-adjusted incidence rates did not differ between groups. Although no clear correlation could be detected for higher doses of ixekizumab there was a trend towards more candida infections with ixekizumab 80 mg Q2W versus 80 mg Q4W during the induction phase and for ixekizumab 80 mg Q4W vs ixekizumab Q12W during the maintenance phase. Serious infections were also reported while exposed to ixekizumab in the pivotal studies but the incidence of infection-related SAEs did not differ significantly between the ixekizumab dosing groups and placebo.

Serious infections are addressed as a potential safety concern in the RMP. However, there is an increased number of upper respiratory tract infections, oral candidiasis, conjunctivitis, and tinea infections in the ixekizumab treatment group compared to placebo. These are adequately reflected in 4.8 of the SmPC. A contraindication for use in patients with active infection has also been included in the SmPC. Although serious infections have not been reported more frequently for ixekizumab than for placebo it should be noted that any patient who had a serious infection (within 12 weeks prior to baseline) or had any active or recent infection within 4 weeks that could pose a risk for the patient were excluded from the trials and that this could influenced the outcome. Based on the biological target and previous experiences of immune-modulating biological medicinal products in real life, it has been proposed that "Infections" is addressed as an important identified risk in the RMP.

Bronchitis was also noted to be numerically more common in the ixekizumab group although during maintenance dosing exposure adjusted incidence rates of bronchitis per 100 patient-years were not statistically significantly different in the placebo group (IR 2.1) compared to the Taltz 80 mg Q4W group (IR 3.8; p=0.317). Nevertheless, bronchitis will be kept under surveillance in future PSURs.

Taltz should not be used with live vaccines as there are no data available on the response to live vaccines. Furthermore, data on responses to inactive vaccines are insufficient. The responses to inactive vaccination as well as live vaccines will be addressed as missing information in the RMP.

Allergic reaction / hypersensitivity events

Hypersensitivity events defined as non-anaphylactic excluding injection site reactions were more commonly reported in the total ixekizumab treatment group (3.4%) compared to the placebo group (1.9%) during the induction stage. Urticaria was the more frequently reported allergic reaction in the ixekizumab treated patients of all analysed datasets. This is addressed in section 4.8 of the SmPC. In addition, from the data presented "Dermatitis" and "Contact dermatitis" were consistently numerically

increased in frequency in all different datasets. These types of events will continue to be monitored by the applicant as more data become available.

As it is not possible to exclude the possibility of late hypersensitivity reactions the following information is included in the SmPC in section 4.4 under the heading “Hypersensitivity”: Serious hypersensitivity reactions, including some cases of angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration of ixekizumab should be discontinued immediately and appropriate therapy initiated.”

In addition, the CHMP recommended that “Serious hypersensitivity” is addressed as an important identified risk in the Risk Management Plan.

Injection site reactions

Injection site reactions were significantly more frequent in ixekizumab-treated patients than in placebo-treated patients, but similar in etanercept-treated patients. The frequency was significantly higher for Q2W than for Q4W, but the incidence rates per 100 active injections did not differ between these groups. Most injection site reactions were mild or moderate in severity and did not lead to treatment discontinuation. No association between injection site reactions and treatment-emergent anti-drug antibodies was established. Injection site reactions are addressed as very common in the SmPC.

Immunogenicity

Approximately 9–17 % of patients treated with Taltz (induction and maintenance periods) at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres. Approximately 1 % of patients treated with Taltz had confirmed neutralizing antibodies associated with low drug concentrations and reduced clinical response. An association between immunogenicity and treatment emergent adverse events has not been established.

Of 3678 ixekizumab treated patients 2.0% were detected to have NAb at some point by Week 60. Highest number of NAb positivity developed during the first 12 weeks. However, data are incomplete as all 3 pivotal studies remain unfinished. From an efficacy point of view it is also not considered possible to claim continuing clinical efficacy in the presence of neutralising antibodies and undetectable Taltz concentration in the blood samples. The issue pf Nabs development will therefore be monitored post-authorisation and the company is requested to re-submit analysis of the overall incidence for onset of NAb positivity and the cumulative frequency of development of NAb for all 3 of the primary Phase 3 studies (RHAZ, RHBA, and RHBC) once all studies are completed and further data are available. The commitment of the Applicant in this regard is detailed in the Risk Management Plan.

