CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125521Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA:	STN 125,521
Submission Type:	Original BLA (new molecular entity)
Brand Name:	TALTZ®
Drug Name:	Ixekizumab
Submission Date:	03/23/2015
PDUFA Goal Date:	03/23/2016
Priority:	Standard
Proposed Indication:	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Proposed Dosing Regimen:	The proposed dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks
Dosage Forms and Strength:	▪ 80 mg/mL solution in a single-dose autoinjector ▪ 80 mg/mL solution in a single-dose prefilled syringe
Applicant:	Eli Lilly and Company
Clinical Pharmacology Reviewer:	Jie Wang, Ph.D.
Pharmacometrics Reviewer:	Dhananjay Marathe, Ph.D.
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1. EXECUTIVE SUMMARY

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass-4 (IgG4) monoclonal antibody (mAb) that binds to interleukin 17A (IL-17A). IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis.

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 160 mg by subcutaneous (SC) injection (two 80 mg injections) at week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. The proposed dosage forms for ixekizumab SC injection include 80 mg/mL solution in a single-dose prefilled syringe (PFS), and 80 mg/mL solution in a single-dose autoinjector (AI).

The ixekizumab psoriasis development program included one Phase 1 study (RHAG), one Phase 2 study (RHAJ), three pivotal Phase 3 studies (RHAZ, RHBA, and RHBC), and one Phase 3 open-label study that compared the PK of ixekizumab administered via the PFS and AI devices (RHBL). All studies were conducted in subjects with psoriasis; therefore, PK of ixekizumab has not been evaluated in healthy subjects.

1.1. Recommendations

The Clinical Pharmacology information provided in the BLA is sufficient to support a recommendation for approval of TALTZ (ixekizumab) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

1.2. Post-Marketing Requirements/Commitments

- *PMC #1:* We recommend that the Applicant conduct a clinical drug-drug interaction (DDI) study to evaluate the potential of ixekizumab to alter the pharmacokinetics or metabolism of CYP substrates in subjects with psoriasis treated with ixekizumab. This recommendation is based on the current understanding that psoriasis patients have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following the biological treatment.

1.3. Summary of Clinical Pharmacology Findings

1.3.1. Biopharmaceutics and product comparability

The biopharmaceutics information provided in the BLA is sufficient to support the approval for both PFS and AI presentations. These two proposed presentations contain the same ixekizumab solution for injection (80 mg/mL) which was used in one Phase 2 and the pivotal Phase 3 studies. All three pivotal Phase 3 trials used the PFS presentation.

The PFS and AI presentations have been demonstrated to have comparable PK in subjects with psoriasis (Study RHBL). Based on comparative PK data collected over a 2-week dosing interval after the initial dose of 160 mg ixekizumab in Study RHBL, the point estimates and 90% confidence intervals for geometric mean ratio (AI-to-PFS ratio) of $AUC_{(0\text{-}14days)}$ and C_{max} were 0.99 [0.89, 1.10] and 0.98 [0.89, 1.10], respectively, all within the [0.8, 1.25] bioequivalence boundaries.

1.3.2. Dose-/Exposure-response relationships and recommended dosing regimen

Overall, the Phase 3 efficacy and safety data as well as the dose-/exposure-response relationships for efficacy and safety support the recommendation of the "160 mg at week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks" dosing regimen for all adult patients with psoriasis as proposed by the Applicant.

The efficacy and safety of ixekizumab were evaluated in three Phase 3 trials (RHAZ, RHBA and RHBC). The induction dosing period (from Week 0 to Week 12) had similar study designs across the Phase 3 trials and evaluated two ixekizumab dosing regimens: an initial dose of 160 mg at Week 0 followed by 80 mg q2w or 80 mg q4w. At Week 12, sPGA (0,1) (achievement of static Physician Global Assessment 0 or 1 in a 6-point sPGA scale) responders in Studies RHAZ and RHBA were re-randomized to receive ixekizumab 80 mg q4w, 80 mg q12w, or placebo for the 48-week maintenance dosing period (up to Week 60).

The co-primary efficacy endpoints were PASI 75 (≥ 75% improvement from baseline PASI [Psoriasis Area and Severity Index] score) and sPGA (0,1) at Week 12.

*Efficacy in **induction dosing period** of Phase 3 trials*

Both the 80 mg q2w and 80 mg q4w dosing regimens achieved significantly higher PASI 75 and sPGA (0,1) response rates than the placebo group from Week 1 through Week 12 of treatment; and the 80 mg q2w dosing regimen achieved significantly higher response rates than the 80 mg q4w dosing regimen from Week 8 to Week 12. The temporal profiles of clinical response rates for both co-primary endpoints in the pooled Phase 3 trials (RHAZ, RHBA and RHBC) are shown in Figure 1.3.2.a.

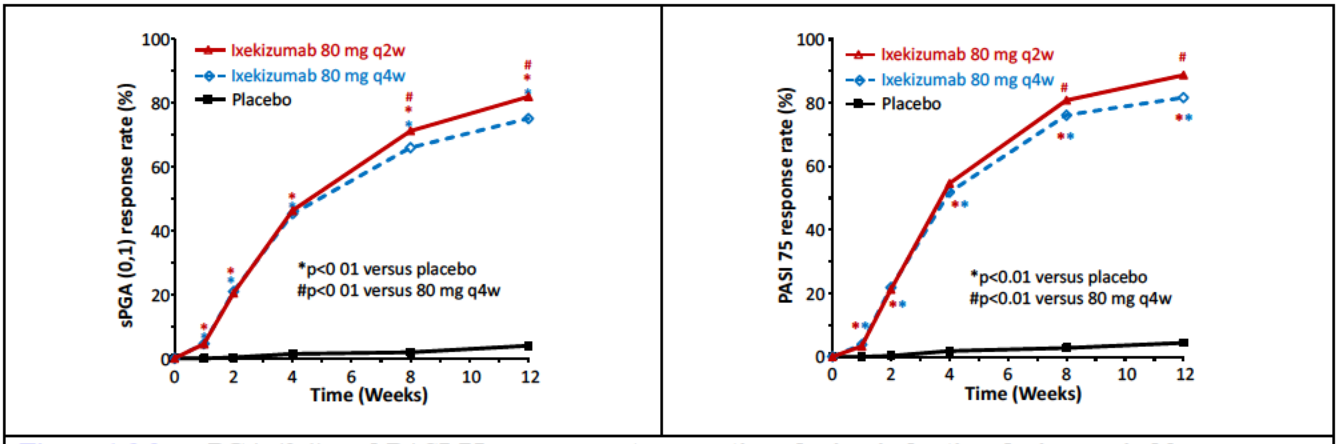


Figure.1.3.2.a. sPGA (0,1) and PASI 75 response rates over time during induction dosing period by treatment arms based on combined data from Phase 3 Studies RHAZ, RHBA&RHBC. *(Data source: Figure 2.7.3.15, Figure 2.7.3.16, Table App.2.7.3.6.54, Table App.2.7.3.6.55, Summary of Clinical Efficacy.)*

At Week 12, 82%, 75%, and 4% of subjects achieved sPGA (0,1) response in the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w and placebo treatment groups, respectively; 89%, 82%, and 4% of subjects achieved PASI 75 response in the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups, respectively. Overall, the ixekizumab 80 mg q2w dosing regimen in the induction dosing period showed approximately 7% higher response rates for both sPGA (0,1) and PASI 75 compared to the 80 mg q4w dosing regimen.

*Efficacy in **maintenance dosing period** of Phase 3 trials*

At Week 60, the 80 mg q4w dosing regimen maintained a higher response rate for sPGA (0,1) compared to the 80 mg q12w dosing regimen among Week 12 sPGA (0,1) responders who were randomized to receive the two maintenance study treatment. Based on the integrated data from studies RHAZ and RHBA, the proportion of patients who maintained the sPGA (0,1) response at Week 60 was 71% for 80 mg q4w and 36% for 80 mg q12w.

Effects of induction dosing regimens on efficacy outcome at Week 60

The ixekizumab 80 mg q2w induction dosing regimen was associated with improved efficacy outcome at Week 60 when compared to the 80 mg q4w induction dosing regimen. Of the sPGA (0,1) responders at Week 12, 75% (135/181) of those who received 80 mg q2w induction dosing regimen followed by 80 mg q4w maintenance dosing regimen (q2w/q4w) maintained their sPGA (0,1) response in comparison to 67% (112/167) for responders whose induction dose was 80 mg q4w and maintenance dose was 80 mg q4w (q4w/q4w).

Effect of body weight on efficacy

Body weight was the most significant covariate on ixekizumab clearance in subjects with psoriasis and, as a result, serum trough concentrations decrease as body weight increases. Subgroup analysis using a pre-specified 100 kg body weight cutoff showed that after the induction treatment with 80 mg q2w subjects with lower body weight (<100 kg) had 9% higher response rate for sPGA (0, 1) and 4% higher response rate for PASI 75 compared to subjects with higher body weight (≥100 kg), see Table 1.3.2.

Because the ixekizumab efficacy with 80 mg q2w dosing regimen has approached the plateau of the exposure-response curve for the Week 12 efficacy data, it is not necessary to further explore a higher dose in the high body weight group. Additionally, while the Week 12 response rates were similar for subjects with high body weight receiving 80 mg q2w dosing and subjects with low body weight receiving 80 mg q4w dosing, we would not recommended 80 mg q4w for the first 12 weeks of treatment in subjects with low body weight because the data also showed that the 80 mg q2w dosing regimen achieved greater sPGA (0,1) and PASI 75 response rates in each body weight subgroup (<100 kg or ≥100 kg). Overall, the proposed dosing regimen regardless of body weight is acceptable.

Table 1.3.2. Week 12 sPGA (0,1) and PASI 75 response rates in the induction dosing period based on the combined data from Phase 3 studies RHAZ, RHBA and RHBC stratified by body weight and treatment groups. *(Data source: Table 2.7.3.22, Summary of Clinical Efficacy)*

	Week 12 Clinical Response Rates (%)					
	Placebo (N=792)		**IXE 80 mg q4w (N=1165)**		**IXE 80 mg q2w (N=1169)**	
Body weight	**<100 kg (N1=538)**	**≥100 kg (N2=251)**	**<100 kg (N1=791)**	**≥100 kg (N2=368)**	**<100 kg (N1=819)**	**≥100 kg (N2=349)**
sPGA (0,1)	4.8%	2.0%	79.0%	67.4%	84.5%	75.6%
PASI 75	5.0%	3.2%	85.6%	74.2%	90.1%	85.7%

Dose- and Exposure-Response for safety

Overall, no apparent dose- or exposure-response relationship for treatment emergent adverse events (TEAEs) was observed based on the pooled safety analysis across three Phase 3 Studies (RHAZ, RHBA, and BHBC).

Pooled analysis of the safety data in the induction dosing period of the three pivotal Phase 3 trials showed an overall TEAE rates of 46.8%, 58.8% and 58.4%, respectively, for the placebo, ixekizumab 80 mg q4w and ixekizumab 80 mg q2w treatment groups, respectively, indicating little to no apparent dose-response for safety.

The exposure-adjusted incidence rates (incidence per 100 person-years) of patients reporting at least 1 TEAE were 125.5, 109.1 and 97.9, for the placebo, ixekizumab 80 mg q12w and ixekizumab q4w treatment groups in the maintenance dosing period of Phase 3 studies RHAZ and RHBA combined.

Benefit-risk assessment based on treatment arm and body weight for efficacy and safety

A benefit-risk assessment was conducted based on pooled data from three Phase 3 studies (RHAZ, RHBA and RHBC) for selected efficacy [sPGA (0,1) and PASI 75] and adverse [incidence for overall infections and moderate to severe infections] events during the 12-week induction dosing period. Results are summarized by treatment arms (80 mg q2w, 80 mg q4w, and placebo) and further stratified by body weight subgroups (<100 kg and ≥100 kg) to evaluate the role of body weight on the benefit-risk assessment. The results show that the risk of any grade infections and moderate to severe infections is similar between the ixekizumab 80 mg q2w and 80 mg q4w dosing regimens for both body weight subgroups (Figure 1.3.2.b). The incidence of infections was numerically higher in the ixekizumab treatment arms compared to placebo, though this increase was not a concern given the small difference between incidences and the marked improvement in efficacy with treatment. The 80 mg q2w dosing regimen achieved greater sPGA (0,1) and PASI 75 response rates in each body weight subgroup compared to the 80 mg q4w dosing regimen. Overall, the benefit-risk assessment supports the 80 mg q2w dosing regimen in all adult patients regardless of body weight for the induction dosing period.

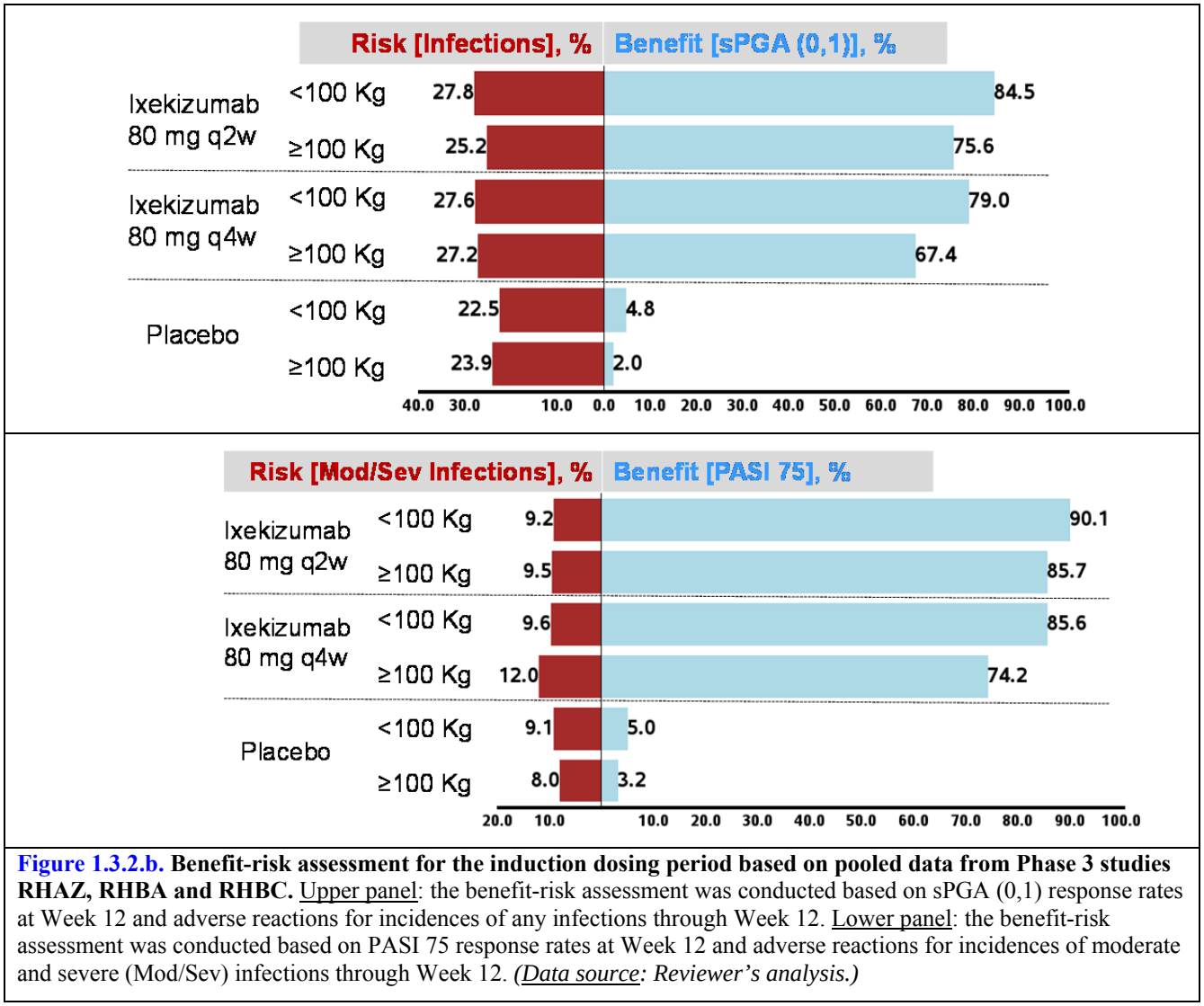


Figure 1.3.2.b. Benefit-risk assessment for the induction dosing period based on pooled data from Phase 3 studies RHAZ, RHBA and RHBC. Upper panel: the benefit-risk assessment was conducted based on sPGA (0,1) response rates at Week 12 and adverse reactions for incidences of any infections through Week 12. Lower panel: the benefit-risk assessment was conducted based on PASI 75 response rates at Week 12 and adverse reactions for incidences of moderate and severe (Mod/Sev) infections through Week 12. *(Data source: Reviewer's analysis.)*

1.3.3. Pharmacokinetics

Healthy subjects

PK of ixekizumab has not been evaluated in healthy subjects.

Subjects with psoriasis

Following intravenous administration, the geometric mean (geometric CV%) value was 0.39 L/day (37%) for systemic clearance, 13 days (40%) for half-life, and 7.11 L (29%) for volume of distribution at steady-state. Ixekizumab clearance and volume of distribution increase as the body weight increases. Ixekizumab exhibited dose-proportional pharmacokinetics over a dose range from 5 to 160 mg following subcutaneous administration. Ixekizumab bioavailability ranged from 60% to 81% following subcutaneous injection based on population PK results from multiple studies. Administration of ixekizumab via injection in the thigh achieved 8% to 35% higher bioavailability relative to that achieved using other injection sites including the arm and the abdomen across the two presentations.

Following a single subcutaneous dose of 160 mg, ixekizumab reached peak mean (±SD) serum concentrations (C_{max}) of 15 ± 6 mcg/mL by approximately 4 days post dose. Steady-state concentrations were achieved by Week 8 following the 160 mg starting dose and 80 mg q2w dosing regimen. The median steady-state trough concentration was 8 mcg/mL. After switching from the 80 mg q2w dosing regimen to the 80 mg q4w dosing regimen at Week 12, steady-state concentrations were achieved after approximately 10 weeks. The median steady-state trough concentration was 3 mcg/mL.

1.3.4. Immunogenicity and its impact on PK and efficacy

Across all psoriasis clinical trials, approximately 20% of subjects treated with ixekizumab developed antibodies to ixekizumab after treatment for up to 60 weeks. The clinical effects of antibodies to ixekizumab are dependent on the antibody titer; increasing titer was associated with decreasing drug concentration and clinical response.

Using the current methodology, approximately 11% of the subjects who developed antibodies to ixekizumab had antibodies that were classified as neutralizing. Neutralizing antibodies were associated with reduced drug concentrations and loss of efficacy. However, the current immunogenicity assay has limitations in detecting neutralizing antibodies in the presence of ixekizumab; therefore, the incidence of neutralizing antibodies development might not have been reliably determined.

1.3.5. Psoriasis disease-drug-drug-interactions

Clinical drug-drug interaction (DDI) studies have not been conducted for ixekizumab.

2. QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What are the highlight of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass-4 (IgG4) monoclonal antibody (mAb) that binds to interleukin 17A (IL-17A). Ixekizumab is comprised of two identical light chain polypeptides of 219 amino acids each and two identical heavy chain polypeptides of 445 amino acids each. Ixekizumab has a molecular weight of 146,158 Daltons.

The proposed formulation and presentation for ixekizumab include the following:

- Injection: 80 mg/mL solution in a single-dose autoinjector (AI).
- Injection: 80 mg/mL solution in a single-dose prefilled syringe (PFS).

2.1.2. What are the proposed mechanism of action and therapeutic indication?

Ixekizumab selectively binds to interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. IL-17A is a pro-inflammatory cytokine and plays a role in the pathogenesis of plaque psoriasis.

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

2.1.3. What are the proposed dosages and routes of administration?

Ixekizumab is administered by subcutaneous (SC) injection. The Applicant proposed the following dosing regimen for all patients:

- 160 mg by SC injection (two 80 mg injections) at Week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology, biopharmaceutics and clinical studies used to support dosing or claims?

The ixekizumab psoriasis development program included one Phase 1 study (RHAG), one Phase 2 study (RHAJ), three pivotal Phase 3 studies (RHAZ, RHBA, and RHBC), and one Phase 3 open-label study that compared the PK of ixekizumab administered via the PFS and AI devices (RHBL). All studies were conducted in subjects with psoriasis; therefore, PK of ixekizumab has not been evaluated in healthy subjects. Table 2.2.1 summarizes the clinical trials containing clinical pharmacology assessments relevant to the proposed indication and the proposed product labeling.