Malignancies

The incidence of malignancies was consistent with observed background rates in the general psoriasis population. However, the observed time is limited considering the length of tumour induction and patients with a history of malignancies were excluded from the pivotal studies. Therefore, malignancies should be followed in the RMP as an important potential risk.

Cerebro-cardiovascular events (MACE including QT prolongation)

The incidence of adjudicated MACEs among ixekizumab-treated patients in the 12 week Induction Dosing Period was low (0.1% to 0.2%) and did not differ significantly between treatment groups.

There were in addition no clinically relevant differences for any ixekizumab treatment group compared with either etanercept or placebo with respect to vital signs or QTc intervals, nor were there any clinically relevant mean changes from baseline, or categorical changes, for vital signs or QTc intervals in any treatment group. However, when comparing the incidence rate of MACE of the placebo group to the recommended maintenance dosing group of ixekinumab, IXE 80 Q4W, both non-adjusted and adjusted, there is a slight increase -0.2 vs 0.7 and 0.5 vs 0.9 respectively. Patients with an uncontrolled cerebro-cardiovascular disease were excluded from the pivotal trials. The CHMP recommended that MACE should be addressed in the RMP as an important potential risk and further followed up.

Autoimmune disease including Crohn's Disease and Ulcerative Colitis

Several studies demonstrate an increased prevalence of IBD among psoriasis patients than in the general population. In the performed clinical studies, a total of 2 cases of Crohn's disease were reported during the induction period in the ixekizumab treated group and during the maintenance period additional 3 cases in the placebo group. However, apparently these three patients were receiving ixekizumab during the induction period and given the long pharmacodynamics activity of ixekizumab it cannot be excluded that the drug may have contributed to these events. Crohn's disease is addressed as important potential risk in the RMP.

Hepatic evaluations

In the Psoriasis Placebo- and Active-Controlled Integrated Analysis Set, there was a statistically significant difference in the percentage of patients reporting hepatic-related TEAEs compared to placebo, for both the etanercept and the ixekizumab Q2W treatment groups. However, across the Primary Psoriasis Placebo-Controlled Integrated Analysis Set, the Psoriasis Placebo- and Active Controlled Integrated Analysis Set, and the Maintenance Integrated Analyses Set, there were no significant differences between ixekizumab treatment groups and placebo or etanercept in the proportions of patients with TE elevations in ALT or AST $\geq$ 3xULN, 5xULN, and 10xULN or ALP >2xULN. Few patients experienced a serious hepatic-related AE or discontinued due a hepatic AE. For most patients, ALT values returned to baseline level or were trending to baseline level while still in treatment on ixekizumab or after discontinuation of ixekizumab during the follow-up study period. Given that there were no significant TE findings in higher ALT elevations and in hepatic events for ixekizumab as compared with placebo and etanercept, there is no increased risk of hepatotoxicity associated with ixekizumab treatment.

Neutropenia

Significantly greater reductions in total neutrophils were noted for ixekizumab- and etanercept treated patients compared to placebo-treated patients and greater number of ixekizumab-treated patients shifted to a higher grade of neutropenia compared to placebo.

There is a possible association between systemic IL-17A blockade and reductions in peripheral neutrophil counts, based on roles of IL17A in innate immunity and neutrophil biology. Within the Phase III studies there was a significant increase in neutropenia and in a shift to a higher grade of neutropenia for ixekizumab treatment compared to placebo. Neutropenia is addressed in section 4.8 of the proposed SmPC: "Laboratory assessment of Neutropenia: 9% of patients receiving Taltz developed neutropenia. In most cases, the blood neutrophil count was ≥1,000 cells/mm^3. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving Taltz developed a neutrophil count <1000 cells/mm^3. In general, neutropenia did not require discontinuation of Taltz.

The time period with highest risk of developing low neutrophil count was within the first 18 weeks of exposure and the time period with highest risk of developing low platelet count is within the first 6-18 weeks of exposure. The risk for both continues throughout exposure though at a lower level after 18 weeks.

'Thrombocytopenia' is therefore also included in section 4.8 of the SPC.

Based on the biological target of ixekizumab and since neutropenia ≥ Grade 3 (< 1000 cells/mm^3) has been observed, neutropenia is also included as an important identified risk in the RMP.

SAEs and deaths

There were no findings of significant differences between the ixekizumab and placebo groups in the overall percentage of patients reporting SAEs in the Primary Psoriasis Placebo-Controlled Integrated Analysis Set and no significantly higher incidences of specific SAEs in the total ixekizumab group compared with the etanercept group. There were also no significant differences between the ixekizumab and placebo groups in the overall incidence rate of patients reporting SAEs in the Psoriasis Maintenance Integrated Analysis Set. In addition there was no significantly higher incidence rate for specific SAEs in the total ixekizumab group, the ixekizumab 80 mg Q4W group, or the ixekizumab 80 mg Q12W group compared with placebo.

However, considering that an increased risk of MACE has been associated with other immune-modulating biological treatments and even though there is no robust evidence to link these type of events with the use of ixekizumab, MACE has been included in the RMP as an important potential risk.

Safety in special populations

The number of patients aged >75 years was not sufficient to determine whether such patients responded differently than younger patients. Therefore, use in the very elderly (≥ 75 years) is included in the RMP as missing information.

There is also no information on the use of ixekizumab in the paediatric population. The applicant has been requested to include this as missing information in the RMP.

Pregnancy and lactation: The number of exposures during pregnancy was too limited to draw meaningful conclusions about the effects of ixekizumab during pregnancy. This is reflected in the proposed SmPC, where use of ixekizumab during pregnancy because of the limited human data available is not recommended. The company plans to conduct an observational study using medical record data to evaluate the use of the ixekizumab in pregnant women and is included in the PhV plan of the RMP.

2.6.2. Conclusions on the clinical safety

The most commonly reported adverse events following 12 weeks treatment with ixekizumab were nasopharyngitis, upper respiratory tract infection, injection site reactions and headache with higher rates than the placebo group. Reactions at the injection site, including erythema, swelling, pruritus and pain were very common and significantly higher than for placebo. The most frequent treatment-emergent adverse events upon exposure to ixekizumab compared to placebo were injection site

erythema and reactions, oropharyngeal pain, nausea and there was a trend for diarrhoea, headache, cough, sinusitis, fatigue and bronchitis to be more commonly experienced with ixekizumab. The long term safety of ixekizumab, evaluated following 48 weeks of treatment, was mainly similar to the 12 week induction period, though the exposure-adjusted incidence rate of ixekizumab-treated patients reporting at least 1 TEAE was somewhat lower in the Maintenance Dosing Period than in the Induction Dosing Period. The exposure-adjusted incidence rate of any serious adverse event (SAE) among ixekizumab-treated patients were similar to placebo in the Maintenance Dosing Period, and were similar to the rate of any SAE among ixekizumab-treated patients in the Induction Dosing Period.

Due to the biological target of ixekizumab important safety concerns such as infections, serious hypersensitivity and inflammatory bowel disease have been identified. Treatment during clinically important active infections (e.g. active TB) has been contraindicated and a warning of late (10-14 days following injection) hypersensitivity reactions with urticaria, dyspnea and high antibody titers is stated in 4.4 of the SmPC. Furthermore, malignancies, MACE, and neutropenia will be followed as safety concerns in the risk management plan and paediatric patients, patients with severe hepatic impairment, patients with severe renal impairment, use in patients with active infections (HIV, hepatitis B or hepatitis C) and use in the very elderly will be addressed as missing information in the RMP. The information in the RMP on pregnancy and breastfeeding women will include plans to conduct an observational study using medical record data to evaluate the risks associated with the use of ixekizumab in pregnant women.