Table 2.2.1. The clinical trials and their utilities to support clinical pharmacology assessments of ixekizumab for the treatment of psoriasis. PFS, prefilled syringe [redacted] (b) (4) powder; AI, autoinjector

Clinical Trials	Study design	Ixekizumab Dosing regimen (number of subjects randomized)	Formulation	Main Clinical Pharmacology data
RHAG	Phase 1 dose escalation for assessment of safety and PK	– Placebo (n=9) – 5 mg SC q2w×3 (n=8) – 15 mg SC q2w×3 (n=8) – 50 mg SC q2w×3 (n=8) – 150 mg SC q2w×3 (n=8) – 15 mg IV q2w×3 (n=5)	LYO	– Descriptive PK – SC bioavailability – Population PK

RHAJ	Phase 2 dose-ranging	Part A: SC at Weeks 0, 2, 4, 8, 12, and 16 (n=27-30 per group) − Placebo − 10 mg − 25 mg − 75 mg − 150 mg Part B: eligible patients rolled over from Part A to receive 120 mg SC q4w and 80 mg SC q4w (after a protocol amendment) for up to 5 years	LYO (Part A) PFS (Part B)	− Descriptive PK − Population PK − Dose-ranging for efficacy/safety
RHBL	Phase 3 PK comparability between PFS and AI	SC 160 mg starting dose (PFS or AI)→ SC 80 mg q2w for 12 weeks (PFS or AI) →SC 80 mg q4w extension (PFS) − PFS (n=102) − AI (n=102)	PFS AI	− Descriptive PK − PK comparability between PFS and AI − Impact of injection site on PK − Impact of body weight on PK − Population PK
RHAZ	Phase 3 randomized, double-blind, placebo-controlled, efficacy/safety trial	Induction to Week 12: − Placebo (n=431) − SC 80 mg q4w, 160 mg at Week 0 (n=432) − SC 80 mg q2w, 160 mg at Week 0 (n=433) At Week 12, ixekizumab sPGA (0,1) responders were re-randomized to placebo, 80 mg q4w and q12w in approximately 1:1:1 ratio.	PFS	− Immunogenicity − Descriptive PK − Population PK − E-R analysis for efficacy/safety
RHBA	Phase 3 randomized, double-blind, placebo-controlled, active-comparator, efficacy/safety trial	Induction to Week 12: − Placebo (n=168) − SC 80 mg q4w, 160 mg at Week 0 (n=347) − SC 80 mg q2w, 160 mg at Week 0 (n=351) − Etanercept* (358) At Week 12, ixekizumab responders were re-randomized to placebo, 80 mg q4w and q12w in approximately 1:1:1 ratio.	PFS	− Immunogenicity − Efficacy/safety ** Data from the etanercept treatment arm are presented in the "individual study summary" only.*
RHBC	Phase 3 randomized, double-blind, placebo-controlled, active-comparator, efficacy/safety trial	Induction to Week 12: − Placebo (n=193) − SC 80 mg q4w, 160 mg at Week 0 (n=386) − SC 80 mg q2w, 160 mg at Week 0 (n=385) − Etanercept* (382) At Week 12, eligible subjects received 80 mg q4w for long-term safety assessment.	PFS	− Immunogenicity − Efficacy/safety ** Data from the etanercept treatment arm are presented in the "individual study summary" only.*

2.2.2. What are the clinical endpoints for efficacy evaluation and how are they measured?

In the psoriasis Phase 3 trials, the efficacy evaluation was based on two clinical endpoints: the Psoriasis Area and Severity Index (PASI) and the static Physician Global Assessment (sPGA) as described below.

- *PASI:* PASI score is a standard and validated measurement for chronic plaque psoriasis. PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions. PASI 50, PASI 75, and PASI 90 responders, respectively are defined as ≥ 50%, ≥ 75%, ≥ 90% improvement (reduction) in PASI score, and PASI 100 responders have complete clearance of psoriasis (absolute PASI score of 0).
- *sPGA:* sPGA is the physician's global assessment of the patient's psoriasis at a given time point. In ixekizumab psoriasis Phase 3 trials, a 6-point sPGA scale was used: "0 = clear", "1 = minimal", "2 = mild", "3 = moderate", "4 = severe", and "5=very severe".

PASI 75 and sPGA (0,1) response rates were two co-primary efficacy endpoint evaluated at Week 12 and at week 60, respectively, for the induction dosing period and the maintenance dosing period in the pivotal trials (Studies RHAZ, RHBA and RHBC).

2.2.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, ixekizumab concentrations in human serum were determined using a validated enzyme linked immunosorbent assay (ELISA). This method was used in all psoriasis clinical studies that included ixekizumab PK evaluations.

Because ixekizumab is expected to be degraded into small peptides and amino acids, there are no additional active moieties. The current BLA did not evaluate ixekizumab concentrations in other clinically relevant human tissues (e.g., skin). *Refer to Section 2.10 for more details.*

2.3. Dose-/Exposure-Response

2.3.1. What are the characteristics of the dose- or exposure-response relationship for effectiveness? Is the dose and dosing regimen selected consistent with the known dose- or exposure-response relationship?

Yes, the overall efficacy data and dose-/exposure-response relationship support the recommendation of the 160 mg by SC injection (two 80 mg injections) at Week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks dosing regimen as proposed by the Applicant.

The dose-/exposure-response characteristics of ixekizumab for the induction and maintenance dosing period are summarized below.

Primary efficacy results in Phase 3 trials: induction dosing period

The short-term efficacy up to 12 weeks (the "induction dosing period") was evaluated in three Phase 3 trials (RHAZ, RHBA and BHBC) with co-primary efficacy endpoints of sPGA (0,1) and PASI 75 measured at Week 12. All patients randomized to ixekizumab received a starting dose of SC 160 mg then received either 80 mg q2w or 80 mg q4w. Table 2.3.1.a presents a summary of the clinical response rates for both primary endpoints at Week 12. See Figure 1.3.2.a for the temporal profiles of clinical response rates for both co-primary endpoints.

Overall, the primary efficacy results support the selection of the 80 mg q2w dosing regimen in the induction dosing period. At Week 12, 81.8% and 88.7% of patients treated with ixekizumab 80 mg q2w dosing regimen achieved sPGA (0,1) and PASI 75 response, respectively. In comparison, 75.0% and 81.6% of patients treated with ixekizumab 80 mg q4w dosing regimen achieved sPGA (0,1) and PASI 75 response, respectively.

Both 80 mg q2w and 80 mg q4w dosing regimens of ixekizumab achieved a significantly higher response rate (*p*-value <0.001) compared to the placebo starting as early as Week 1.

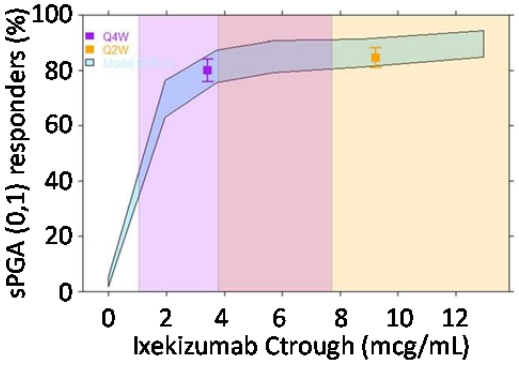
The 80 mg q2w dosing regimen achieved higher response rates (*p*-value <0.001) compared to the 80 mg q4w dosing regimen at Week 8 and Week 12.

Table 2.3.1.a. Clinical response rates at Week 12 in the induction dosing period across Phase 3 studies by treatment groups. **p<0.001 versus 80 mg q4w (Data source: Figure 2.7.3.1, Figure 2.7.3.13, Table App.2.7.3.6.52, Summary of Clinical Efficacy)*

	Week 12 Response Rates (%)											
Trial	**RHAZ**			**RHBA**			**RHBC**			**Integrated RHAZ, RHBA&RHBC**		
Treatment (N)	**PBO (431)**	**Ixekizumab**		**PBO (168)**	**Ixekizumab**		**PBO (193)**	**Ixekizumab**		**PBO (792)**	**Ixekizumab**	
		80mg q4w (432)	**80mg q2w (433)**		**80mg q4w (347)**	**80mg q2w (351)**		**80mg q4w (386)**	**80mg q2w (385)**		**80mg q4w (1165)**	**80mg q2w (1169)**
sPGA (0,1)	3.2	76.4	81.8	2.4	72.9	83.2	6.7	75.4	80.5	3.9	75.0	81.8*
PASI 75	3.9	82.6	89.1	2.4	77.5	89.7	7.3	84.2	87.3	4.4	81.6	88.7*

Exposure-response for efficacy at Week 12 in Phase 3 trials

An exposure-response relationship was observed for both co-primary efficacy endpoints PASI 75 and sPGA (0,1) with the population PK model-predicted serum concentrations at Week 12 (Figure 2.3.1.a). Exposures in subjects receiving the 80 mg q2w regimen resulted in approximately 4% greater predicted response rates for both PASI 75 and sPGA (0,1) than the 80 mg q4w dosing regimen, indicating the clinical responses have reach plateau with the dosing regimens tested in Phase 3 trials.



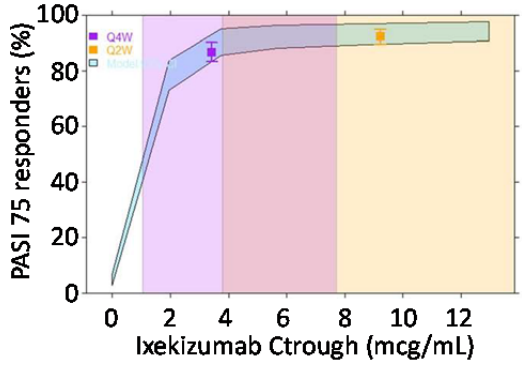


Figure 2.3.1.a. Exposure-response for the co-primary efficacy endpoints sPGA (0,1) (left) and PASI 75 (right) at Week 12. The light blue shaded curve is the 95% CI of response predicted from the model. The purple shaded area shows the range (5th percentile to 95th percentile) of predicted concentrations for q4w dosing. The orange shaded area is the range (5th percentile to 95th percentile) of predicted concentrations for q2w dosing. The darker shaded area in the middle represents the overlaps between q2w and q4w dosing regimens. The points are the observed sPGA (0,1) or PASI 75 response rates, with the error bars representing the confidence interval of the observed response rates. (*Data source: Figure 2.7.2.7., Summary of Clinical Pharmacology*)

Exposure-response relationships were also observed among subjects receiving the same dosing regimen, i.e., 80 mg q2w or 80 mg q4w. Table 2.3.1.b shows the sPGA (0,1) and PASI 75 response rates by predicted Week 12 trough serum ixekizumab concentration quartiles for each dosing regimen. The median values of predicted concentrations for the four quartiles ranged from 1.7 mcg/mL to 5.8 mcg/mL for the q4w regimen, and ranged from 5.2 mcg/mL to 14 mcg/mL for the q2w regimen. Increasing ixekizumab exposure was associated with increased sPGA (0,1) and PASI 75 response rates for both q2w and q4w regimens; however, the differences in response rates across exposure quartiles were greater with the q4w dosing regimen compared to the q2w dosing regimen. For example, within the same dosing regimen, a difference of only 2% (for 92% to 94%) in PASI 75 response rates was predicted for the q2w dosing regimen across the exposure quartiles, while the difference became 10% (83% to 93%) for the q4w dosing regimen. The sPGA (0,1) predicted response rates in the lowest quartile exposure group (Q1) were 82% and 70% for the q2w and q4w dosing regimens, respectively; a difference of 12%.

The data overall would support the benefit of using the q2w dosing regimen as the induction dosing regimen.

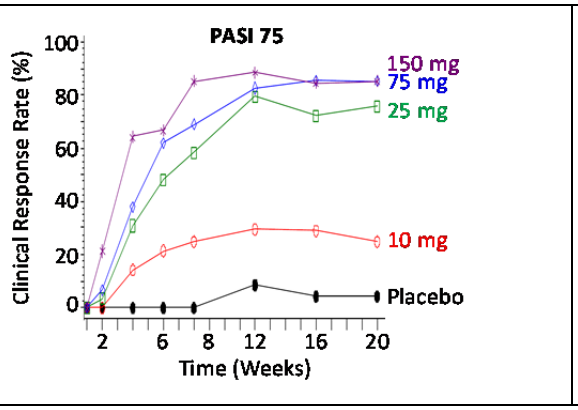
Table 2.3.1.b. Predicted sPGA (0,1) and PASI 75 response rates by C_{trough} quartiles at Week 12 in induction dosing period. C_{trough} was model-predicted trough concentration estimates at steady state using the primary population PK and exposure-response analyses dataset. (*Data source: Table 2.7.2.6, Summary of Clinical Pharmacology*)

	Clinical response rates by ixekizumab C_{trough} quartiles (80 mg q2w)			
	Q1	**Q2**	**Q3**	**Q4**
C_{trough}, mcg/mL (median, [range])	5.2 [0.0-6.7]	8.1 [6.7-9.2]	11 [9.2-12]	14 [12-27]
sPGA%	82	86	88	92
PASI 75%	92	93	94	94
	Clinical response rates by ixekizumab C_{trough} quartiles (80 mg q4w)			
	Q1	**Q2**	**Q3**	**Q4**
C_{trough}, mcg/mL (median, [range])	1.7 [0.0-2.3]	2.9 [2.4-3.4]	4.1 [3.4-4.7]	5.8 [4.8-16]
sPGA%	70	82	85	90
PASI 75%	83	89	91	93

Dose-response relationship in Phase 2 trials and rationale for Phase 3 dose selection

The efficacy results of Phase 2 dose ranging study RHAJ demonstrated dose response for PASI 75 and PASI 90 across the ixekizumab doses of 10 mg, 25 mg, 75 mg, and 150 mg administered at Week 0, 2, 4, 8, 12 and 16 in the double blinded period A (Figure 2.3.1.b). The Week 12 PASI 75 response rates were 7.7% (n=26), 28.6% (n=28), 76.7% (n=30), 82.8% (n=29), and 82.1% (n=28) for the placebo, 10 mg, 25 mg, 75 mg, and 150 mg dosing regimens, respectively. The Week 12 PASI 90 response rates were 0% (n=26), 17.9% (n=28), 50.0% (n=30), 58.6% (n=29), and 71.4% (n=28) for the placebo, 10 mg, 25 mg, 75 mg, and 150 mg dosing regimens, respectively.

In the pivotal Phase 3 studies (RHAZ, RHBA, RHBC), the selected induction dosing regimens (80 mg q4w and 80 mg q2w) were predicted to provide exposures comparable to the ixekizumab 75 mg and 150 mg Phase 2 dose regimens, respectively. A 160-mg starting dose was included for earlier attainment of steady-state concentration. The maintenance dosing period included a dosing regimen of 80 mg q12w to evaluate whether less frequent dosing would maintain clinical responses.



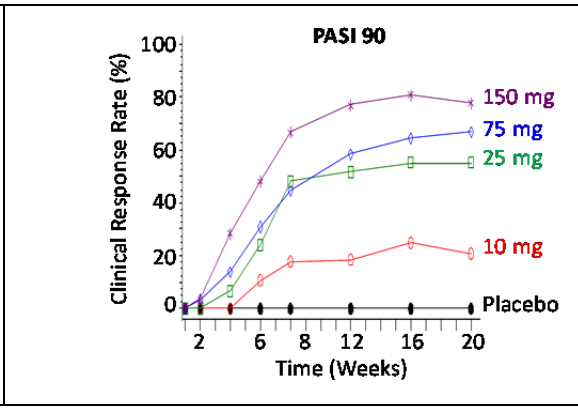
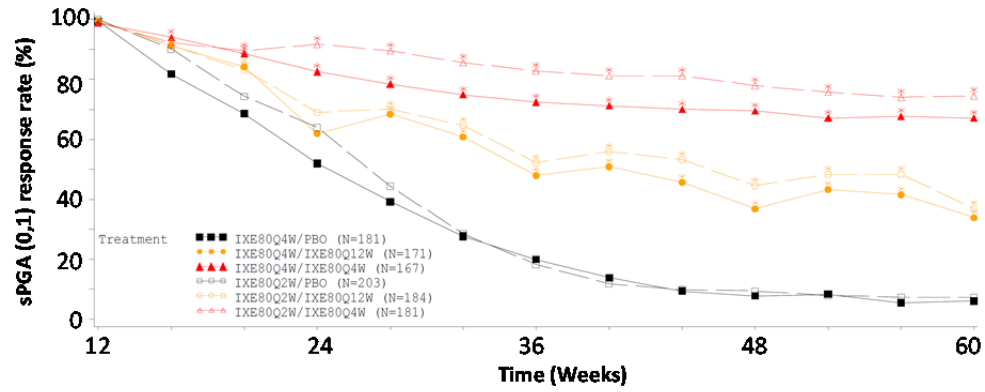


Figure 2.3.1.b. Dose-response for PASI 75 and PASI 90 in Phase 2 dose-ranging Study RHAJ. (*Data source: Figure RHAJ.11.1. and Figure RHAJ.11.3.*)

2.3.2. What are the dose- and/or exposure-response relationships for the efficacy results in the maintenance dosing period?

The Week 12 sPGA (0,1) responders in Studies RHAZ and RHBA were re-randomized to ixekizumab 80 mg q4w, 80 mg q12w, or placebo for the 48-week maintenance dosing period (i.e., from Week 12 up to Week 60). Figure.2.3.2.a. shows sPGA (0,1) and PASI 75 response rates over time during maintenance dosing period by treatment arms in two studied combined.



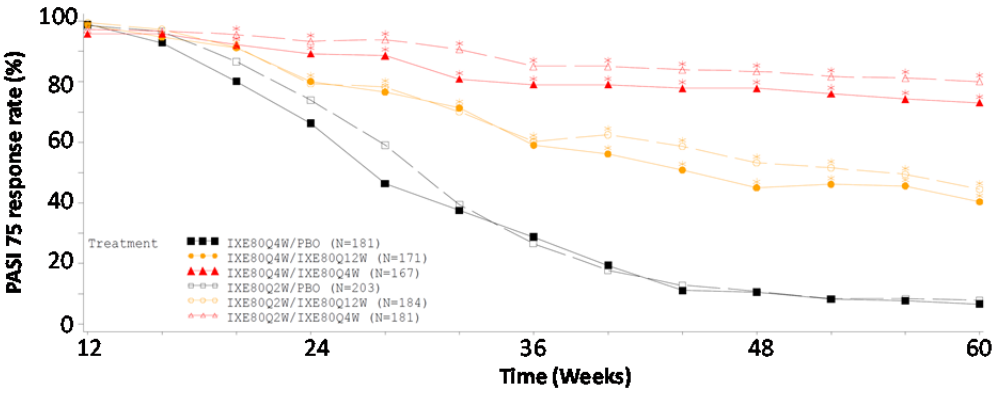


Figure.2.3.2.a. sPGA (0,1) and PASI 75 response rates over time during maintenance dosing period by treatment arms in combined Phase 3 Studies RHAZ and RHBA. *(Data source: Figure 2.7.3.20, Summary of Clinical Efficacy.)*

At Week 60, sPGA (0,1) and PASI 75 response rates were up to two-fold higher in patients treated with 80 mg q4w compared with patients treated with 80 mg q12w in each of two Phase 3 studies (RHAZ and RHBA) as well as in two studies combined (Table 2.3.2.a).

The proportion of patients who maintained the sPGA (0,1) response at Week 60 was statistically higher for ixekizumab 80 mg q4w (71.2%) than for 80 mg q12w (35.5%) in combined Studies RHAZ and RHBA. Similarly, the proportion of patients who maintained or achieved PASI 75 response at Week 60 was statistically higher for ixekizumab 80 mg q4w (76.7%) than for 80 mg q12w (42.5%).

Table 2.3.2.a. Clinical response rates at Week 60 in the maintenance dosing period across Phase 3 studies by treatment groups. **p<0.001 versus 80 mg q12w (Data source: Figure 2.7.3.8, Figure 2.7.3.9, Figure 2.7.3.19, Summary of Clinical Efficacy)*

	Week 60 Response Rates (%)								
Trial	**RHAZ**			**RHBA**			**RHAZ & RHBA**		
Treatment (N)	**PBO (226)**	**Ixekizumab**		**PBO (158)**	**Ixekizumab**		**PBO (384)**	**Ixekizumab**	
		80mg q12w (227)	**80mg q4w (229)**		**80mg q12w (128)**	**80mg q4w (119)**		**80mg q12w (355)**	**80mg q4w (348)**
sPGA (0,1)	7.5	37.4	72.9	5.7	32.0	68.1	6.8	35.5	71.2*
PASI 75	8.8	45.8	77.7	5.1	36.7	75.6	7.3	42.5	76.7*

Effects of induction dosing regimen on efficacy outcome at Week 60

The ixekizumab 80 mg q2w induction dosing regimen was associated with improved efficacy outcome at Week 60 when compared to the 80 mg q4w induction dosing regimen. Of the sPGA (0,1) responders at Week 12, 74.6% (135/181) of those who received 80 mg q2w induction dosing regimen followed by 80 mg q4w maintenance dosing regimen (q2w/q4w) maintained their sPGA (0,1) response in comparison to 67.1% (112/167) for responders whose induction dose was 80 mg q4w and maintenance dose was 80 mg q4w (q4w/q4w) (Table 2.3.2.b). A similar advantage with ixekizumab 80 mg q2w/q4w compared with ixekizumab 80 mg q4w/q4w was observed for PASI 75 at Week 60 (80.1% vs. 73.1% response rate).

Table 2.3.2.b. Clinical response at Week 60 for subjects receiving 80 mg q4w maintenance dosing regimen stratified by the induction dosing regimen. sPGA (0,1) responders were re-randomized at Week 12. The response rate at Week 60 for sPGA (0,1) reflects maintenance of efficacy for the sPGA (0,1) endpoint. PASI 75 response at Week 60 is referred to as "maintained or achieved" because there could be sPGA (0,1) responders who did not achieve PASI 75 at Week 12. (*Data source: Clinical Overview, Table 2.5.4.1*)

Endpoint at Week 60	**Maintenance dose: 80 mg q4w**	
	Induction dose 80 mg q4w (N=167)	**Induction dose 80 mg q2w (N=181)**
sPGA (0, 1) response rate	67.1%	74.6%
PASI 75* response rate	73.1%	80.1%

2.3.3. What are the characteristics of the dose- and exposure-response relationships for safety?

Overall, no apparent dose- or exposure-response relationship for overall treatment emergent adverse events (TEAEs) was observed based on the pooled safety analysis across Phase 3 Studies RHAZ, RHBA and BHBC. Although there are only a limited number of events, a trend for more frequent oral candida infections with more frequent dosing was observed.

Overall adverse events in induction period: 80 mg q2w versus 80 mg q4w

An overview of AEs from the induction dosing period is presented in Table 2.3.3.a. Overall, the rates of any treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and discontinuation due to AEs did not differ significantly between the ixekizumab 80 mg q4w and 80 mg q2w treatment groups.

Table 2.3.3.a. Adverse events in the induction dosing period by treatment groups in pooled Phase 3 Studies RHAZ, RHBA and RHBC. TEAE, treatment-emergent adverse events; SAEs, serious adverse events. (*Data source: Table 2.5.5.3, Clinical Overview*)

	Placebo (N=791)	Ixekizumab 80 mg q4w (N=1161)	Ixekizumab 80 mg q2w (N=1167)
Any TEAE%	46.8	58.8	58.4
--Mild%	25.3	32.2	33.3
--Moderate%	18.0	23.1	21.9
--Severe	3.5	3.5	3.1
SAE	1.5	2.2	1.7
Discontinuations due to AE%	1.1	2.1	2.1

Overall adverse events in maintenance period: 80 mg q4w versus 80 mg q12w

The exposure-adjusted incidence rate (incidence per 100 person-years) of patients reporting at least 1 TEAE for the ixekizumab 80 mg q4w maintenance dosing group was 97.9, comparing to the rate of 109.1 for the q12w group (Table 2.3.3.b).

Table 2.3.3.b. Exposure-adjusted incidence rate of treatment-emergent adverse events (TEAEs) in the maintenance dosing period by ixekizumab treatment groups and placebo in combined Phase 3 Studies RHAZ and RHBA. (*Data source: Table 2.5.8.3, Clinical Overview*)

	Placebo (N=402)	Ixekizumab 80 mg q12w (N=408)	Ixekizumab 80 mg q4w (N=416)
TEAE Incidence Rate (incidence per 100 person-years)	125.5	109.1	97.9

Injection site reactions:

The frequency of injection site reactions was higher in the ixekizumab 80 mg q2w group than in the 80 mg q4w group in the induction period (Table 2.3.3.c). However, the incidence rates of injection site reactions per 100 active injections were approximately 6% for each ixekizumab dosing regimen, indicating the higher frequency of injection site reactions associated with the q2w dosing was probably due to the higher dosing frequency compared to the q4w (*Summary of Clinical Safety*).

Table 2.3.3.c. Incidences of injection site reactions (ISR) by treatment groups in pooled Phase 3 trials. IXE, ixekizumab. (*Data source: Table 2.5.5.4, Clinical Overview*)

	Induction Period (Studies RHAZ, RHBA and RHBC)			Maintenance Period (Studies RHAZ and RHBA)		
	Placebo (N=791)	IXE 80 mg q4w (N=1161)	IXE 80 mg q2w (N=1167)	Placebo (N=402)	IXE 80 mg q12w (N=408)	IXE 80 mg q4w (N=416)
ISR (%)	3.3	12.9	16.8	2.0	5.1	8.9

Infections:

The frequency of infections appeared to be similar between ixekizumab 80 mg q2w and 80 mg q4w treatment groups in the induction dosing period. The frequency of infections was higher in the 80 mg q4w group than the 80 mg q12w group in the maintenance dosing period; however, the exposure-adjusted incidence rates were similar between the two groups (Table 2.3.3.d).

There appeared to be a dose-response relationship for *candida* infections: higher incidences in the ixekizumab 80 mg q2w group (compared to the 80 mg q4w group) in the induction dosing period and higher incidences in the ixekizumab 80 mg q4w group (compared to the 80 mg q12w group) in the maintenance dosing period.

Table 2.3.3.d. Incidences of infections by treatment groups in pooled Phase 3 trials. IR, incidence rate (exposure-adjusted) per 100 person-year; *$p<0.05$, between ixekizumab 80 mg q12w and 80 mg q4w. (*Data source: Tables 2.5.5.4, 2.5.5.5, and 2.5.5.7 Clinical Overview; Tables 2.7.4.44 and 2.7.4.46 Summary of Clinical Safety*)

	Induction Period (Studies RHAZ, RHBA and RHBC)			Maintenance Period (Studies RHAZ and RHBA)		
	Placebo (N=791)	Ixekizumab 80 mg q4w (N=1161)	Ixekizumab 80 mg q2w (N=1167)	Placebo (N=402)	Ixekizumab 80 mg q12w (N=408)	Ixekizumab 80 mg q4w (N=416)
Infection%	22.9	27.4	27.0	35.6	48.3	56.0*
Infection-IR	100.5	119.6	117.3	77.7	73.1	71.3
Ser. infections%	0.4	0.7	0.4	n/a	n/a	n/a
Ser. infections-IR	1.7	3.0	1.9	1.6	1.1	1.8
Candida infections%	0.5	0.6	1.4	2.2 (IR)	2.2 (IR)	4.9 (IR)
Oral candidiasis%	0	0.2	0.7	0.5 (IR)	1.9 (IR)	2.1 (IR)

Exploratory E-R for safety

The Applicant conducted primary E-R analyses for safety based on PK data from Study RHAZ and did not identify apparent E-R relationships for AEs other than injection site reactions (*see discussion above*). The Applicant further conducted secondary E-R analyses for safety using population PK model predicted trough ixekizumab concentrations in pooled Phase 3 studies (RHAZ, RHBA and RHBC). The exploratory analysis indicated an E-R trend for the incidences of neutropenia (Grade 2).

- *E-R for neutropenia (Grade 2)*
  In the induction dosing period, there is a trend toward more frequent neutropenia in the highest exposure quartiles (1.3%, 1.9%, 1.9% and 4.7%, Table 2.3.3.e). The incidence of neutropenia events during the maintenance dosing period was 2.7%, 1.2%, 2.7% and 3.0%, in the order of increasing exposure quartile (Table 2.3.3.f). The Applicant's analysis further showed that neutropenia was in general transient and was not associated with an increased frequency of infections (*Summary of Clinical Safety, section 2.7.4.5.10.2.7*).

- *E-R for Candida infections*
  In both the induction dosing period and the maintenance dosing period, there were insufficient events to identify a relationship between exposure and *Candida* infections (Table 2.3.3.e and Table 2.3.3.f). The incidence of *Candida* infection during the induction period was lowest in the placebo group and highest in the highest exposure quartile. For the maintenance dosing period, the incidence of *Candida* infections was lowest in the lowest exposure quartile.

Table 2.3.3.e. Exposure-response for neutropenia and candida infections by ixekizumab trough serum concentration quartiles in the pooled analysis for the induction dosing period of Phase 3 Studies RHAZ, RHBA and RHBC. (*Data source: Figure 2.7.2.11, Summary of Clinical Pharmacology, candida infections-I, II, III represent 3 methods of candida infection categorizations: Candida high level terms [HLTs], Candida infections [HLT plus MedDRA preferred terms], and oral candida infections*).

		AE rate by ixekizumab concentration quartiles (Induction dosing period in Studies RHAZ, RHBA and RHBC)			
	Placebo	Q1	Q2	Q3	Q4
		<2.79 mcg/mL	≥2.79 to <5.25 mcg/mL	≥5.25 to <9.40 mcg/mL	≥9.40 mcg/mL
Neutropenia, n(%)	7 (0.9%)	7 (1.3%)	10 (1.9%)	10 (1.9%)	25 (4.7%)
Candida infections-I	3 (0.4%)	3 (0.6%)	4 (0.8%)	4 (0.8%)	5 (0.9%)
Candida infections-II	4 (0.5%)	4 (0.8%)	5 (1%)	4 (0.8%)	8 (1.5%)
Candida infections-III	0	2 (0.4%)	1 (0.2%)	2 (0.4%)	4 (0.8%)

Table 2.3.2.f. Exposure-response for neutropenia and *candida* infections by ixekizumab trough serum concentration quartiles in the pooled analysis for the maintenance dosing period of Phase 3 Studies RHAZ, RHBA and RHBC. (*Data source: Figure 2.7.2.11, Summary of Clinical Pharmacology, candida infections-I, II, III represent 3 methods of candida infection categorizations: Candida high level terms [HLTs], Candida infections [HLT plus MedDRA preferred terms], and oral candida infections*).

	AE rate by ixekizumab concentration quartiles (maintenance dosing period in Studies RHAZ, RHBA and RHBC)			
	Q1	Q2	Q3	Q4
	<1.30 mcg/mL	≥1.30 to <2.48 mcg/mL	≥2.48 to <3.98 mcg/mL	≥3.98 mcg/mL
Neutropenia, n(%)	11 (2.7%)	5 (1.2%)	11 (2.7%)	12 (3%)
Candida infections-I	9 (2.2%)	12 (2.9%)	19 (4.6%)	12 (3%)
Candida infections-II	10 (2.5%)	14 (3.4%)	20 (4.9%)	12 (3%)
Candida infections-III	4 (1%)	10 (2.4%)	9 (2.2%)	7 (1.7%)

2.3.4. Does this drug prolong QT/QTc Interval?

Thorough QT/QTc studies were not conducted for ixekizumab because it is generally not required for a monoclonal antibody biological product.

2.4. Pharmacokinetics

2.4.1. What are the PK characteristics of ixekizumab in healthy subjects and in subjects with psoriasis?

Ixekizumab PK has not been evaluated in healthy subjects.

Based on population PK analysis of the combined data from Studies RHAG, RHAJ, and RHAZ, a 2-compartment PK model with first-order absorption and linear clearance best described the PK of ixekizumab in patients with psoriasis. The geometric mean (geometric CV%) estimates for clearance (CL), total volume of distribution (central + peripheral) at steady-state, and elimination half-life ($t_{1/2}$) was 0.39 L/day (37%), 7.11 L (29%), and 13 days (40%), respectively.

See *section 2.9* for ixekizumab single dose PK parameters in psoriasis patients following an initial 160 mg SC administration using a PFS or AI device.

2.4.2. What are the characteristics of drug absorption following SC administration?

Following a single SC dose of 160 mg in psoriasis patients, ixekizumab reached peak mean (±SD) serum concentrations (Cmax) of 15±6 mcg/mL by approximately 4 days post dose (Study RHBL).

Ixekizumab showed an estimated absolute bioavailability of 54% (with 35% inter-individual variability) in Study RHAG with the (b) (4). The population PK analysis estimated that ixekizumab had an average bioavailability of 60-81% following SC administration based on pooled data from Studies RHAG (b) (4)), RHAJ and RHAZ (liquid formulation in PFS).

Effect of injection site

The PK results from Study RHBL indicated that administrations of ixekizumab via the thigh resulted in a higher exposure (increase in mean $AUC_{0\text{-}14days}$ ranged from 8% to 35%) when compared with other injection sites including arm and abdomen across the two devices (Figure 2.4.2), although there was substantial overlap between the exposure ranges in the various subgroups by injections sites and delivery devices.

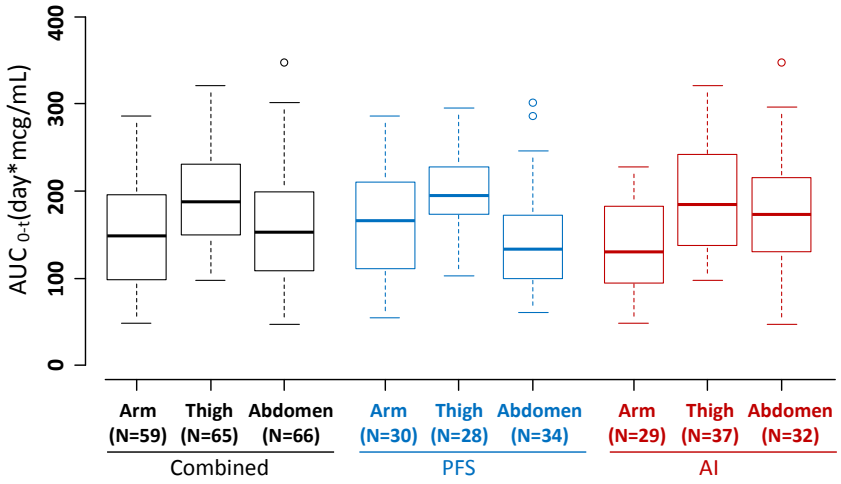


Figure 2.4.2. Ixekizumab $AUC_{0\text{-}14days}$ following a 160-mg SC dose in psoriasis patients stratified by injection site and device type in Study RHBL. *(Data source: Reviewer's plot. The plot is similar to the Applicant's plots shown in Figure RHBL.11.11, 11.14 and 11.16 in I1F-MC-RHBL Clinical Study Report Body)*

2.4.3. What are the characteristics of drug distribution?

Based on the population PK Analyses, the geometric mean estimates (CV%) for V2 (central), V3 (peripheral), and total volume of distribution at steady state were 2.73 L (44%), 4.28 L (19%), 7.11 L (29%), respectively.

2.4.4. What are the characteristics of drug elimination?

In subjects with psoriasis, based on the population PK analyses, the geometric mean (CV%) estimates for CL and elimination half-life was 0.39 L/day (37%) and 13 days (40%), respectively.

The metabolic pathway of ixekizumab has not been characterized. As a human IgG4 monoclonal antibody ixekizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

2.4.5. What is the degree of the proportionality of the dose-concentration relationship?

Ixekizumab had dose proportional PK over a dose range from 5 to 150 mg given as SC injection (data from Study RHAG). Population PK analysis results further supported dose proportional PK because dose was not a significant covariate for ixekizumab clearance across a dose range from SC 5 mg to SC 160 mg.

In Study RHAG subjects with psoriasis were randomized to receive ixekizumab treatment at Weeks 0, 2, and 4 (q2w×3) of ixekizumab at 5 mg SC, 15 mg SC, 50 mg SC, 150 mg SC, and 15 mg IV. Serum ixekizumab concentrations were measured at 1, 3, 9, 48, and 96 hours post-dose, on Days 7 and 10, and on Day 14 (pre-dose) to characterize the PK profile of ixekizumab following the first dose administration. The non-compartmental PK parameters following the first dose administration across treatment groups are presented in Table 2.4.5. The data overall supported that the C_{max} and AUC are generally dose proportional with respect to the SC dose range from 5 mg to 150 mg.

Table 2.4.5. Ixekizumab non-compartmental pharmacokinetic parameters following a single dose administration in subjects with psoriasis in Study RHAG. PK parameters for Cmax and AUC are presented as geometric mean with CV%. $AUC_{(0\text{-}14days)}$ is the area under the concentration time curve from time zero to Day 14. *(Data source: Table RGAG.7.1, I1F-MC-RHAG Clinical Pharmacology Study Report)*

	SC				IV
	5 mg (N=8)	**15 mg (N=8)**	**50 mg (N=8)**	**150 mg (N=8)**	**15 mg (N=5)**
C_{max} (mcg/mL)	0.336 (44%)	0.612 (48%)	3.000 (67%)	8.190 (39%)	3.640 (24%)
$AUC_{(0\text{-}14days)}$ (day*mcg/mL)	3.66 (40%)	6.75 (52%)	32.8 (70%)	95.1 (39%)	21.4 (25%)

2.4.6. What are exposures following chronic dosing?

In Study RHAZ, the median ixekizumab serum trough concentrations were 7.5 and 8.5 mcg/mL at Weeks 8 and 12, respectively, for subjects who received the 80 mg q2w induction dosing regimen after the initial 160 mg dose at Week 0. Following chronic dosing with the 80 mg q4w dosing regimen in maintenance, the median ixekizumab serum trough concentrations ranged from 2.6 to 3.2 mcg/mL from Week 24 to Week 48. Geometric mean concentrations were approximately 10 times higher for the 80 mg Q4W regimen than for the Q12W regimen. Table 2.4.6.a. and Table 2.4.6.b. summarize the ixekizumab trough concentrations by treatment groups at different time-points.

Table 2.4.6.a. Ixekizumab trough serum concentrations in the induction dosing period of Phase 3 Study RHAZ. [a] with an initial loading dose of 160 mg at Week 0. (*Data source: Table RHAZ.11.17. I1F-MC-RHAZ Clinical Study Report*)

Time		Serum ixekizumab concentrations (mcg/mL)[a]	
		80 mg q2w	**80 mg q4w**
Week 8	**N**	67	93
	Median	7.53	3.10
	Geometric mean (CV%)	6.56 (118%)	2.50 (97%)
Week 12	**N**	192	215
	Median	8.51	3.28
	Geometric mean (CV%)	7.73 (79%)	2.94 (89%)

Table 2.4.6.b. Ixekizumab trough serum concentrations in maintenance dosing period of Phase 3 Study RHAZ. (*Data source: Table RHAZ.11.18. I1F-MC-RHAZ Clinical Study Report*)

Time		Serum ixekizumab concentrations (mcg/mL)	
		80 mg q4w	**80 mg q12w**
Week 24	**N**	223	60
	Median	2.63	0.32
	Geometric mean (CV%)	2.36 (111%)	0.28 (175%)
Week 36	**N**	262	55
	Median	3.08	0.22
	Geometric mean (CV%)	2.68 (114%)	0.195 (114%)
Week 48	**N**	227	38
	Median	3.188	0.28
	Geometric mean (CV%)	2.70 (123%)	0.259 (152%)

The population PK model-simulated results showed that steady state serum ixekizumab concentrations were achieved by Week 8 with the 80 mg Q2W dosing regimen and >80% of steady state was already achieved with the 160 mg starting dose. At steady state, the mean (±SD) C_{max} and C_{trough} were 21.5±9.16 mcg/mL and 5.23±3.19 µg/mL for the q2w dosing regimen, and 14.6 ±6.04 µg/mL and 1.87 ±1.30 mcg/mL for the q4w dosing regimen, respectively (*Data source: Table 2.7.2.4, Summary of Clinical Pharmacology*).

2.5. Intrinsic Factors

2.5.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure in psoriasis patients?

The inter-subject exposure variability and the intrinsic factors contributing to the variability in subjects with psoriasis were assessed by population PK analysis. Additionally, Study RHBL evaluated the effect of body weight on ixekizumab PK. Body weight was the most significant covariate on apparent clearance and volume of distribution of ixekizumab PK in subjects with psoriasis. As a result, there was an overall trend for serum trough concentrations to decrease as body weight increased.

Population PK model-estimated PK parameters and inter-subject variability

Population PK model-estimated PK parameters and inter-subject variability are shown in Table 2.5.1. The structural model was a linear two-compartmental distribution model with first-order absorption for SC administration. Covariates retained in the population PK analyses were body weight (on clearance and volume of distribution), study (on bioavailability), injection site (on bioavailability), and ADA titer and presence of NAb (on clearance).