Reported adverse events are consistent with what would be expected for this type of biological product and should be able to be managed via the routine risk minimisation measures and the pharmacovigilance activities described in the RMP. In particular, the Applicant has been requested and agreed to follow-up in the RMP the presence of neutralising antibodies and clinical response to more fully understand the consequence of development of neutralising antibodies, in the extension phases of the phase 3 studies.

2.7. Risk Management Plan

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	Infections Hypersensitivity Neutropenia
Important Potential Risks	Inflammatory bowel disease (Crohn's disease and ulcerative colitis) MACE Malignancies
Missing Information	Long-term safety (such as events with a low frequency and/or long latency) Use in pregnancy and lactation Use in very elderly (≥75 years) Use in paediatrics Use in patients with severe hepatic impairment Use in patients with severe renal impairment Use in patients with active infections (human immunodeficiency virus [HIV], hepatitis B, or hepatitis C)

	Immune response to live and inactive vaccines

Pharmacovigilance plan

Study / Activity Type and Title	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
3-years clinical follow-through of all recipients of Taltz in the ongoing extensions of Studies RHAZ, RHBA, and RHBC (Category 3)	• Immunogenicity: (i) describe development of antibodies and neutralising antibodies to Taltz, (ii) fully describe effect of antibody titre on pharmacokinetics of Taltz, and (iii) effect of neutralising antibodies on clinical efficacy (loss of efficacy is anticipated)	Not applicable	Started	The annual reports[a] will be submitted with the PSURs: • Annual Report 1 [Containing 2-years follow-up]: PSUR #1 [~Nov 2016]. • Annual Report 2 (Final) [Containing 3-years follow-up] PSUR #3 [~Nov 2017]
	• AEs sorted by relative risk with incidence by treatment group and relative risk of an event in active versus placebo arm • Time-dependency of AEs • All causes of withdrawal, and in addition, also separate withdrawal caused by AEs • Durations of study drug exposure			• Annual report 1 [Containing Week 60 data, and 2-years follow-up]: PSUR #1 [~Nov 2016]. • Annual Report 2 (Final) [Containing 3-years follow-up] PSUR #3 [~Nov 2017]
US observational postmarketing safety registry (Corrona Registry) (Category 3)	To monitor the incidence rate and nature of infections, hypersensitivity reactions, inflammatory bowel disease, MACE, and malignancies in clinical practice. To provide additional	Important identified risks: infections and hypersensitivity Important potential risks: inflammatory bowel disease, MACE, and malignancies	Planned Study synopsis submitted October 2015	No formal interim reports are planned. The final study report is anticipated in Q3 2029.[b]

Study / Activity Type and Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	information on the long-term safety (effects which are infrequent, and/or have a longer latency period) in routine clinical practice. To monitor the incidence and nature of AEs in the very elderly in routine clinical practice. Signal detection. To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real world setting.	Missing information: long-term safety; use in the very elderly		
US observational pregnancy study using medical record data (Category 3)	To monitor the incidence of adverse maternal and foetal outcomes following exposure to ixekizumab during pregnancy. Signal detection. To determine if the use of ixekizumab in pregnancy could lead to adverse effects.	Missing information: use in pregnancy	Planned Study synopsis submitted October 2015	An interim report is anticipated by Q2 2021.[c] The final study report is anticipated in Q2 2025.[d]

Abbreviations: ~ = approximately; AE = adverse event; MACE = major adverse cerebro-cardiovascular events; PSUR = periodic safety update report; Q2 = second quarter; Q3 = third quarter; RMP = risk management plan; US = United States.

a The content of these reports as described in "Response to CHMP Day 180 List of Outstanding Issues, Clinical Aspects, Question 18" - January 2016. The reports will be submitted with the PSURs or sooner should there be findings that warrant more expeditious communication.

b The final study report will be submitted with the PSUR/RMP and within 12 months of study completion.

c An interim analysis will be performed once one-third of targeted ixekizumab exposures have accrued. If a sufficient number of exposures have not accrued for an interim analysis by Q2 2021, available data will be

summarised and reported in the PSUR according to regulated timelines.

d If sufficient sample size can be obtained by Q2 2021 and an interim analysis is performed, the study will continue for a maximum of 8 years to obtain the targeted sample size. A final study report will be submitted with the PSUR/RMP and within 12 months of study completion (anticipated Q2 2025). If there is insufficient use among pregnant women as of Q2 2021, no additional reports will be submitted.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Infections	The proposed text in the SmPC (4.4 Special warnings and precautions for use) will inform about the association of ixekizumab treatment with an increased risk of certain infections, and will advise caution and monitoring in patients with clinically important chronic or active infection. The proposed text in the SmPC (4.3.Contraindications) will contraindicate the use of ixekizumab in patients with clinically important active infections (for example, active TB). The text will furthermore provide information when to discontinue patients from treatment and how to manage patients with latent TB. The proposed text in the SmPC (4.8 Undesirable effects; Tabulated list of adverse reactions; Description of selected adverse reactions) will inform about the association of ixekizumab treatment with an increased risk of infections and provide further characterisation of the ADR to prescribers.	None
Hypersensitivity	The proposed text in the SmPC (4.3 Contraindications) contraindicates the use of ixekizumab in patients with known serious hypersensitivity to the active substance or to any of the excipients. The proposed text in the SmPC (4.4 Special warnings and precautions for use) informs about cases of serious hypersensitivity reactions reported with the use of ixekizumab and advises on appropriate actions if such a reaction occurs.	None
Neutropenia	The proposed text in the SmPC (4.8 Undesirable Effects; Description of selected adverse reactions) will inform health care professionals about the association of ixekizumab treatment with an increased risk of neutropenia.	None
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	The proposed text in the SmPC (4.4 Special warnings and precautions for use) will inform that cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported for ixekizumab and will advise caution and monitoring	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	for patients with preexisting inflammatory bowel disease.	
MACE	No specific measures are required for patients receiving ixekizumab; standard of care is adequate.	None
Malignancies	No specific measures are required for patients receiving ixekizumab; standard of care is adequate.	None
Long-term safety (such as events with a low frequency and/or long latency)	None	None
Use in pregnancy and lactation	The proposed text in the SmPC (4.6 Fertility, pregnancy, and lactation) will inform about the limited data available regarding the safety of ixekizumab in pregnancy and lactation and will advise to avoid the use of ixekizumab during pregnancy, and to assess the benefit-risk to determine whether to continue Taltz or to continue breastfeeding.	None
Use in very elderly (≥75 years)	The proposed text in the SmPC (4.2 Posology and method of administration) informs health care providers that there is limited information in this patient population.	None
Use in paediatrics	The proposed text in the SmPC (4.2 Posology and method of administration) informs about the lack of data in children below the age of 18 years.	None
Use in patients with severe hepatic impairment	The proposed text in the SmPC (4.2 Posology and method of administration) states that ixekizumab has not been studied in this patient population and no dose recommendations can be made.	None
Use in patients with severe renal impairment	The proposed text in the SmPC (4.2 Posology and method of administration) states that ixekizumab has not been studied in this patient population and no dose recommendations can be made.	None
Use in patients with active infections (HIV, hepatitis B or hepatitis C)	The proposed text in the SmPC (4.3 Contraindications) contraindicates the use of ixekizumab in patients with clinically important active infections.	None
Immune response to live and inactive vaccines	The proposed text in the SmPC (4.4 Special warnings and precautions for use; Immunisations) informs health care providers that ixekizumab should not be used with live vaccines and that no data are available on the response to live vaccines and insufficient data are available for inactive vaccines. Section 5.1 provides information on a study with 2 inactive vaccines that demonstrated no safety concerns, but immunisation data were considered	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	insufficient to conclude that there was an adequate immune response.	

Conclusion

The CHMP and PRAC considered that the risk management plan version 4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, TALTZ (ixekizumab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Taltz solution for injection 80 mg has been developed for treatment of moderate to severe plaque psoriasis. Ixekizumab is a humanised monoclonal antibody (MAb) designed to selectively inhibit interleukin 17A (IL-17A).