Table 2.5.1. PK parameters and inter-subject variability of ixekizumab determined by population PK analyses in subjects with psoriasis. RSE, relative standard error.
Individual CL=CL*(bodyweight/90)$^{1.05}$*(1+0.035*LOG[ADA titer])*(1+7.09*NAb), where NAb is 0 or 1;
Individual Q= Q*(bodyweight/90)$^{1.05}$; Individual V2= V2*(bodyweight/90)$^{0.73}$;
Individual V3= V3*(bodyweight/90)$^{0.73}$; (*Data source: Summary of Clinical Pharmacology, Table 2.7.2.3*)

Population PK parameters	Model estimate (RSE%)	Inter-individual Variability %CV (RSE%)
Clearance (CL) (L/h)	0.0156 (1.6)	30 (5.8)
Inter-compartmental Clearance, Q (L/h)	0.0332 (4.5)	15 (Fixed)
Weight effect on CL and Q (allometric scaling)	1.05 (4.1)	--
ADA titer on CL (fractional increase)	0.035 (11)	--
Neutralizing antibodies on CL (fractional increase)	7.09 (12)	--
Central Volume of Distribution, V2 (L)	2.6 (15)	84 (27)
Peripheral Volume of Distribution, V3 (L)	4.3 (4.4)	15 (Fixed)
Weight effect on V2 and V3 (allometric scaling)	0.73 (7.2)	--
Bioavailability (F) for RHAG and RHAJ	0.60 (Fixed)	54 (Fixed)
Bioavailability (F) for RHAZ	0.81 (Fixed)	54 (Fixed)
First order absorption rate constant, Ka (h-1)	0.010 (4.7)	15 (Fixed)d
Residual Error Proportional (%)	32 (1.2)	

Body weight

- Study RHBL

  Study RHBL evaluated the effect of body weight on ixekizumab PK following administration of the initial 160 mg SC in subjects with psoriasis. Figure 2.5.1.a shows the PK profiles stratified by three body weight categories: Low (BW<80 kg), Medium (BW=80-100 kg), and High (BW>100 kg). Subjects with higher body weight had lower serum ixekizumab concentrations and lower $AUC_{0\text{-}14days}$ (Figure 2.5.1.b). Compared to the High body weight category, the mean $AUC_{0\text{-}14days}$ was 27% and 58% higher for the Medium and Low body weight categories, respectively.

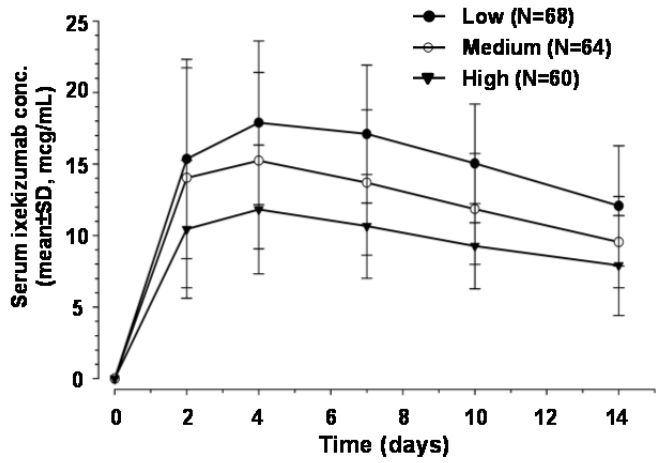


Figure 2.5.1.a. Mean (±SD) serum ixekizumab concentration versus time profiles following the initial 160 mg SC dose in psoriasis patients stratified by weight categories in Study RHBL. The $AUC_{0\text{-}14days}$ was 193, 155, and 122 day*mcg/mL for the Low, Medium, and High body weight groups, respectively. *(Data source: Figure RHBL.11.5, I1F-MC-RHBL Clinical Study Report Body)*

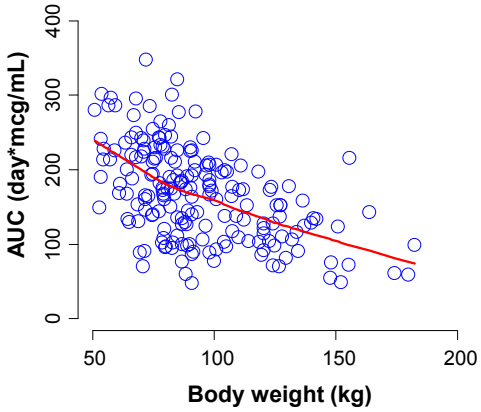
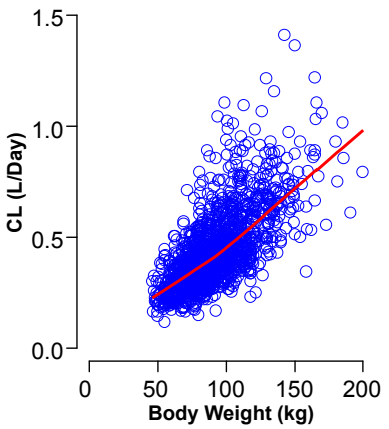
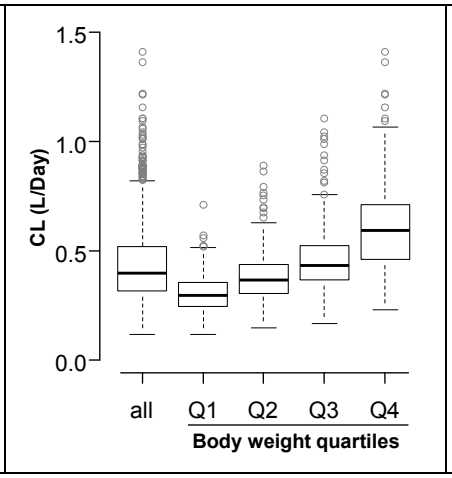


Figure 2.5.1.b. The effect of body weight as a continuous variable on ixekizumab exposure ($AUC_{0\text{-}14days}$) following the initial 160 mg SC dose in psoriasis patients in Study RHBL. *(Data source: reviewer's plot)*

- Population PK

In the population PK analysis body weight was a significant intrinsic factor for the CL, the central volume of distribution, and the peripheral volume of distribution with estimated allometric exponents of 1.05, 0.73, and 0.73, respectively. The ixekizumab clearance increases with increasing body weight and, consequently, subjects with higher body weight had lower ixekizumab trough concentrations when compared to the subjects with lower body weight receiving the same dosing regimen (Figure 2.5.1.c).





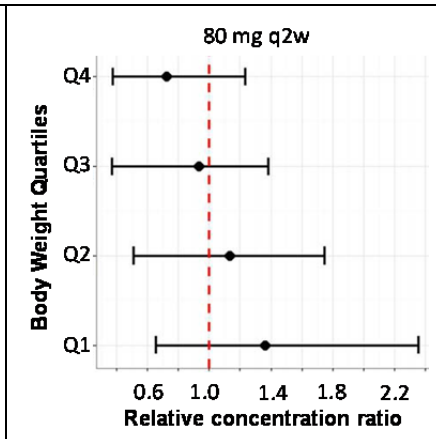


Figure 2.5.1.c. The effect of body weight on ixekizumab clearance and exposure (Week 12 trough concentration) in psoriasis patients by population PK analysis. The clearance values were based on *post-hoc* estimates of individual clearance in the primary population PK analysis. Week 12 trough concentrations were simulated based on Study RHAZ 80 mg q2w dosing regimen in the induction dosing period. Concentration ratio was the ratio relative to the concentration predicted in subjects with median body weight. A similar trend was predicted for the 80 mg q4w dosing regimen. *(Data source: reviewer's plots for the clearance data; Figure 2.7.2.5 for the concentration plot in Summary of Clinical Pharmacology.)*

Age

Age did not affect ixekizumab PK based on the finding in the population PK analyses that age was not a significant covariate (Figure 2.5.1.d). The age range for patients in the population PK analyses was 17 to 88 years (median of 46 years, N=1419 patients in total); with 87 (6.13%) patients ≥65 years and <75 years and 12 (0.85%) patients ≥75 years.

Sex

The population PK analyses revealed that sex (68% male; 32% female; N=1419) did not affect ixekizumab PK (Figure 2.5.1.d).

Ethnicity/Race

Ethnicity/race (Caucasian versus African Descent versus Asian) was not a significant covariate in the population PK analyses (N=1419) and the clearance values for various ethnicity/race groups had substantial overlaps (Figure 2.5.1.d). The dataset contained the following distribution of ethnicities/races: Caucasian (92.4%), Asian (4.37%), African Descent (2.18%), Native American (0.35%), Hispanic (0.28%), and Other (0.42%).

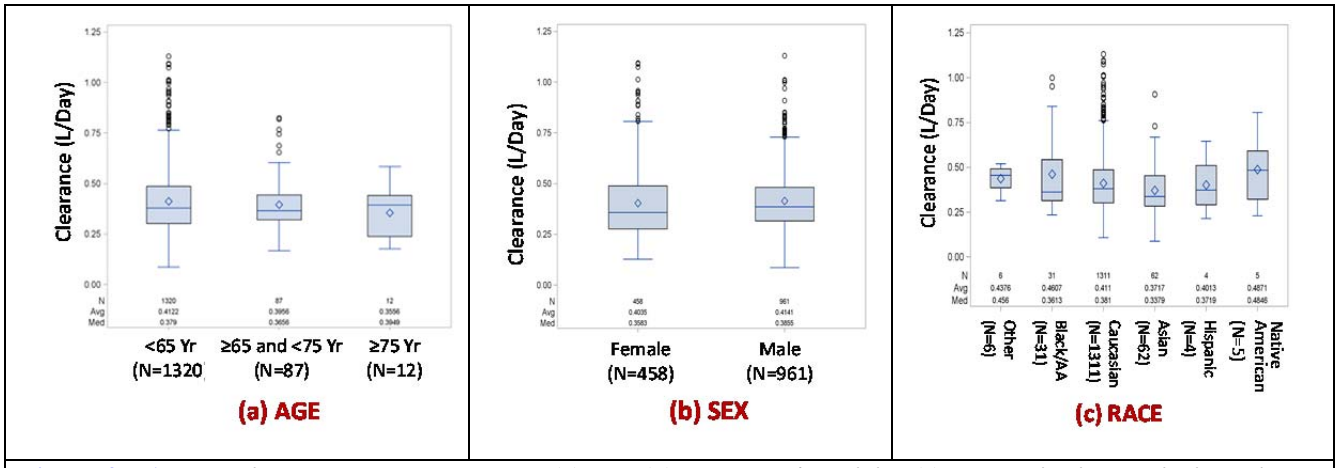


Figure 2.5.1.d. Ixekizumab clearance by age (a), sex (b), and race/ethnicity (c) categories in psoriasis patients as assessed by population PK analysis. The clearance values were based on *post-hoc* estimates of individual clearance in the primary population PK analysis. *(Data source: reviewer's plots)*

Renal impairment

No formal studies were conducted in subjects with renal impairment. Ixekizumab is a human IgG4 immunoglobulin with large molecular size of approximately 146 kDa; therefore, intact ixekizumab is unlikely to be filtered by kidney or excreted in urine.

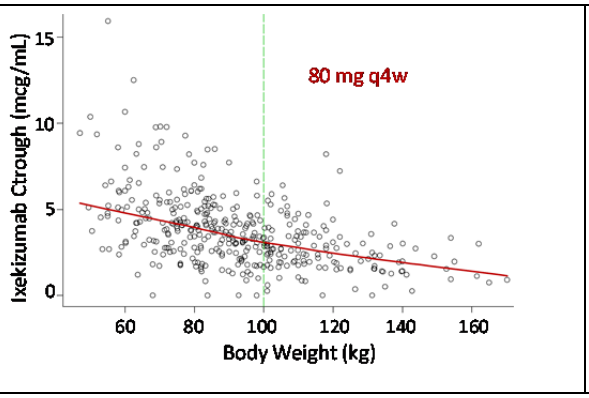
Hepatic impairment

No formal studies were conducted in subjects with hepatic impairment. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of IgG antibodies such as ixekizumab.

2.5.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended?

The Applicant proposes 160 mg at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg q4w dosing regimen for all patients. We do not recommend dosing regimen adjustments based on the currently available PK and E-R data.

Body weight was the most significant covariate on ixekizumab clearance in subjects with psoriasis and, as a result, serum trough concentrations decreased as body weight increased (Figure 2.5.2.a). Subgroup analysis using a pre-specified body weight cut off showed that subjects with lower body weight (<100 kg) had 9% higher response rate for sPGA (0, 1) and 4% higher response rate for PASI 75 compared to subjects with higher body weight (≥100 kg) with the proposed 80 mg q2w dosing regimen (Table 2.5.2.a).



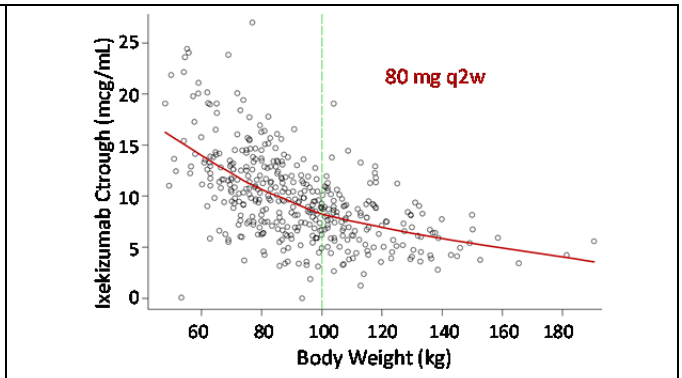


Figure 2.5.2.a. Impact of body weight on ixekizumab serum concentrations at Week 12 in the induction dosing period. Ixekizumab C_{trough} values were population PK model predicted concentrations based on demographic data in Study RHAZ. *(Data source: Figure 2.7.2.4, Summary of Clinical Pharmacology)*

Table 2.5.2.a. Week 12 sPGA and PASI 75 response rates in the induction period in pooled Phase 3 studies RHAZ, RHBA and RHBC stratified by body weight and treatment groups. *(Data source: Table 2.7.3.22, Summary of Clinical Efficacy)*

	Week 12 Clinical Response Rates (%)					
	Placebo (N=789)		**IXE 80 mg q4w (N=1159)**		**IXE 80 mg q2w (N=1168)**	
Body weight	**<100 kg (N1=538)**	**≥100 kg (N2=251)**	**<100 kg (N1=791)**	**≥100 kg (N2=368)**	**<100 kg (N1=819)**	**≥100 kg (N2=349)**
sPGA (0,1)	4.8%	2.0%	79.0%	67.4%	84.5%	75.6%
PASI 75	5.0%	3.2%	85.6%	74.2%	90.1%	85.7%

Because the ixekizumab efficacy with 80 mg q2w dosing regimen has approached the plateau of the exposure-response curve for the Week 12 efficacy data, it is not necessary to further explore a higher dose in the high body weight group. Additionally, while the Week 12 response rates were similar for subjects with high body weight receiving 80 mg q2w dosing and subjects with low body weight receiving 80 mg q4w dosing, we would not recommended 80 mg q4w for the first 12 weeks of treatment in subjects with low body weight because the data also showed that the 80 mg q2w dosing regimen achieved greater sPGA (0,1) and PASI 75 response rates in each body weight subgroup (<100 kg or ≥100 kg). Additionally, the 80 mg q2w induction dosing regimen was associated with higher sPGA (0,1) and PASI 75 response rates at Week 60 indicating that 80 mg q2w dosing regimen is desirable for subjects with low body weight as well as subjects with high body weight. Overall, the proposed dosing regimen regardless of body weight is acceptable.

2.5.3. Does genetic variation impact exposure and/or response?

No formal studies were conducted to evaluate the impact of genetic variation on ixekizumab exposure or response.

2.6. Extrinsic Factors

2.6.1. What are the extrinsic factors that influence exposure and/or response?

Extrinsic factors that could significantly affect ixekizumab exposure and/or response have not been studied or identified.

2.6.2. What are the drug-drug interactions?

Drug-drug interaction (DDI) studies in psoriasis patients have not been investigated for ixekizumab. Refer to *Individual Study Summaries* for evaluation of the effect of IL-17 on CYP enzyme mRNA expression and activity *in vitro*.

2.6.3. Does the label specify co-administration of another drug?

No.

2.6.4. What other co-medications are likely to be administered to the target population(s)?

Ixekizumab will be prescribed to patients with moderate to severe plaque psoriasis. Potential medications co-administered to these patients may include low molecular weight immunosuppressants.

2.6.5. Is there a known mechanistic basis for pharmacodynamic- or disease-drug-drug interactions?

Yes, there is a potential for psoriasis disease-drug-drug interaction (disease-DDI) based on the current understanding that psoriasis patients have elevated proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon disease improvement following biological treatment. Therefore, we recommend that the Applicant conducts a clinical trial to determine the potential for ixekizumab to alter the metabolism of CYP substrates in psoriasis patients.

2.7. Pharmacodynamics

2.7.1. What are the impacts of ixekizumab treatment on tissue or serum IL-17A level in subjects with psoriasis?

The Applicant did not conduct formal clinical studies to evaluate the effect of ixekizumab on PD markers (e.g., serum or tissue IL-17A) in psoriasis patients.

2.8. Immunogenicity

2.8.1. What was the incidence (rate) of the formation of the anti-drug antibodies (ADA)? Did the ADA have neutralizing activity?

Induction dosing period of Phase 3 trials: immunogenicity data through Week 12

In the induction dosing period through Week 12 of the psoriasis Phase 3 trials, the incidence of treatment-emergent anti-drug antibodies (TE-ADA) positive patients was 11% (256 of 2293). Among the TE-ADA positive subjects, 39% (99 of 256) had ADA titers ≥1:160 and 9% (24 of 256) were NAb positive (Table 2.8.1).

Table 2.8.1. Immunogenicity incidence during induction dosing period through Week 12 in the combined dataset from psoriasis Phase 3 Studies RHAZ, RHBA, and RHBC. [a] percentage calculated by n/N(total number of evaluable subjects)*100%; [b] percentage calculated by n/(number of TE-ADA positive subjects)*100%. ADA, anti-drug antibodies; TE-ADA, treatment-emergent ADA; NAb, neutralizing ADA. (*Data source: Table 2.7.2.12 and Table 2.7.2.13, Summary of Clinical Pharmacology Studies*)

	Ixekizumab induction treatment		
	80 mg q4w N=1143	**80 mg q2w N=1150**	**combined N=2293**
TE-ADA positive, n(%)[a]	153 (13.4%)	103 (9.0%)	256 (11.2%)
TE-ADA titer <1:160, n(%)[b]	91 (59.5%)	66 (64.1%)	157 (61.3%)
TE-ADA titer ≥1:160, n(%)[b]	62 (40.5%)	37 (35.9%)	99 (38.7%)
NAb positive, n(%)[b]	19 (12.4%)	5 (4.9%)	24 (9.4%)
NAb negative, n(%)[b]	15 (9.8%)	4 (3.9%)	19 (7.4%)
NAb inconclusive, n(%)[b]	119 (77.8%)	94 (91.3%)	213 (83.2%)

Maintenance dosing period of Phase 3 trials: immunogenicity data through Week 60

In the maintenance dosing period through Week 60 of the psoriasis Phase 3 trials, the incidence of TE-ADA positive patients was 21.4% (141 of 659). Among the TE-ADA positive subjects, 9% (13 of 141) had ADA titers ≥1:160 and 4% (5 of 141) were NAb positive (Table 2.8.2).

Table 2.8.2. Immunogenicity incidence during maintenance dosing period through Week 60 in the combined dataset from psoriasis Phase 3 Studies RHAZ and RHBA. [a] percentage calculated by n/N(total number of evaluable subjects)*100%; [b] percentage calculated by n/(number of TE-ADA positive subjects)*100%. ADA, anti-drug antibodies; TE-ADA, treatment-emergent ADA; NAb, neutralizing ADA. (*Data source: Table 2.7.2.14, Table 2.7.2.15, and Table 2.7.2.17, Summary of Clinical Pharmacology Studies*)

	Maintenance treatment groups			
	Placebo	**Ixekizumab maintenance treatment groups**		
	N=330	**80 mg q12w N=329**	**80 mg q4w N=330**	**Combined N=659**
TE-ADA positive, n(%)[a]	80 (24.2%)	84 (25.5%)	57 (17.3%)	141 (21.4%)
TE-ADA titer <1:160, n(%)[b]	68 (85.0%)	74 (88.1%)	54 (94.7%)	128 (90.8%)
TE-ADA titer ≥1:160, n(%)[b]	12 (15.0%)	10 (11.9%)	3 (5.3%)	13 (9.2%)
NAb positive, n(%)[b]	4 (5%)	4 (4.8%)	1 (1.8%)	5 (3.5%)
NAb negative, n(%)[b]	68 (85%)	62 (73.8%)	1 (1.8%)	63 (44.7%)
NAb inconclusive, n(%)[b]	8 (10%)	18 (21.4%)	55 (96.5%)	73 (51.8%)

Integrated immunogenicity data across all psoriasis studies

Across all ixekizumab psoriasis studies, the incidence of TE-ADA positive patients was 20.1% (826 of 4107). Among the TE-ADA positive subjects, 10.8% (89 of 826) were NAb positive (Table 2.8.3).

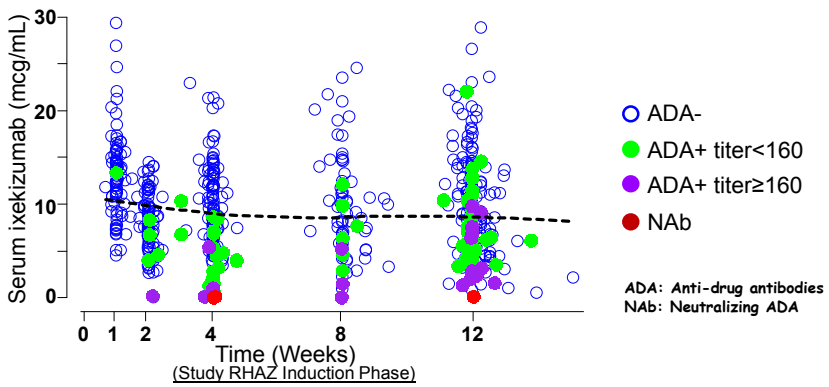
Table 2.8.3. Immunogenicity incidence across all ixekizumab psoriasis studies. [a] percentage calculated by n/N(total number of evaluable subjects)*100%; [b] percentage calculated by n/(number of TE-ADA positive subjects)*100%. ADA, anti-drug antibodies; TE-ADA, treatment-emergent ADA; NAb, neutralizing ADA. (*Data source: Table 2.7.2.18, Summary of Clinical Pharmacology Studies*)

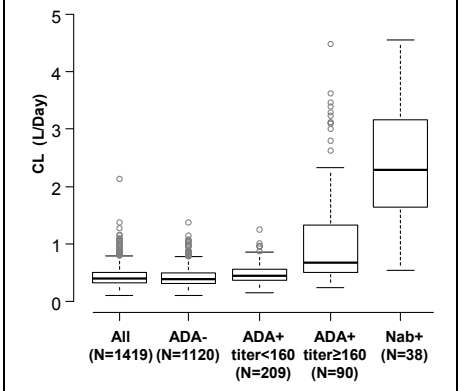
	Pooled ixekizumab treatment patients across studies (N=4107, number of evaluable patients)
TE-ADA positive, n(%)[a]	826/4107 (20.1%)
TE-ADA titer <1:160, n(%)[b]	N/A
TE-ADA titer ≥1:160, n(%)[b]	N/A
NAb positive, n(%)[b]	89/826 (10.8%)
NAb negative, n(%)[b]	100/826 (12.1%)
NAb inconclusive, n(%)[b]	637/826 (77.1%)

2.8.2. What are the impacts of ADA on PK?

The formation of ADA was associated with increased ixekizumab clearance and reduced ixekizumab serum concentrations. ADA with higher titers (≥1:160) or with neutralizing activity had greater impact with respect to the increased clearance and reduced serum drug concentrations, compared to ADA

with low titers (<1:160) (Figure 2.8.2.a). Based on the *post-hoc* estimate of individual clearance values in the Applicant's population PK analysis, the median CL was approximately 2-fold higher in subjects with higher ADA titer (≥1:160) compared with ADA negative subjects, whereas subjects with low ADA titer (<1:160) had similar clearance values as ADA negative subjects. Subjects who were NAb positive had approximately 8-fold increase in CL compared to ADA negative patients.





2.8.2.a. Impact of ADA formation, the ADA titer and neutralizing ADA on ixekizumab exposure and clearance. The left panel shows the ixekizumab serum concentration time course in the induction dosing period of Study RHAZ for the 80 mg q2w dosing regimen by sample immunogenicity status. The right panel shows the *post-hoc* estimates of clearance values by subject immunogenicity status based on population PK analysis of pooled Studies RHAJ, RHAG and RHAZ. (*Data source: Reviewer's plots*).

2.8.3. What are the impacts of ADA on efficacy?

Of the subjects who developed antibodies to ixekizumab in psoriasis phase 3 trials, high ADA antibody titer (≥1:160) subjects were associated with reduced clinical response and neutralizing antibodies were associated with loss of efficacy. Efficacy response rates were similar between patients who were ADA negative and subjects who had low ADA titer (<1:160).

Week 12 efficacy results

Table 2.8.3.a. summarizes the sPGA (0,1) response rates at Week 12 in subgroups by subject immunogenicity status and ixekizumab treatment groups across the ixekizumab psoriasis Phase 3 studies. The results show the following:

- Formation of TE-ADA during the induction phase of treatment was associated with reduced sPGA (0,1) response rates.
  - In patients treated with ixekizumab 80 mg q2w dosing regimen, the sPGA (0,1) response rate was 70.9% (73 out of 103) in TE-ADA positive patients, comparing to 83.6% (875 out of 1047) in TE-ADA negative patients.
  - In patients treated with ixekizumab 80 mg q4w dosing regimen, the sPGA (0,1) response rate was 62.1% (95 out of 153) in TE-ADA positive patients, in comparison to 78.5% (777 out of 990) in TE-ADA negative patients.
  - In patients treated with either ixekizumab dosing regimen (80 mg q2w or 80 mg q4w), the sPGA (0,1) response rate was 65.6% (168 out of 256) in TE-ADA positive patients, in comparison to 81.1% (1652 out of 2037) in TE-ADA negative patients.

- TE-ADA positive patients with titer <1:160 showed slightly lower (<5%) sPGA (0,1) response rates than TE-ADA negative patients.
  - In patients treated with ixekizumab 80 mg q2w dosing regimen, the sPGA (0,1) response rate was 78.8% (52 out of 66) in TE-ADA positive patients with titer <1:160, comparing to 83.6% (875 out of 1047) in TE-ADA negative patients.
  - In patients treated with ixekizumab 80 mg q4w dosing regimen, the sPGA (0,1) response rate was 74.7% (68 out of 91) in TE-ADA positive patients with titer <1:160, comparing to to 78.5% (777 out of 990) in TE-ADA negative patients.
  - In patients treated with either ixekizumab dosing regimen (80 mg q2w or 80 mg q4w), the sPGA (0,1) response rate was 76.4% (120 out of 157) in TE-ADA positive patients with titer <1:160, comparing to 81.1% (1652 out of 2037) in TE-ADA negative patients.
- TE-ADA positive patients with titer ≥1:160 showed lower sPGA (0,1) response rates compared to TE-ADA negative patients.
  - In patients treated with ixekizumab 80 mg q2w dosing regimen, the sPGA (0,1) response rate was 56.8% (21 out of 37) in TE-ADA positive patients with titer ≥1:160, comparing to 83.6% (875 out of 1047) in TE-ADA negative patients.
  - In patients treated with ixekizumab 80 mg q4w dosing regimen, the sPGA (0,1) response rate was 43.5% (27 out of 62) in TE-ADA positive patients with titer ≥1:160, comparing to to 78.5% (777 out of 990) in TE-ADA negative patients.
  - In patients treated with either ixekizumab dosing regimen (80 mg q2w or 80 mg q4w), the sPGA (0,1) response rate was 48.5% (48 out of 99) in TE-ADA positive patients with titer ≥1:160, comparing to 81.1% (1652 out of 2037) in TE-ADA negative patients.
- Among the 24 TE-ADA positive patients with confirmed NAb, only 1 (4%) patients achieved sPGA (0,1) response, indicating the lack of efficacy of ixekizumab in patients who developed NAb.

Table 2.8.3.a. sPGA (0,1) response rates at Week 12 in subgroups by subject immunogenicity status and ixekizumab treatment groups in pooled ixekizumab psoriasis Phase 3 studies RHAZ, RHBA and RHBC.
(Data source: Table 2.7.3.23, Summary of Clinical Efficacy)

Ixekizumab treatment groups	Week 12 sPGA (0,1) response rate% (n/N)					
	Ixekizumab treated patients by ADA status					Placebo
	TE-ADA negative	TE-ADA positive				
		Titer<1:160	Titer≥1:160	NAb+	Combined	
80 mg q4w	78.5% (777/990)	74.7% (68/91)	43.5% (27/62)	5.3% (1/19)	62.1% (95/153)	3.9% (30/777)
80 mg q2w	83.6% (875/1047)	78.8% (52/66)	56.8% (21/37)	0% (0/5)	70.9% (73/103)	
Combined	81.1% (1652/2037)	76.4% (120/157)	48.5% (48/99)	4.2% (1/24)	65.6% (168/256)	

2.8.4. What are the impacts of ADA on safety?

In psoriasis phase 3 trials, formation of TE-ADA did not show an association with the incidence of overall adverse events, injection sites reactions or hypersensitivity. Table 2.8.4 presents an overview of AEs, injection site reactions, and hypersensitivities by TE-ADA status and treatment groups through Week 12 of the combined Phase 3 trials.

Table 2.8.4. Summary of adverse events (AEs), injection site reactions (ISR) and hypersensitivities by treatment groups and subjects TE-ADA status through Week 12 of pooled Phase 3 studies RHAZ, RHBA and RHBC. TE-ADA, treatment-emergent anti-drug antibodies; (*Data source: Table App.2.7.4.85, Summary of Clinical Safety-Appendix*)

Adverse events	Incidence by treatment and TE-ADA status (%, n/N)						
	Placebo (ADA-)	Ixekizumab 80 mg q4w		Ixekizumab 80 mg q2w		Ixekizumab Combined	
		ADA+	ADA-	ADA+	ADA-	ADA+	ADA-
AEs	47.1% (366/777)	31.4% (48/153)	59.1% (585/990)	38.8% (40/103)	57.5% (602/1047)	34.4% (88/256)	58.3% (1187/2037)
ISR	3.3% (26/777)	4.6% (7/153)	11.5% (114/990)	11.7% (12/103)	15.6% (163/1047)	7.4% (19/256)	13.6% (277/2037)
Hypersensitivities/ Anaphylaxis	0.3% (2/777)	0% (0/153)	0.4% (4/990)	0% (0/103)	0.4% (4/1047)	0% (0/256)	0.4% (8/2037)

2.9. Biopharmaceutics

2.9.1. Were there manufacturing process changes during the development program? What were the drug substances and drug products used in ixekizumab psoriasis clinical trials?

Yes, drug substance (DS) and drug product (DP) manufacturing changes were introduced during the clinical development of ixekizumab for the psoriasis indication. Table 2.9.1 summarizes the DS and DP used in the psoriasis clinical trials.

Table 2.9.1. Ixekizumab drug substance and drug product (formulations and presentations) used in psoriasis clinical trials. The ixekizumab drug substance was produced in clonally-derived Chinese Hamster Ovary (CHO) cell lines. The drug substance produced [redacted] (b) (4) was used for study RHAG, and the drug substance produced [redacted] (b) (4) was used for all other psoriasis clinical trials. The PFS and AI presentations contain the same liquid formulation with an identical ixekizumab concentration and the same primary syringe; they only differ in the [redacted] (b) (4). [redacted] (b) (4); PFS, pre-filled syringe; AI, autoinjector.

Clinical Trials	Formulation/Presentations used in Psoriasis Clinical Trials			
	LYO		Solution (80 mg/1 mL)	
	20 mg/vial	48 mg/vial	PFS	AI
Phase 1	RHAG			
Phase 2		RHAJ (Part A)	RHAJ (Part B)	
Phase 3			RHAZ (Pivotal) RHBA (Pivotal) RHBC (Pivotal)	
Phase 3 with PK comparability			RHBL	RHBL

2.9.2. Was the proposed to-be-marketed formulation/presentation comparable to the formulation/presentation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?

Yes. Ixekizumab solution for injection (80 mg/mL) was used in the Phase 2 study and all pivotal Phase 3 studies and is identical to the formulation proposed for registration in two presentations: PFS and AI.All three pivotal Phase 3 trials used the PFS presentation. The AI presentation was not tested in pivotal trials. The PK comparability between PFS and AI was demonstrated by the PK results from Study RHBL.

The PFS and AI achieved comparable ixekizumab serum concentration-time profiles following the initial 160 mg SC dose during the 0 to 14 days interval (Figure 2.9.2.a). The PK comparability analysis showed that the point estimates [90% confidence interval] for geometric mean ratio of C_{max}

and $AUC_{(0\text{-}14\ days)}$ were 0.99 [0.89, 1.10] and 0.98 [0.89, 1.08], respectively, which were all within the [0.8, 1.25] acceptance limit of the bioequivalence (BE) criteria (Figure 2.9.2.b-c). Thus the PK comparability between PFS and AI was demonstrated by the PK results from Study RHBL.

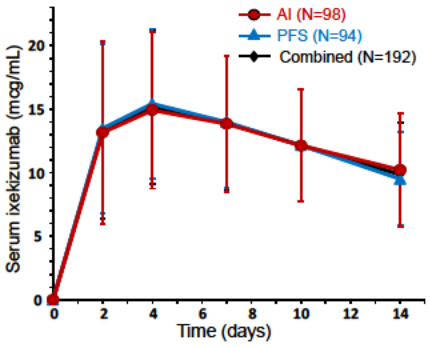


Figure 2.9.2.a. PFS and AI achieved similar serum ixekizumab concentration-time profiles following the initial 160 mg dose in Study RHBL. The median Tmax was 4 days for both PFS and AI. *(Data source: reviewer's plot)*

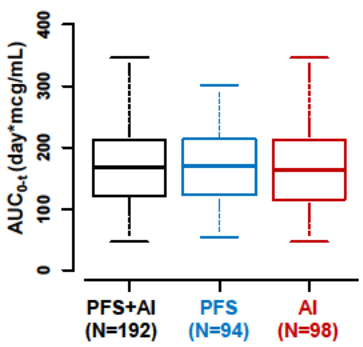


Figure 2.9.2.b. PFS and AI achieved comparable $AUC_{0\text{-}14days}$. The geometric means were 157 day*mcg/mL and 154 day*mcg/mL for PFS and AI, respectively. *(Data source: reviewer's analysis and plot)*

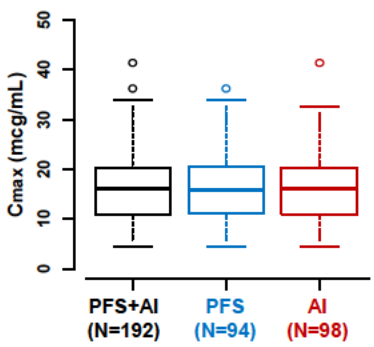


Figure 2.9.2.c. PFS and AI achieved comparable Cmax. The geometric means were 15.0 day*mcg/mL and 14.8 day*mcg/mL for PFS and AI, respectively. *(Data source: reviewer's analysis and plot)*

Study RHBL was a Phase 3, multicenter, randomized, open-label, parallel-group study with the primary objective to examine the effect of the drug delivery device (PFS or AI) on the PK of ixekizumab in psoriasis patients. The ixekizumab dose regimen was 80 mg SC q2w with a starting dose of 160 mg; a total of 204 patients were randomized at a 1:1 ratio to receive ixekizumab administrations by PFS and by AI during the 12-week treatment period. After Week 12, all eligible patients continued with 80 mg q4w regimen by PFS for long-term safety assessment. Ixekizumab serum concentrations were evaluated during the 0 to 14 days interval following the initial 160 mg ixekizumab dose administration. The PK parameters C_{max} and $AUC_{(0\text{-}14\ days)}$ were used for the evaluation of the PK comparability between the PFS and AI presentations.

2.10. Bioanalytical methods

2.10.1. What bioanalytical methods are used to determine ixekizumab concentrations in human serum? Briefly describe the performance of the assay.

The ixekizumab serum concentrations were analyzed using an enzyme linked immunosorbent assay (ELISA). Briefly, standards, controls, and test serum samples (with 1:5 minimum required dilution) (b) (4)

(b) (4) Based on the assay principle and the expected low level of IL-17A in human serum, the total serum ixekizumab concentrations measured by the ELISA method could reasonably represent the free ixekizumab concentrations (not bound to IL-17A).

The validation parameters of the ELISA for measurement of human serum ixekizumab concentrations, and related clinical trials are summarized in Table 2.10.1.a. This reviewer found the assay validation acceptable.

Table 2.10.1.a. Assay validation parameters of the ELISA method used for measurement of human serum ixekizumab (LY2439821) concentrations. ELISA: enzyme linked immuno-sorbent assay; LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; QC, quality control. (*Referenced validation reports and data source: Assay Validation Report with document ID of "AR1827"*)

Assay description and validation parameters	***Data Source: Original Method Validation Report: ALTA Report AR1827 (09/25/2006); Document ID in the BLA: AR1827***
Assay validation report title	Quantitative determination of LY2439821 in human serum using an enzyme linked immunosorbent assay (ELISA)
Method	ELISA
Platform	Microtiter plate
Compound analyzed	Ixekizumab (LY2439821)
Matrix	Human serum
Minimum required dilution (MRD)	1:5
LLOQ	1.5 ng/mL
ULOQ	60 ng/mL
Range of Quantitation	7.5 ng/mL (=LLOQ×MRD) to 300 ng/mL (=ULOQ×MRD)
Standard Curve	Eight standard curve samples: 0, 0.6, 1.3, 2.5, 5, 10, 20, 40, 80, and 160 ng/mL (anchor point).
Intra-assay accuracy (%relative error)	-5.8% to 3.4%
Inter-assay precision (%CV)	11.8% to 17.3% (QC samples) 0.9% to 7.8% (Standard curve)
Intra-assay precision (%CV)	1.8% to 4.0% (QC samples) 1.2% to 9.5% (Standard curve)
Stability	Sample stability at room temperature: 4 hours. Long-term stability at approximately -70°C and at approximately -20°C: 365 days. Freeze (-70°C)/thaw stability: 8 cycles (*Additional data source: Method Validation Report Addendum A; Method Validation Report Addendum D; Table APP.2.7.1.3, Summary of Biopharmaceutics-Appendix*).
Dilution Effect	Dilution linearity was observed at dilutions tested up to 1:32000. The highest dilution factor reported for clinical studies was <3000.
Standard Curve	Sample concentrations were determined by interpolation from the standard curve that was fitted using a 5-parameter logistic regression algorithm.
Incurred sample reanalysis	Incurred sample reanalysis was conducted for Study RHAG. The results showed that 100% (20/20) of the samples demonstrated original and reanalysis values within ±30% of the average mean concentration. (*Additional data source: Method Validation Report, Addendum C*)
Selectivity	Ten individual human serum samples were spiked with ixekizumab for final concentrations of 50 ng/mL (n=10) and 20 ng/mL (n=10). At 50 ng/mL, 100% (10 out of 10) of samples had recovery of 100±20%; at 20 ng/mL, 100% (10 out of 10) of samples had recovery of 100±25%
Clinical Studies and Clinical Study Reports (CSR) related to the ELISA assay	All psoriasis clinical trials and CSR including I1F-MC-RHAG, I1F-MC-RHAJ, I1F-MC-RHAZ, I1F-MC-RHBL, I1F-MC-RHBA, and I1F-MC-RHBC. (*Additional data source: Table APP.2.7.1.2, Summary of Biopharmaceutics-Appendix*).

2.10.2. What bioanalytical methods are used for immunogenicity assessment? Briefly describe the performance of the assays.

Immunogenicity sample ADA status was evaluated using a 4-tiered approach (Table 2.10.2.a).

Table 2.10.2.a. Summary of immunogenicity assays and sample ADA status determination. ADA, anti-drug antibodies; ACE ELISA, affinity capture elution enzyme-linked immunosorbent assay; MSD, MesoScale Discovery platform.