A European guideline is available for products indicated for treatment of psoriasis (CHMP/EWP/2454/02, 2004) and standard efficacy variables for plaque psoriasis have been used to assess efficacy of ixekizumab in the phase II and III studies, in accordance with the guideline. Both physicians reported psoriasis efficacy evaluations (PASI and sPGA) and patient reported psoriasis efficacy evaluations have been used (e.g. DLQI and an itch numeric rating scale).

Short-term efficacy (induction)

Three phase 3 studies of basically similar design and performed in an adequate psoriasis population met their co-primary end-points, to demonstrate superiority vs. placebo with respect to PASI 75 response and sPGA (0,1) response at week 12. This was observed for both ixekizumab induction dose regimens (80 mg Q2W and 80 mg Q4W). Based on integrated data across the three studies, PASI 75 response was 89% for the Q2W regimen, 82% for the Q4W regimen vs. approximately 4% for placebo and 48% for etanercept. Corresponding figures for sPGA (0,1) response were 82%, 75%, 4% and 39%, respectively. Thus, 4-7% higher response rates were observed for the Q2W vs. the Q4W induction dose regimen for the co-primary end-points as well as for secondary end-points.

Secondary end-points were also met, e.g. PASI 90, PASI 100 and sPGA (0) response vs. placebo at week 12. Response rates of almost 40% were observed for the end-points PASI 100 and sPGA (0), meaning complete clearance of psoriasis symptoms.

In studies RHAB and RHBC, both ixekizumab doses were superior to the active comparator etanercept with respect to both PASI 75, sPGA (0,1), sPGA (0), PASI 100 and PASI 90 as well as for several other end-points. The posology of etanercept in the study was in accordance with the labelling for Enbrel (highest recommended dose). Previous use of etanercept was not allowed in the study.

With respect to onset of response, the difference in response between patients treated with either ixekizumab regimen compared with placebo was significant from Week 1. At week 2, about 20% of the ixekizumab-treated patients had reached PASI 75 and sPGA (0,1) and at week 4, 40-50% had reached these end-points.

Long-term efficacy (maintenance therapy)

The effect of ixekizumab was maintained up to week 60 to a high extent in studies RHAZ and RHAB. Relapse was experienced by 84% of patients treated with placebo, 44% in the 80 mg Q12W group and 11% in the 80 mg Q4W group. The median time to relapse was 164 days for patients treated with placebo, i.e. about 5 months. An updated analysis further confirmed the difference as initially observed between Q4W/Q4W and Q2W/Q4W regimens; a greater percentage of patients (18%) from the Q4W/Q4W treatment group relapsed, compared with 6% of patients from the Q2W/Q4W group.

The PASI 75 response rate at week 60 was approximately 83% for the 80 mg Q2W/Q4W dose regimen (integrated analysis of the Maintenance Dosing Period – RHAZ and RHBA). The sPGA (0,1) response rate at week 60 was 78% for ixekizumab. The differences between the two maintenance dose regimens (Q4W vs. Q12W) were in the range 30-40%.

Also for the stricter end-points, the response rates in the Q2W/Q4W dose group remained around 76% for PASI 90 and around 58% for PASI 100 and sPGA (0). The same pattern was observed for other end-points, such as Itch NRS response rates, DLQI and NAPSI, assessing nail psoriasis.

Of the patients who were etanercept non-responders during the induction phase in study RHBA, 73% achieved sPGA (0,1) and 84% met PASI 75 response after treatment with ixekizumab 80 mg Q4W for 12 weeks. This suggests that non-responders to etanercept can respond to ixekizumab treatment.

Adequate sub-group analyses have been performed. There were no major differences in responder rates based on age, gender, race or region.