Procedure	**Tier 1 →**	**Tier 2 →**	**Tier 3 →**	**Tier 4 →**
Assay	ACE ELISA	ACE ELISA	ACE ELISA	MSD
Purpose	Screening	Confirmation	Titration	Neutralizing activity determination
Samples analyzed	All samples	Samples above the assay cut point in Tier 1	Confirmed ADA in Tier 2	Confirmed ADA in Tier 2
Results and reporting	Detected or not detected	Confirmed or not confirmed	Titer values	Neutralizing ADA positive or negative

ACE ELISA for screening, confirmation and titration

An affinity capture elution enzyme-linked immunosorbent assay (ACE ELISA) was used for ADA screening, confirmation and titration. (b) (4)

(b) (4)

Reviewer's comments: *The drug tolerance of the ADA assay is acceptable for measurement of the ADA responses in psoriasis Phase 3 trials. The drug tolerance level* (b) (4) *is* (b) (4) *higher than the observed median trough concentrations ranging from* (b) (4) *across different dosing regimens through Week 48 in Phase 3 Study RHAZ (see Section 2.4.7).*

Neutralizing ADA assay

(b) (4)

(b) (4)

Reviewer's comments: *The neutralizing ADA assay could be interfered with the presence of ixekizumab. The following statement is recommended to be included in the product labeling: "However, the immunogenicity assay has limitations detecting neutralizing antibodies in the presence of ixekizumab; therefore, the incidence of neutralizing antibodies development might not have been reliably determined". Whether or not the Application needs to develop a more sensitive neutralizing antibody assay with a higher drug tolerance level remains to the further assessed by the Product Quality review team.*

3. LABELING RECOMMENDATIONS

Labeling recommendations at this time are summarized as below.

Proposed labeling by the Applicant	Labeling recommendations
6.2 Immunogenicity (b) (4)	6.2 Immunogenicity As with all therapeutic proteins there is a potential for immunogenicity with TALTZ. Approximately (b) (4)% of subjects treated with TALTZ developed antibodies to ixekizumab in up to 60 weeks of treatment. The clinical effects of antibodies to ixekizumab are dependent on the antibody titer; increasing titer was associated with decreasing drug concentration and clinical response. Of the subjects who developed antibodies to ixekizumab, approximately (b) (4)% had antibodies that were classified as neutralizing. Neutralizing antibodies were associated with reduced drug concentrations and loss of efficacy. However, the immunogenicity assay has limitations detecting neutralizing antibodies in the presence of ixekizumab; therefore, the incidence of neutralizing antibodies development might not have been reliably determined.
7. DRUG INTERACTIONS (b) (4)	*The labeling language as proposed by the Applicant is acceptable.*

12.2 Pharmacodynamics (b) (4)	**12.2 Pharmacodynamics** No formal pharmacodynamic studies have been conducted with TALTZ.
12.3 Pharmacokinetics (b) (4)	**12.3 Pharmacokinetics** <u>Absorption</u> Following a single subcutaneous dose of 160 mg in subjects with plaque psoriasis, ixekizumab reached peak mean (±SD) serum concentrations (C_{max}) of (b) (4) ± 6 mcg/mL by approximately 4 days post dose. Steady-state concentrations were achieved by Week 8 following the 160 mg starting dose and 80 mg every 2 weeks dosing regimen. The median steady-state trough concentration was (b) (4) mcg/mL. After switching from the 80 mg every 2 weeks dosing regimen to the 80 mg every 4 weeks dosing regimen at Week 12, steady-state concentrations were achieved after approximately 10 weeks. The median steady-state trough concentration was (b) (4) mcg/mL. In studies of subjects with plaque psoriasis, ixekizumab bioavailability ranged from 60% to 81% following subcutaneous injection. Administration of ixekizumab via injection in the thigh achieved a higher bioavailability relative to that achieved using other injection sites including the arm and abdomen. <u>Distribution</u> The mean (geometric CV%) volume of distribution at steady-state was 7.11 L (29%) in subjects with plaque psoriasis. <u>Elimination</u> The metabolic pathway of ixekizumab has not been characterized. As a humanized IgG4 monoclonal antibody ixekizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. The mean (geometric CV%) systemic clearance was 0.39 L/day (37%) and the mean (geometric CV%) half-life was 13 days (40%) in subjects with plaque psoriasis. <u>Weight</u> Ixekizumab clearance and volume of distribution increase as body weight increases. <u>Dose Linearity</u> Ixekizumab exhibited dose-proportional pharmacokinetics in subjects with plaque psoriasis over a dose range from 5 (not

(b) (4)	the recommended dose) to 160 mg following subcutaneous administration. <u>Specific Populations</u> *Age: Geriatric Population* Population pharmacokinetic analysis indicated that age did not significantly influence the clearance of ixekizumab in adult subjects with plaque psoriasis. Subjects who are 65 years or older had similar ixekizumab clearance to subjects less than 65 years old. *Renal or Hepatic Impairment* No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of ixekizumab was conducted.

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	BLA 125521
Compound	Ixekizumab (TALTZ®); 80 mg/mL solution in a single-dose autoinjector (AI) and 80 mg/mL solution in a single-dose prefilled syringe (PFS)
Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Submission Date	03/23/2015
Sponsor	Eli Lilly and Company
PM Reviewer	Dhananjay D. Marathe, PhD
PM Team Leader	Jeffry Florian, PhD
Related IND	100834

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 Does the benefit-risk assessment based on dose- and exposure-response relationships for efficacy and safety support the proposed dose of 160 mg by subcutaneous injection at week 0, followed by 80 mg Q2W injections to week 12, then 80 mg Q4W thereafter?

Yes. The rationale supporting the proposed dose of 160 mg at week 0, followed by 80 mg Q2W injections to week 12, then 80 mg Q4W thereafter, has been described in detail in Section 2.3 of Clinical Pharmacology review. Briefly, there were dose-response and exposure-response relationships for efficacy endpoints based on sPGA and PASI scoring scales across all three Phase 3 studies. The dose- and exposure-response relationship for efficacy was nearing the plateau at the highest dose of 80 mg Q2W in the induction period. In the maintenance period, there was a subsequent loss of response seen in a fraction of patients who were sPGA(0,1) responders at week 12 and were re-randomized to receive either 80 mg Q4W ixekizumab, 80 mg Q12W ixekizumab or placebo for an additional 48 weeks. Approximately 71% patients maintained the sPGA (0,1) response at Week 60 on 80 mg Q4W ixekizumab compared to just ~36% on 80 mg Q12W ixekizumab; this difference in response was statistically significant.

There was no apparent dose- or exposure-response relationship for most treatment emergent adverse events of interest between the two ixekizumab dose levels and placebo across the three Phase 3 Studies. There were numerically higher incidences of oral candidiasis on 80 mg Q2W treatment compared to 80 mg Q4W during the induction period, but these infections were not serious and did not lead to treatment discontinuation. There was a trend of higher incidences of neutropenia with higher exposures (induction dosing period) and higher incidence rates when adjusted for drug exposure time (maintenance dosing period); however these neutropenia events were transient and did not lead to an increase in the event rate of infections.

The reviewer conducted a benefit-risk assessment based on sPGA and PASI efficacy endpoints and infection related safety events during the 12-week induction dosing period based on pooled data from three Phase 3 studies (RHAZ, RHBA and RHBC). Results are summarized by treatment arms (80 mg Q2W, 80 mg Q4W, and placebo) and further stratified by body weight subgroups (<100 and ≥100 kg; <90 and ≥90 kg) to verify the role of body weight on the benefit-risk assessment during the induction dosing period. The results show no consistent trend with respect to the risk of overall infections or moderate/severe infections between the two ixekizumab dose regimens (Figure 2.3.3.a in the Clinical Pharmacology Review and **Table 1**). Moderate/severe infections were analyzed here since these events normally require either oral or intravenous anti-infective treatment. Various other infections, such as oral candidiasis, were also summarized since IL-17 has a role in host defense against oral and skin fungal infections, and inhibition from ixekizumab may hinder this function of this pathway. Given the favorable treatment benefit for 80 mg Q2W, the overall benefit-risk assessment supports the 80 mg Q2W dosing regimen in all adult patients regardless of body weight for the induction dosing period.

Table 1: Benefit-risk assessment using sPGA [(0) and (0,1)] and PASI (50, 75, 90, and 100) based efficacy responses and infection related safety events during the 12-week induction period for pooled data from three phase 3 studies (RHAZ, RHBA and RHBC).

			Risk						Benefit					
Treatment	BW subgroup	N	All infections (%)	Serious Infections (%)	Mod/Severe Infections (%)	Fungal Infections (%)	Oral Candidiasis (%)	Tinea Infections (%)	sPGA(0) (%)	sPGA(0,1) (%)	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Ixekizumab 80 mg Q2W	<100 kg	818*	27.8	0.4	9.2	2.8	0.86	1.3	44.9	84.5	94.6	90.1	74.1	42.7
	≥100 kg	349	25.2	0.6	9.5	1.4	0.29	0.9	26.9	75.6	93.1	85.7	60.2	25.8
Ixekizumab 80 mg Q4W	<100 kg	791	27.6	0.6	9.6	1.5	0.25	0.8	39.7	79.0	91.2	85.6	68.6	38.6
	≥100 kg	338	27.2	0.8	12.0	1.4	0.00	1.1	23.1	67.4	86.1	74.2	52.7	22.0
Placebo	<100 kg	533	22.5	0.6	9.1	0.6	0.00	0.2	0.2	4.8	13.2	5.0	1.7	0.2
	≥100 kg	251	23.9	0.0	8.0	0.4	0.00	0.0	0.0	2.0	8.0	3.2	0.0	0.0

			Risk						Benefit					
Treatment	BW subgroup	N	All infections (%)	Serious Infections (%)	Mod/Severe Infections (%)	Fungal Infections (%)	Oral Candidiasis (%)	Tinea Infections (%)	sPGA(0) (%)	sPGA(0,1) (%)	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Ixekizumab 80 mg Q2W	<90 kg	621*	28.3	0.5	9.3	2.6	0.81	1.0	46.3	85.4	94.4	90.8	75.9	44.7
	≥90 kg	546	25.5	0.4	9.2	2.2	0.55	1.5	31.9	77.8	94.0	86.4	63.2	29.7
Ixekizumab 80 mg Q4W	<90 kg	593	28.0	0.7	10.5	1.4	0.17	0.5	41.7	79.4	90.9	85.6	70.7	41.0
	≥90 kg	576	26.9	0.7	10.2	1.6	0.17	1.2	27.1	71.2	88.2	78.3	56.4	25.5
Placebo	<90 kg	422	24.2	0.7	10.0	0.7	0.00	0.2	0.2	5.5	14.5	5.0	1.9	0.2
	≥90 kg	362	21.5	0.0	7.4	0.3	0.00	0.0	0.0	2.2	8.2	3.8	0.3	0.0

* 1 additional subject in this subgroup for efficacy analysis

Source: Reviewer's analysis

1.1.2 Is there an association between on-treatment response at Week 12 and on-treatment response at earlier time points (i.e., Week 8 or earlier)?

Yes, improvement in treatment response at earlier induction period visits (i.e., prior to Week 12) is associated with an increased likelihood of treatment response at the Week 12 primary endpoint. Subjects who achieved a reduction in sPGA ≥1 unit by Week 8 were likely to maintain that response and constituted the majority of subjects (99%, 1816/1827) who achieved sPGA(0,1) response at Week 12. There was also a subset of patients without any improvement in sPGA by Week 8 who demonstrated improvement or achieved sPGA(0,1) with an additional four weeks of treatment. As such, it is not considered appropriate to alter treatment based on an individual patient's Week 8 (or earlier) sPGA response.

On-treatment response was influenced by multiple factors (body weight and anti-drug antibodies (ADA) response for PK and independently body weight and palmoplantar involvement for PD [sPGA] response). The response rates based on ADA status indicate a lower likelihood of achieving a response at Week 12 in subjects who developed neutralizing ADAs (see Section 2.8.3 of Clinical Pharmacology review). **Figure 1** shows the results from the three Phase 3 studies grouped by ADA status: no ADA [N~2030], low titer ADA (<1:160) [N~151], high titer ADA (≥1:160) [N~80] or neutralizing antibodies [N~22]. The time course plots further show that in the subjects who developed neutralizing antibodies, there is reversal of initial gain in efficacy and separation from the other groups prior to Week 8; in contrast no pronounced differences were observed among the other three groups. Based on these observations it was hypothesized that on-treatment response prior to Week 12 may be utilized to identify patients who are not responding to treatment.

Towards this, a correlation analysis was conducted to assess whether efficacy (change in sPGA) at early time points can identify non-responders with acceptable sensitivity and specificity. The binary predictor variable selected for assessment was reduction from baseline in sPGA score by ≥1 units (event) or no reduction in sPGA (non-event) at various visits. The correlation analysis was done for various visits (Week 1, Week 2, Week 4, Week 8) to find the time point that best correlates to sPGA(0,1) at Week 12. The analysis also assessed reduction from baseline in sPGA score by ≥1 units (event) or no reduction in sPGA from baseline (non-event) at Week 12.

The data in **Table 2** shows that out of 77 subjects who had no reduction in sPGA score from baseline by Week 8, 31 (40.3%) subjects had sPGA reduction ≥1 units by Week 12. Thus there

is gradual betterment in efficacy going from Week 8 to Week 12 in subjects who did not have any reduction in sPGA by Week 8. In addition, of the 2146 subjects who had ≥1 unit reduction in sPGA score from baseline by Week 8, the majority (99%, 2126/2146) at least maintained this efficacy and only 20 (0.9%) regressed to baseline sPGA response at Week 12. Furthermore, as shown in **Table 2**, of the 77 subjects who had no reduction in sPGA score from baseline by Week 8, 66 (85.7%) would be classified as non-responders (sPGA≥2) and 11 (14.3%) subjects would be classified as responders (sPGA(0,1)) by Week 12. This implies that if a decision tree was implemented to discontinue or switch therapy based on Week 8 response using these criteria, then ~14% of the subjects identified would have treatment prematurely discontinued when they may have achieved the desired response with just four additional weeks of treatment. Due to the continued incremental benefit over time with ixekizumab therapy, even in those subjects who may not have achieved any sPGA gains by Week 8, as well as no major safety concerns observed with short term ixekizumab administration (see Question 1.1.1) such a decision tree may not be appropriate to guide treatment decisions in individual patients.

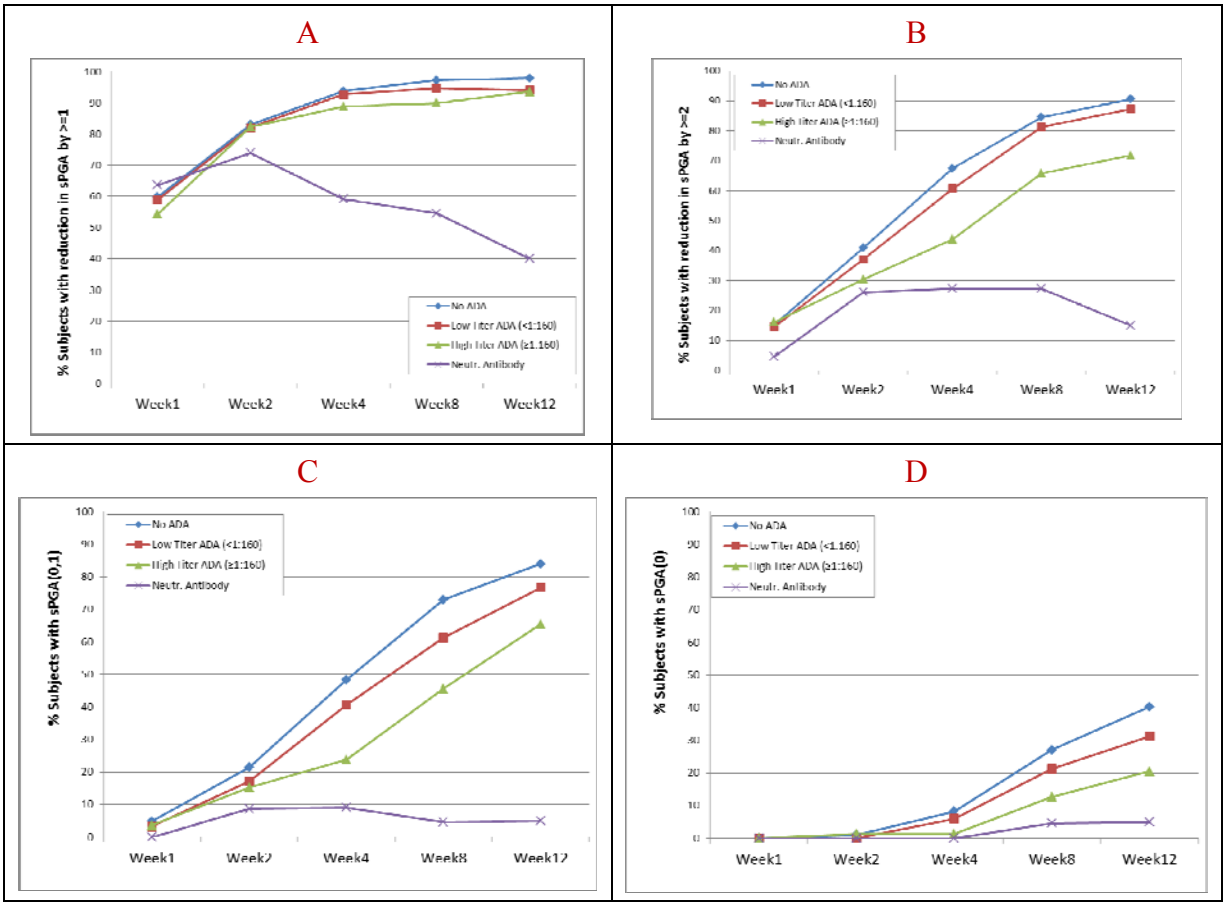


Figure 1: (A) Percentage of subjects with reduction in sPGA score by ≥1 units from baseline, (B) percentage of subjects with reduction in sPGA score by ≥2 units from baseline, (C) percentage of subjects with sPGA(0,1) response and (D) percentage of subjects with sPGA(0) response as a function of time for subjects treated with ixekizumab in Phase 3 Studies RHAZ, RHBA and RHBC. The subjects are categorized into 4 subgroups: i) with no ADA, ii) with low titer (<1:160) of ADA, iii) with high titer (≥1:160) of ADA, and iv) with neutralizing antibodies. These categories are based on each subject's highest immunogenicity status (from no ADA to neutralizing Ab) at any time point through 12 weeks. *(Source: Reviewer's plots for efficacy data categorized by immunogenicity response)*

Table 2: Correlation analysis of sPGA response at Week 8 vs. Week 12 using sPGA score data for patients treated with ixekizumab for 12 weeks in combined Phase 3 Studies RHAZ, RHBA and RHBC. The binary predictor variable is reduction by ≥1 unit or more in sPGA score from baseline to Week 8 (event) or no reduction in sPGA score from baseline to Week 8 (non-event). The response variables are: i) reduction from baseline in sPGA score by ≥1 unit or more (event) or no reduction in sPGA from baseline (non-event) at Week 12, and ii) responders (event) and non-responders (non-event) at Week 12 based on sPGA(0,1) endpoint.

		Week 8 Status	
		No reduction in sPGA* n (% for column)	sPGA reduction by ≥1* n (% for column)
Week 12 Status	No reduction in sPGA*	46 (59.7%)	20 (0.9%)
	sPGA reduction by ≥1*	31 (40.3%)	2126 (99.1%)
		77 (100 %)	2146 (100 %)
	sPGA(0,1) Non-responder	66 (85.7%)	330 (15.4%)
	sPGA(0,1) Responder	11 (14.3%)	1816 (84.6%)
		77 (100 %)	2146 (100 %)
* from baseline score			

Source: Reviewer's analysis

1.1.3 Are dose adjustments recommended based on intrinsic factors such as body weight, age, sex or race/ethnicity?

No. Ixekizumab dose adjustments are not recommended based on intrinsic factors such as body weight, age, sex or race/ethnicity. Body weight was a significant covariate on ixekizumab apparent clearance and volume of distribution in psoriasis patients. The absolute impact of body weight on efficacy through week 12 was less pronounced for 80 mg Q2W compared to 80 mg Q4W in the phase 3 trials, and there was no direct impact on safety as seen from benefit-risk assessments based on dosing regimen and body weight (described in section 1.1.1 above). Additional details about effect of intrinsic factors on ixekizumab PK have been described in Section 2.5 of the Clinical Pharmacology Review.

2 PERTINENT REGULATORY BACKGROUND

Ixekizumab (LY2439821) is a humanized IgG4 monoclonal antibody (mAb) that binds to IL-17A. IL-17A is a naturally occurring cytokine involved in normal inflammatory and immune responses and is purported to play a role in the pathogenesis of plaque psoriasis. Ixekizumab is currently being developed by Eli Lilly and Company for the indication of treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The previously approved anti-cytokine biologics for this indication include etanercept, infliximab, adalimumab, ustekinumab, and secukinumab.

The Applicant conducted three multinational, double-blind, placebo-controlled parallel-group phase 3 trials for ixekizumab. All three trials evaluated two ixekizumab dosing regimens in the 12 week induction period: 80 mg Q2W and 80 mg Q4W. Two of the three trials also had an additional etanercept treatment arm. The primary efficacy analysis was the proportion of patients with sPGA (0,1) and the proportion of patients with PASI 75 at Week 12 using non-responder imputation (NRI) for missing values with ITT population. Further, the subjects

achieving an sPGA(0,1) response from two of the three phase 3 studies were combined and re-randomized to receive either 80 mg Q4W, or 80 mg Q12W or placebo for another 48 weeks to assess maintenance of response. The efficacy response for both the dosing regimens was 73-83% compared to 2-7% for placebo (**Figure 2**) and the results for both treatment arms demonstrated statistically significant response over placebo.

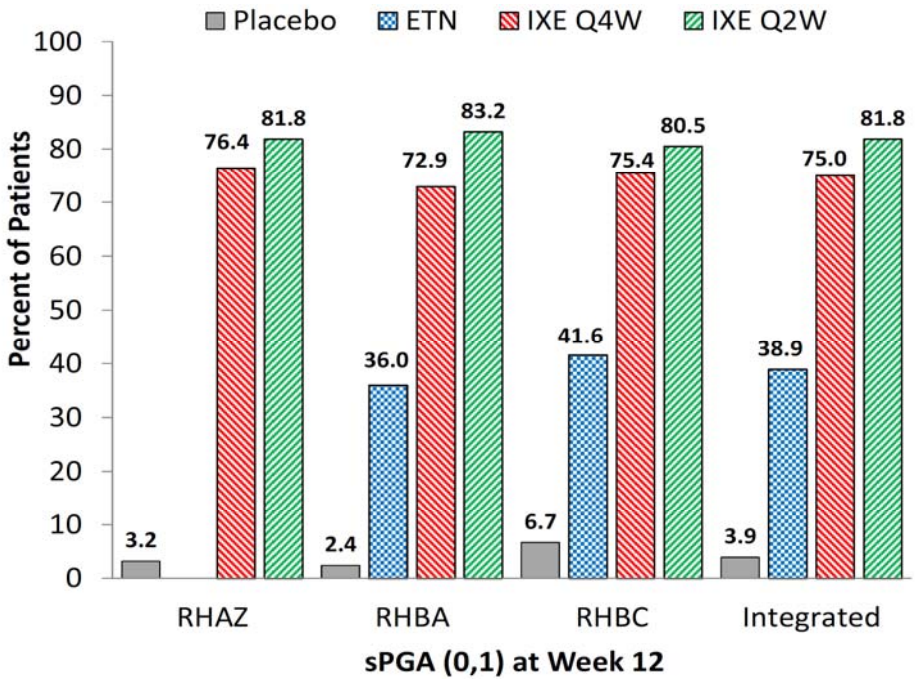


Figure 2: Overview of efficacy (sPGA(0,1) response) at week 12 (induction period) in the three phase 3 studies for ixekizumab. PASI 75 data is not shown here. *(Source: Figure 2.5.4.1, Applicant's Clinical Overview Report)*

The main safety events of interest were frequency and severity of infections.

The following reports from the ixekizumab program are the main contributors to this review:

1. A population PK analysis based on a phase 1 (Study RHAG), a phase 2 (RHAJ) and a phase 3 (RHAZ) study in psoriasis patients
2. Exposure-response (E-R) analysis, immunogenicity analysis and integrated summary of efficacy and safety based on the pooled data from the three phase 3 studies (RHAZ, RHBA, RHBC) in psoriasis patients

The sponsor provided pharmacometric reports for a population PK model developed based on studies mentioned above and exposure-response analysis for efficacy and safety.

3 RESULTS OF SPONSOR'S ANALYSIS AND REVIEWER'S COMMENTS

3.1 Dose Selection

Dose selection for phase 3 was based on the phase 2 dose ranging study RHAJ where ixekizumab doses of 10 mg, 25 mg, 75 mg, and 150 mg were administered at Week 0, 2, 4, 8, 12 and 16 in the double blind period. The results and rationale for a loading dose of 160 mg at week 0, the selection of induction dosing regimens of 80 mg Q2W and 80 mg Q4W, and selection of maintenance dosing regimens of 80 mg Q12W, 80 mg Q4W, and placebo for the phase 3 studies have been described in detail in Section 2.3 of Clinical Pharmacology Review

under the heading of "Dose-response relationship in Phase 2 trials and rationale for Phase 3 dose selection".

3.2 Population Pharmacokinetic and Pharmacodynamic Exposure-Response Analyses

The sponsor performed population pharmacokinetic (popPK) and pharmacodynamic exposure response analyses in patients to:

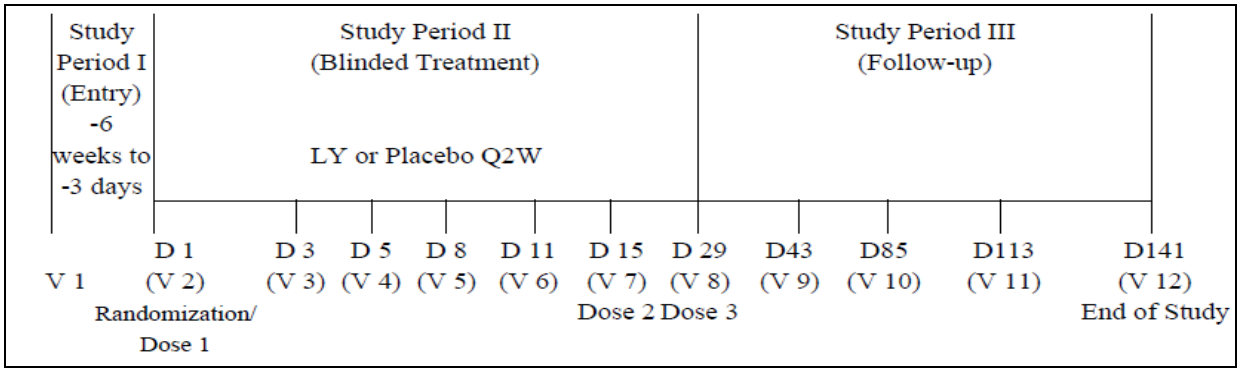
1. Characterize the PK of ixekizumab, determine intra- and inter-subject variability and identify potential intrinsic and extrinsic factors that can impact ixekizumab PK
2. Characterize dose-/exposure-response relationship for efficacy endpoints (sPGA and PASI score) and identify patient factors that may impact this relationship
3. Characterize dose-/exposure-response relationships to describe key safety endpoints
4. Evaluate the impact of anti-ixekizumab antibodies on PK and efficacy

3.2.1 Methods

3.2.1.1 Population PK Analysis

The popPK analysis was based on data from 3 studies: a phase 1 (Study RHAG), a phase 2 (RHAJ) and a phase 3 (RHAZ) study in psoriasis patients. A brief description of these studies and the dosing regimen employed in each is shown in **Figure 3**. The popPK dataset consisted of observed concentrations from 1399 patients with 6059 sampled concentrations (summarized in **Table 3**):

A.



B.

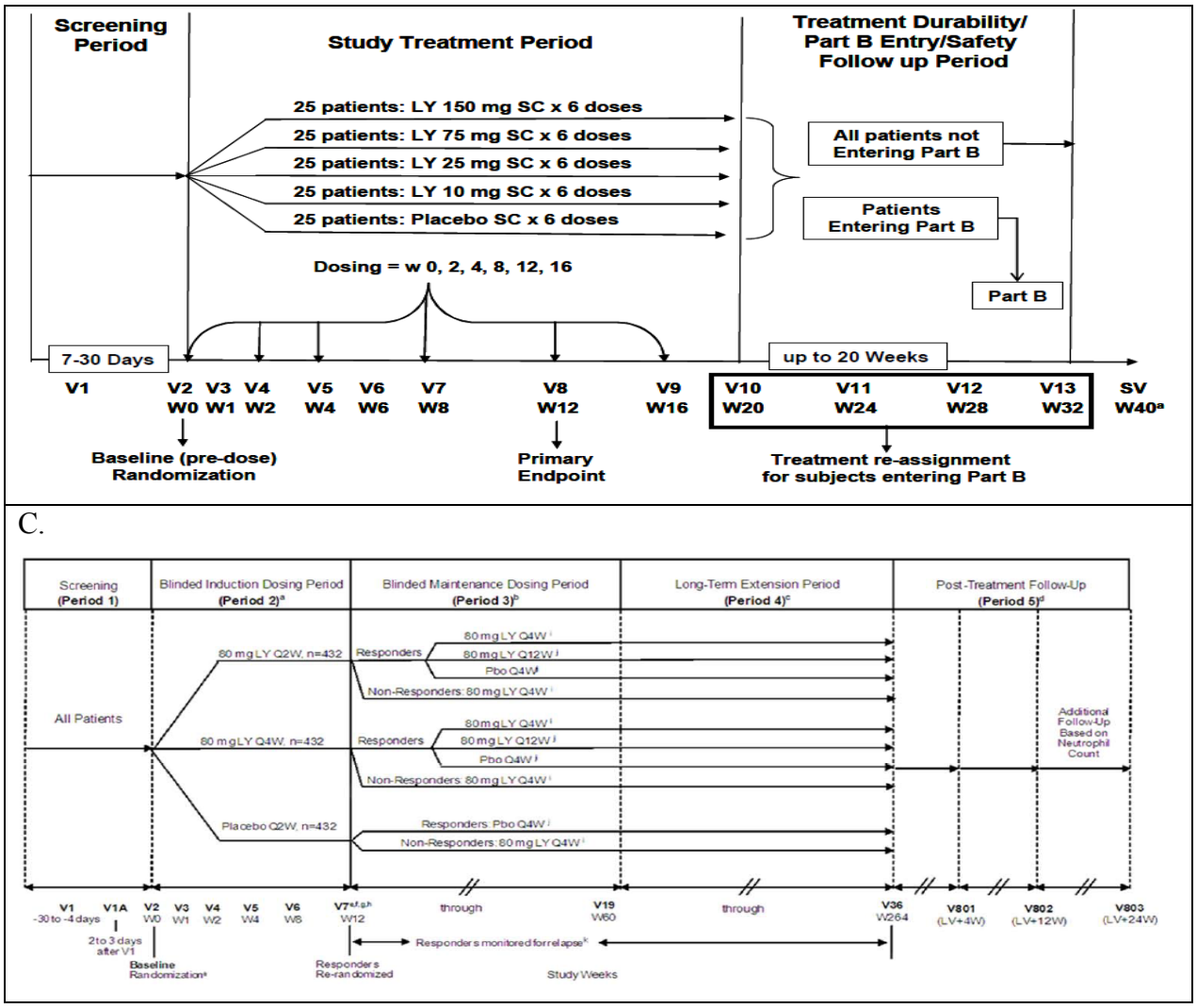


Figure 3: Overview of study designs for the phase 1 Study RHAG (A), phase 2 study RHAJ (B) and the phase 3 study RHAZ in psoriasis patients. (*Source: Applicant's Population PK report, Figure 7.1-7.3, Page 25-27)*

Table 3: Pharmacokinetic datasets

Study	Total Number of PK Samples	Total BQL PK[a]	Number of measurable PK data	BQL data included in PK analysis[b]	Total PK Samples included in PK analysis	Number of Patients included in analysis		Average Number of PK Samples per patient
RHAG	390	30	360	30	390	37		10.5
RHAJ	761	104	657	62	714	115		6.21
RHAZ (Induction Dosing Period)	1993	110	1297	23	1320	823	1247[c]	1.60
RHAZ (Maintenance Dosing Period)	3758	200	3453	183	3635	1208		3.01
RHAZ (Long Term Extension Period)[d]	259	15	234	0	0	0		0
Overall	7161[e]	459	6001	298	6059	1399		4.33

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

Source: Applicant's Population PK Report, Table 8.1, Page 54

Overall, ixekizumab was administered subcutaneously (SC) over 5-160 mg and intravenously (IV) at 15 mg. The PK sampling consisted of both rich and sparse sampling: rich sampling in study RHAG with samples up to 14 days after the first dose and up to 12 weeks after the last (third) dose, sparse sampling with up to 4 samples per patient (majority trough samples) in study RHAJ and RHAZ.

Immunogenicity data about anti-drug antibody (ADA) status (positive/negative), ADA titer and presence of neutralizing antibodies is incorporated in the population PK analyses. The sampling scheme for immunogenicity assessment is described in **Table 4**.

Table 4: Datasets for immunogenicity assessment relevant to popPK analysis

	RHAZ		RHAJ	
Sample Number	Visit	Time in Weeks (days +/- deviation window in days)	Visit	Time in Weeks (days +/- deviation window in days)
1	2	W0	2	W0 (0 +/- 0 days)
2	5	W4 (28 +/- 2 days)	9	W16 (112 +/- 5 days)
3	7	W12 (84 +/- 4 days)	13	W32 (224 +/- 5 days)
4	10	W24 (168 +/- 7 days)	n/a	n/a
5	13	W36 (252 +/- 7 days)	n/a	n/a
6	16	W48 (336 +/- 7 days)	n/a	n/a
7	19	W60 (420 +/- 7 days)	n/a	n/a

Abbreviations: n/a = not applicable; W = week.

Source: Applicant's Population PK Report, Table 7.3, Page 32

3.2.1.2 Dose/Exposure-Response Analysis

Exposure-Efficacy analysis

Efficacy data at week 12 (end of induction period) and week 60 (end of maintenance period) based on sPGA and PASI scales was utilized for exposure-efficacy analyses. The dataset for exposure-efficacy analysis consisted of efficacy endpoints from study RHAJ and study RHAZ. PopPK model predicted individual estimates of C_{trough} at the time of efficacy assessment were correlated to the efficacy outcomes (responder/non-responder for sPGA and PASI scale based criteria) using logistic regression/ ordered categorical response models. For the Week 12 and Week 60 endpoints, missing efficacy categorical data were imputed using the non-responder imputation (NRI) method, i.e. patients who did not meet the clinical response criteria or had missing clinical response data at the analysis time point were considered as non-responders.

A time-course model was also developed by the Applicant for the sPGA scores. For this time course model, missing sPGA data were treated as missing and no imputation was carried out. Overall, the dataset for this time-course analysis contained sPGA data from baseline until week 32 for study RHAJ, and baseline until week 60 for study RHAZ.

Logistic regression/ordered categorical response model for sPGA

Briefly, the logistic regression/ordered categorical response model for sPGA was developed 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. The model equations for Logit are as follows:

$$LOGIT = \theta_1$$

$$L = \frac{e^{LOGIT}}{1 + e^{LOGIT}}$$

Where, θ_1 represents the estimated value of the logit parameter for a particular sPGA responder status (0, 1 or >1) and *L* is the likelihood of a patient achieving that status. Since there were 3 possible categories (0, 1, or >1), the logits were calculated as follows:

$B_1=\theta_1$

$B_2= \theta_2$

$LGE_1=B_1 - DRUG$

$LGE_2= B_1-B_2 -DRUG$

Where, LGE_n is the logit parameter and DRUG is the drug effect incorporated as an E_{max} model as shown below:

$$DRUG = \frac{EMAX \times CONC}{EC50 + CONC}$$

Where, EMAX is the maximum effect of the drug, CONC is C_{trough} concentration, and EC50 is the drug concentration that results in half of the maximum effect. LGE_1 and LGE_2 would then be used to calculate the probability of a particular status as shown below:

$$Like_n = \frac{e^{LGE_n}}{1 + e^{LGE_n}}$$

where $Like_n$ is the likelihood of having greater than or equal to state n for responder status. The probability of a sPGA response was then calculated as follows:

$$P_0 = Like_2 \quad ; non - responder, sPGA > 1$$

$$P_1 = Like_1 - Like_2 \quad ; responder, sPGA = 1$$

$$P_2 = 1 - Like_1 \quad ; responder, sPGA = 0$$

Where P_0, P_1, and P_2 are the probabilities of sPGA>1, =1 or =0 respectively. The base model was first developed without the drug effect included. Inclusion of the drug effect was then tested on the base model.

Logistic regression model for PASI

Briefly, the percent improvement in PASI scores from baseline was calculated as:

$$\text{Percent improvement from baseline} = \frac{\text{Baseline PASI} - \text{Observed PASI}}{\text{Baseline PASI}} \times 100$$

PASI 75 response was defined to be equal to 1 (responder) for percent improvement from baseline in PASI scores of ≥75% and equal to 0 (non-responder) for <75% improvement (categorical variable). Similarly, PASI 90 and PASI 100 response are equal to 1 (responder) for patients with improvements of ≥90% and 100% from baseline in PASI score respectively.

Reviewer's comments:

The individual specific sPGA(0,1) and percent improvement PASI scores from baseline were used in reviewer's analysis to quantify sPGA(0), sPGA(0,1) and PASI 50, PASI 75, PASI 90, and PASI 100 responses across different body weight subgroups ixekizumab treatment and placebo based on pooled data from three phase 3 studies (RHAZ, RHBA, RHBC) as shown in ***Table 1****.*

Exposure-Safety analysis

The Applicant also carried out the exposure-safety analyses for adverse events of interest such as injection site reactions, infections, staphylococcal infections, Candida infections, hypersensitivity reactions, Crohn's Disease, and major adverse cerebro-cardiovascular events (MACE). The dataset for exposure-safety analysis consisted of safety events from study RHAZ alone. PopPK model predicted individual estimates of C_{trough} at week 12 (n=797) and week 60 (n=904) were correlated to the incidences of these adverse events and the relationship was visualized using adverse events summarized by quartiles of trough concentrations. The analysis was done for both the induction and the maintenance period. Placebo patients were included in the induction period analysis (n=431) for comparison with ixekizumab treatment arms.

Further, after the completion of three phase 3 studies, the Applicant also conducted similar analysis for exposure-safety using observed trough concentrations of ixekizumab in both induction and maintenance dosing period by pooling the data from the three phase 3 studies (RHAZ, RHBA and RHBC).

3.2.2 Results

3.2.2.1 Population PK analyses

The presence of IV data from Study RHAG in the popPK dataset enabled exploration of models in which SC bioavailability (F) was estimated across the different studies. Different formulations were used in each of the 3 studies incorporated in popPK analysis including a low

dose [redacted] formulation (RHAG), a high dose [redacted] formulation (RHAJ), and the proposed solution formulation for commercialization (RHAZ). Therefore different F estimates were explored for each study, and were incorporated into the model using a logit function as shown below:

$$TVPHI = LOG\left[\frac{TVBIO_i}{1 - TVBIO_i}\right]$$

$$F = \frac{e^{TVPHI}}{1 + e^{TVPHI}}$$

Where, TVPHI is the logit equivalent of F, LOG is the natural logarithm, $TVBIO_i$ is a study specific biovailability, and F is the bioavailability after back-transforming the logit function.

Due to the potential impact of immunogenicity on reducing exposure (to even BLQ levels in multiple instances), the Applicant incorporated the BQL data into the final popPK analysis using a previously published M3 method to reduce bias when handling BQL data. In this method, the likelihood that the predicted concentration was <7.5 ng/mL (LLOQ) was calculated when a concentration was BQL, and the likelihood that the predicted concentration was equal to the measured value was calculated when concentration value was ≥7.5 ng/mL.

The final Pop-PK model consisted of a two-compartment distribution model with first-order absorption and linear elimination. Final parameter estimates for the population PK model are summarized in **Table 5**. The point estimates in the table represent typical values for a patient with 90 kg bodyweight and no ADA/neutralizing antibody. The goodness of fit (Observed vs individual predicted concentrations etc.) plots are provided in **Figure 4**. The Applicant conducted a visual predictive check (VPC) to assess the general predictability of the model. VPC results for each study are shown in **Figure 5** and seem to suggest general concordance of model predictions with the observed data.

Covariate Effects

Body weight was a significant covariate on apparent clearance and volume parameters and its effect was modeled using an allometric relationship. There was an overall trend of lower serum C_{trough} with increasing bodyweight. The Applicant contended that dose adjustment based on bodyweight is not warranted, since due to random PK variability, there is a large degree of overlap in exposures when patients were stratified either by body weight category (<100 kg and ≥100 kg), or by the lower and upper ends of the weight range studied (that is, 59 kg or 136 kg).

Study and site of administration were found to be significant covariates on bioavailability and were included in the final model. Typical value of SC bioavailability was 75% for thigh administration and 60% for other sites of administration for study RHAG and RHAJ; these values increased to 90% for thigh administration and 81% for other sites of administration for phase 3 study RHAZ. The Applicant contended that since the phase 3 formulation is the same as the commercial formulation, the model estimated difference in bioavailability between the studies does not impact the commercial dose or dose recommendation.