Substantial numbers of subjects had received previous systemic therapy for their psoriasis condition, e.g. >60% had used previous systemic therapies overall, and 25-30% of the study population had used previous biologic therapy. No major differences in sPGA (0,1) and PASI 75 response rates were observed between previous users vs. non-users, however, the responses rates tended to be lower in those patients who had used several different biologics previously. For previous non-biologic systemic therapy, those with previous experience of less than three non-biologics had somewhat higher sPGA (0,1) and PASI 75 response rates compared with those who had used several previous therapies.

Uncertainty in the knowledge about the beneficial effects.

Amongst patients who did not respond to the recommended dose of ixekizumab 80 mg Q2W at Week 12, 33% achieved an sPGA (0,1) and 56% achieved a PASI 75 response at Week 60. The median time to clinical response for these patients was between 16 and 24 weeks. Thus, some patients who don´t respond initially may respond with continued ixekizumab treatment. However, it was not possible to identify any specific factors that could predict patient groups with a delayed response to ixekizumab treatment.

Regarding immunogenicity, the percentage of patients developing Nabs was low (about 1%) based on the results from the pivotal phase 3 studies, so far. However, longer term data are not available and the time course for development of Nabs and recurrence of psoriasis is likely to have a delay. This will be further characterised with the long term studies which are included in the RMP.

Few patients aged ≥ 65 years have been included in the studies (overall 6%) and very few above 75 years (about 1%). This has been reflected in section 4.2 of the SmPC and in the RMP.

Risks

Unfavourable effects

The safety profile for ixekizumab is overall as expected for a substance with this target and it also shows many similarities with the active comparator of the phase III studies, etanercept.

In the pooled ixekizumab groups there were numerically only slightly higher rates of all TEAEs than in the etanercept treated group with all TEAEs in percentage of the different groups during the induction phase 44, 57.5, 57.8 and 54 for placebo, ixekizumab 80mg Q4W, ixekizumab 80mg Q2W and etanercept, respectively.

Significant differences of infectious adverse events compared to placebo in the primary placebo controlled trials were detected for both 80 mg Q2W and 80 mg Q4W during the induction period (22,9 vs 27.0 and 27.4 respectively) with no difference between the two induction doses.

The most common adverse events following 12 weeks treatment with ixekizumab were nasopharyngitis, upper respiratory tract infection, injection site reactions and headache with higher rates than the placebo group. Reactions at the injection site, including erythema, swelling, pruritus and pain were very common and significantly higher than for placebo. The most frequent treatment-emergent adverse events upon exposure to ixekizumab compared to placebo when analysed and

sorted by relative risk and preferred term during the induction period were injection site erythema and reactions, oropharyngeal pain and nausea.

Overall the adverse events were not dose-related. However, when studying specific adverse events evaluated by the investigators as possibly related to study drug the frequency in the ixekizumab 80 mg Q2W was higher than in ixekizumab 80 mg Q4W. This difference appeared to be related to a higher number of injection site reactions and when adjusting the frequency per 100 active injections the incidence rate did not differ between these groups. In addition there was a trend towards more candida infections with ixekizumab 80 mg Q2W versus 80 mg Q4W during the induction phase and for ixekizumab 80 mg Q4W vs ixekizumab Q12W during the maintenance phase.

Uncertainty in the knowledge about the unfavourable effects

Adverse events of special interests evaluated were infections, allergic reaction/hypersensitivity events, injection site reactions, immunogenicity, malignancies, cerebro-cardiovascular events (MACE including QT prolongation), autoimmune disease including Crohn's Disease and Ulcerative Colitis, liver function (hepatic evaluations) and neutropenia. Although at present there is no firm data to establish a correlation between immunogenicity and hypersensitivity reactions this cannot be excluded. A warning concerning late-occurring hypersensitivity reactions is included in the product information and the company has agreed to follow-up on the development of TE-ADA and Nabs as described in the PV plan of the RMP.

The long term safety beyond one year is undefined. Several of the exclusion criteria of the pivotal studies precluded any exposure of patients at increased risk of serious infections, malignancies, cerebrovascular disease and severe neutropenia. Information on these topics will be collected within a psoriasis registry which is included in the PV plan of the RMP.

In addition, there is missing information of the treatment of paediatric patients, patients with severe hepatic impairment, patients with severe renal impairment, and immunisations. A follow up of pregnancy and breastfeeding women is included in the PV plan of the RMP.

Effects table

Table 41. Effects Table for Taltz in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy (data cut-off: 9 April 2015).

Effect	Short description	Unit	ng Q2W	PBO	ETN	Uncertainties/ Strength of evidence	References
Favourable Effects							
PASI 75	At least 75% improvement from baseline PASI at 12 weeks	%	88.7[1] 88.5[2]	4.4[1] 5.0[2]	47.7[2]	Similar results obtained with the more stringent PAS1 90 and 100	[1] Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, RHBC) [2] Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (Studies RHBA and RHBC)
sPGA (0,1)	Minimal plaque severity or complete clearance of psoriatic plaques as assessed by sPGA at 12 weeks	%	81.8[1] 81.8[2]	3.9[1] 4.7[2]	38.9[2]	Similar results obtained with the more stringent sPGA (0)	
Unfavourable Effects							
Infections and Infestations SOC	Incidence	%	27[1] 25.9[2]	22.9[1] 20.6([2]	21.5[2]		
Neutropenia Grade 2 or Worse	Incidence	%	2.4[1] 2.9[2]	0.5[1]	3.9[2]		
Urticaria	Incidence	%	0.8[1] 0.7[2]	0.0[1] 0.0[2]	0.4[2]		
Injection site reactions	Incidence	%	16.8[1] 17.3[2]	3.3[1]	16.4[2]		

Abbreviations: IXE: Ixekizumab, Q2W: every 2 weeks, PBO: Placebo, ETN: Etanercept PASI: Psoriasis area and severity index,

sPGA: static Physician Global Assessment, SOC: System Organ Class

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Benefit-risk balance

Importance of favourable and unfavourable effects

Ixekizumab has clearly demonstrated statistically significant and clinically relevant effects vs. placebo. All three phase 3 studies met their co-primary end-points to demonstrate superiority vs. placebo with respect to PASI 75 response and sPGA (0,1) response at week 12. The results are highly clinically relevant. A short-term effect of ixekizumab for induction therapy is clearly established.

Concerning the 80 mg Q2W induction dose regimen, slightly higher response rates for most end-points were observed compared with the 80 mg Q4W regimen. The better response with a more intense induction regimen seemed to be carried through to the maintenance treatment phase in mainly one of the pivotal studies. Based on the similar safety profiles for the two regimens, the 80 mg Q2W induction posology was recommended.

Also for maintenance treatment, clinically relevant response rates were observed over time. The differences between the two maintenance dose regimens (Q4W vs. Q12W) were more marked, though, with differences between the two regimens in response rates at week 60 in the range 30-40%. The maintenance dosing regimen of Q4W is therefore supported.

The main risks associated with ixekizumab use are typical of similar products authorised for the treatment of psoriasis. Risks like infections, neutropenia and hypersensitivity reactions can be expected to be managed adequately through routine risk minimisation measures as described in the SmPC and the PIL. Further information on the magnitude of these risks is also expected to be collected through an observational post-marketing safety registry.

In common with other monoclonal antibodies, there is also a risk of immunogenicity. Even though available data suggest that the risk of developing neutralising antibodies is small, this will be further characterised in the ongoing extensions of the pivotal phase 3 studies.

Benefit-risk balance

Discussion on the benefit-risk balance

Taltz solution for injection 80 mg has demonstrated a positive effect on the treatment of moderate to severe plaque psoriasis, which is deemed clinically relevant. Even though there were small differences in the initial induction phase between the two studied dosing regimens (Q2W vs Q4W), it is considered appropriate to recommend the highest frequency regimen as this is expected to be more effective especially in treatment-resistant patients. Furthermore, the observed safety profile of ixekizumab is in line with that of other biological treatments for psoriasis including infections, neutropenia and hypersensitivity reactions and with no significant differences between the two dosing regimens.

The benefit-risk balance for ixekizumab can therefore be considered positive in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Taltz in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ixekizumab is qualified as a new active substance.