None of the other covariates tested were significant, e.g., age, sex, race/ethnicity, CRCL, baseline disease severity, baseline C-reactive protein, common comorbidities etc. None of the co-medications typically taken by ≥10% of patients with psoriasis such as HMG Co-A Reductase inhibitors, ACE inhibitors, and NSAIDs were significant covariates on PK parameters.

Steady State Ctrough for two dosing regimens used in Phase 3 Studies

Steady state was achieved by Week 8 with the 80 mg Q2W dosing regimen with >80% of steady-state already achieved with the 160 mg starting dose. At steady state, the predicted mean (SD) $C_{max,ss}$, and $C_{trough,ss}$ were 21.5 (9.16) µg/mL, and 5.23 (3.19) µg/mL for the 80 mg Q2W dosing regimen and 14.6 (6.04) µg/mL, and 1.87 (1.30) µg/mL for the 80 mg Q4W dosing regimen, respectively.

The final PK model was used to predict the estimated C_{trough} at Week 12 (Study RHAJ and RHAZ) and Week 60 (Study RHAZ only) for each patient for subsequent utilization in exposure-response analyses.

Table 5: Pharmacokinetic and covariate parameter estimates of the final model

Parameter Description	Population Estimate (%RSE[a])	Inter-Individual Variability % (%RSE[a])
Clearance (CL) (L/h)	0.0156 (1.6)[b]	30 (5.8)
Inter-compartmental Clearance, Q (L/h)	0.0332 (4.5)[c]	15 (Fixed)[d]
Weight effect on CL and Q (allometric scaling)	1.05 (4.1)	
ADA titer on CL (fractional increase)	0.0354 (11)[b]	
Neutralizing antibodies on CL (fractional increase)	7.09 (12)[b]	
Central Volume of Distribution, V2 (L)	2.59 (15)[e]	84 (27)
Peripheral Volume of Distribution, V3 (L)	4.32 (4.4)[e]	15 (Fixed)[d]
Weight effect on V2 and V3 (allometric scaling)	0.734 (7.2)[e]	
Bioavailability (F) for RHAG and RHAJ	0.60 (Fixed)[f]	54 (Fixed)[f]
Bioavailability (F) for RHAZ	0.81 (Fixed)[f]	54 (Fixed)[f]
Increase in F for thigh injection site	0.705 (23)[g]	
First order absorption rate constant, Ka (h^{-1})	0.00994 (4.7)	15 (Fixed)[d]
Residual Error		
Proportional (%)	32(1.2)	

Abbreviations: ADA = anti-drug antibodies; Q = intercompartmental clearance.

[a] RSE, relative standard error

[b] $CLind = CL*(bodyweight/90)^{1.05}*(1+0.035*LOG(ADA\ titer))*(1+7.09*NAb)$, where NAb is 0 or 1

[c] $Qind = Q * (bodyweight/90)^{1.05}$

[d] Variability fixed to 15% to optimize efficiency of SAEM algorithm (NONMEM 7.3.0 user guide)

[e] $V2,ind = V2 * (bodyweight/90)^{0.73}$, $V3,ind = V3 * (bodyweight/90)^{0.73}$

[f] Estimate fixed to that from FOCE model where BQL data were not included (Appendix 8)

[g] Estimate is on the logit parameter for bioavailability. This translates to an increase in bioavailability for the thigh injection site from 0.60 to 0.75 for RHAG/J and an increase from 0.81 to 0.90 for RHAZ.

Source: Applicant's Population PK report, Table 8.5, Page 63

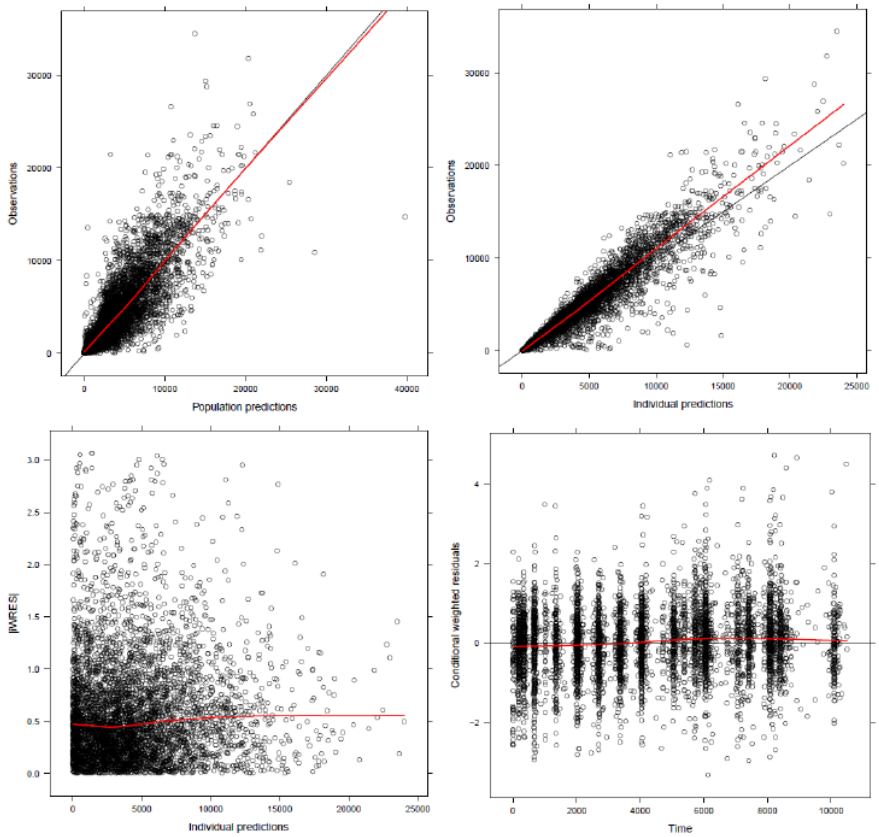


Figure 4: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model (*Source: Applicant's Population PK report, Figure APP.4.2, Page 218)*

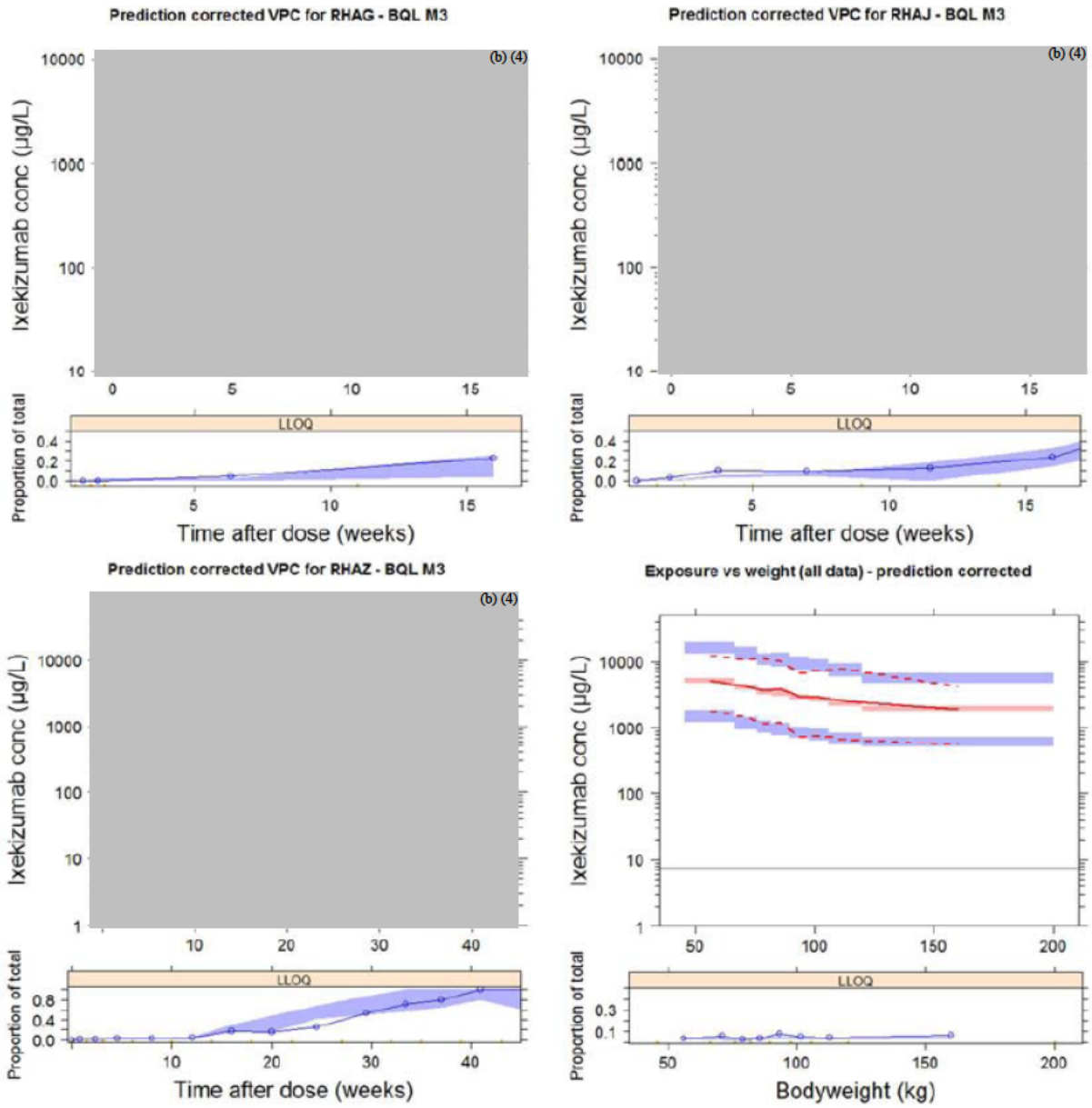


Figure 5: Visual predictive check for all three studies utilized in popPK model development. Upper panel: The blue dots are observations. The solid red line depicts median observed data, while pink shaded area depicts 95% confidence interval around the median of the simulated data. The dashed lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same. Lower panel: The open circles represent the proportion of observed data that was below the limit of quantification. The blue shaded area is the model predicted 95% confidence interval for the proportion of simulated data below 7.5 µg/L. The points for the last VPC (exposure vs weight) have been omitted from the plot because their density overshadowed the percentiles. (*Source: Applicant's Population PK report, Figure 8.3, Page 65)*

Reviewer's comments:

1. *The sponsor's Pop-PK model provides reasonable description of ixekizumab concentrations for individual predictions (observed vs. individual predicted concentrations*

*in **Figure 4**). Visual inspection shows that the model reasonably predicts individual data over a range of concentrations in the studies involved. There appears to be some under-estimation at higher observed concentrations for a limited number of observations.*

2. *Body weight was a significant covariate on clearance. However, with the choice of 80 mg Q2W induction dosing regimen, the efficacy response has approached the plateau of the exposure-response curve for the Week 12 efficacy data. Thus, the incremental benefit with body weight-based dosing or a higher dose for patients with a higher body weight may be limited. Hence, the proposed dosing regimen regardless of body weight is acceptable.*
3. *The details about the effect of intrinsic factors (bodyweight, age, sex, race/ethnicity) on clearance have been described in Section 2.5 and the impact of body weight on safety/efficacy responses has been described in Section 1.3.2 and Section 2.3.2 of Clinical Pharmacology Review.*

3.2.2.2 Dose/Exposure-Response Analysis

Exposure-Efficacy Results

The results of Applicant's analysis of exposure-efficacy relationship have been discussed in detail in Section 2.3.1 of Clinical Pharmacology Review (see Figure 2.3.1.b and Table 2.3.1.b).

Exposure-Safety Results

The results of Applicant's analysis of exposure-safety relationship with the pooled data from three phase 3 studies (RHAZ, RHBA and RHBC) have been discussed in detail in Section 2.3.3 of Clinical Pharmacology Review (see Table 2.3.3.e and Table 2.3.3.f).

4 LISTING OF ANALYSES DATASETS, CODES AND OUTPUT FILES

Table 6: Analysis Data Sets

Study Number	Name	Link to EDR
Population PK: NONMEM control stream PopPK input file	 rhagjz-pk-final-model-bql-fix-mod.txt rhagjz_nm_pk_nov2014_bql.xpt	(b) (4)
Integrated Summary: Subject level data AE dataset sPGA endpoints PASI endpoints	 adslp.xpt adaep.xpt adqspgap.xpt adqpacei.xpt & adqpadpt.xpt	
Integrated Immunogenicity data	rhaz_ba_bc_dv_ig_dataset_06mar15_v2.xpt	
E-R datasets: Exposure-safety Exposure-efficacy	 ixe_meta_ae_dataset.xpt ixe_meta_pk_pasi_w12.	

	xpt ixe_meta_pk_pasi_w60.xpt ixe_meta_pk_spga_w12.xpt ixe_meta_pk_spga_w60.xpt	

Table 7: Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ixekizumab_BLA125521_DDM\
rhagjz-pk-final-model-bql-fix2.mod rhagjz_nm_pk_nov2014_bql.csv patab3_fix.txt	Population PK control stream Population PK input file with dosing records and covariates Output PK parameters file	PK\files\ nmfe_rhagjz-pk-final-model-bql-fix2_003\
Ixekizumab_PK_Analysis.sas	Analysis of clearance vs. intrinsic factors	PK\
ixekizumab_Eff_Safety_DR.sas	Benefit-risk assessment with sPGA and PASI score based efficacy endpoints and incidence of infections across placebo and treatment arms	ER_Analyses\codes\
macro_Universal.sas	SAS macro for data import and data manipulation	ER_Analyses\codes\
ixekizumab_antibody_eff.sas	Efficacy categorized by immunogenicity and correlation analysis for prediction of responders based on efficacy at early time points	ER_Analyses\codes\

CLINICAL PHARMACOLOGY INDIVIDUAL STUDY SUMMARY

BLA:	STN 125,521
Submission Type:	Original BLA (New Molecular Entity)
Brand Name:	TALTZ®
Drug Name:	Ixekizumab (LY2439821)
Submission Date:	03/23/2015
PDUFA Goal Date:	03/23/2016
Priority:	Standard
Proposed Indication:	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Applicant:	Eli Lilly and Company
Clinical Pharmacology Reviewer:	Jie Wang, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	CDER/ODEIII/DDDP

This document provides individual study summaries as a supporting material to the Clinical Pharmacology Review. Refer to the Clinical Pharmacology Review for the regulatory recommendations from a Clinical Pharmacology standpoint.

1. STUDY 440001024 (IN VITRO STUDY: MODULATION OF CYP450 ISOFORMS BY IL-17A IN CULTURED HUMAN HEPATOCYTES)

The Applicant conducted Study 440001024 to evaluate whether IL-17A could induce or inhibit CYP450 enzymes in cultured human hepatocytes *in vitro*.

Study methods

Hepatocytes cultures and treatment with IL-6 and IL-17A

Three lots (Lots 228, 307 and 321) of hepatocytes from three Caucasian human donors (two female and one male) were used in hepatocytes culture in 24-well collagen I-coated plates. The cultured human hepatocytes were incubated for a total of three days with IL-6 at concentrations of 1, 10, 100, 1000, 10,000, 100,000 pg/mL, with IL-17A at 1, 5, 10, 50, 100, 500, 1,000, 5,000, 10,000, 50,000 pg/mL, or with control vehicles, in triplicate. The medium was replaced daily with fresh medium containing the test article or control. IL-6 was used as a positive control in this study. Relative mRNA levels and enzyme activities for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2 (mRNA only), and CYP3A4 were assessed after 3 days of treatments.

CYP activity measurement

Enzyme activity for CYP isoforms was analyzed *in situ* using probe substrates and reaction conditions that are listed in Table 440001024.1. Briefly, cell cultures were washed with culture medium and then incubated with CYP450 probe substrates freshly prepared in culture medium. The reactions were then stopped and the resulting samples were placed on ice and stored at -20 ^{o}C or -80 ^{o}C prior to analysis. The activity of CYP isoforms was assessed by measuring the metabolite formation of the specific probe substrate for each enzyme using LC-MS/MS methods.

Table 440001024.1. CYP450 probe substrates and incubation conditions for measurement of CYP activity. (*Data source: Table 2, Study Report 440001024*).

P450 isoform measured	P450 Probe substrate	Substrate concentration	Reaction catalyzed	Incubation time (min)	Incubation volume (µL)
CYP1A2	Phenacetin	100 µM	O-Deethylation	60	200
CYP2B6	Bupropion	250 µM	Hydroxylation	30	200
CYP2C8	Amodiaquine	100 µM	N-Deethylation	30	200
CYP2C9	Diclofenac	100 µM	4'-Hydroxylation	30	200
CYP2C19	S-Mephenytoin	200 µM	4'-Hydroxylation	120	200
CYP2D6	Dextromethorphan	100 µM	O-Demethylation	60	200
CYP2E1	Chlorzoxazone	250 µM	6-Hydroxylation	120	200
CYP3A4	Testosterone	200 µM	6β-Hydroxylation	30	200

mRNA expression measurement

Briefly, hepatocyte monolayers were lysed and total RNA was isolated from the lysates followed by purification steps. The mRNA expression for CYP isoforms and the house keeping gene β-actin was determined using quantitative reverse transcription polymerase chain reaction (RT-PCR).

Results

Effect of IL-6 (positive control)

For the positive control, IL-6 decreased enzyme activity and/or mRNA expression for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in at least one donor (Lot) of hepatocyte

culture. IL-6 did not induce marked decreases in enzyme activity or mRNA expression for CYP2D6, CYP2E1 and CYP2J2. Table 440001024.2 summarizes the IL-6 effect on enzyme activity and mRNA expression at the highest IL-6 concentration of 100,000 pg/mL as an example illustrating the potential maximum effect at the experimental setting.

Table 440001024.2. Effect of IL-6 on enzyme activity and mRNA expression for different CYP isoforms at the highest IL-6 concentration (1×10^5 pg/mL). "↔" represents that no marked changes for enzyme activity or mRNA expression was observed. "↑" represents that a trend of up-regulation of enzyme activity or mRNA expression was observed; however, the effect was relatively small and not concentration dependent. *(Data source: Reviewer's summary based on information provided in Section 6.0 of Study Report 440001024)*

	Enzyme activity or mRNA expression (% of control)					
	Enzyme activity			mRNA expression		
	Lot 228	Lot 307	Lot 321	Lot 228	Lot 307	Lot 321
CYP3A4	7%	38%	15%	1%	9%	3%
CYP1A2	51%	70%	23%	57%	↔	43%
CYP2B6	34%	39%	20%	22%	57%	28%
CYP2C8	26%	25%	22%	60%	↔	21%
CYP2C9	53%	↔	↔	36%	↔	65%
CYP2C19	54%	↔	↔	53%	↔	48%
CYP2D6	↔	↔	↔	↑	↑	↑
CYP2E1	↑	↑	↑	↑	↑	↑
CYP2J2	↔	↔	↔	↔	↔	↔

Effect of IL-17A

IL-17A appeared to decrease CYP3A4 enzyme activity and mRNA expression at the highest IL-17A concentration (5×10^4 pg/mL) tested. No marked decreases in enzyme activity or mRNA expression for other CYP isoforms were observed (Table 440001024.3).

Table 440001024.3. Effect of IL-17A on enzyme activity and mRNA expression at the highest IL-17A concentration (50,000 pg/mL). "↔" represents that no marked changes for enzyme activity or mRNA expression was observed. "↓" represents that a trend of down-regulation of enzyme activity or mRNA expression was observed; however, the effect was relatively small and not concentration dependent. n/a, data not available. *(Data source: Reviewer's summary based on information provided in Section 6.0 of Study Report 440001024)*

	Enzyme activity or mRNA expression (% of control)					
	Enzyme activity			mRNA expression		
	Lot 228	Lot 307	Lot 321	Lot 228	Lot 307	Lot 321
CYP3A4	80%	79%	70%	35%	65%	↔
CYP1A2	↔	↔	↔	↔	↔	↔
CYP2B6	↔	↔	↔	↔	↔	↔
CYP2C8	↔	↔	↔	↓	↓	↓
CYP2C9	↔	↔	↔	↓	↓	↓
CYP2C19	↔	↔	↔	↓	↓	↓
CYP2D6	↔	↔	↔	↓	↓	↓
CYP2E1	↔	n/a	↔	↔	↔	↔
CYP2J2	n/a	n/a	n/a	↔	↔	↔

2. STUDY LY2439821-2013IV-EXPLOR (IN VITRO STUDY: MODULATION OF CYP450 ISOFORMS BY IL-17A USING HEPATOPAC™)

In an exploratory study, the Applicant evaluated the effect of IL-17A on CYP450 mRNA expression using HepatoPac 3-dimensional cryopreserved hepatocytes in the absence or presence of Kupffer cells co-culture. The results indicated that IL-17A (100 to 100,000 pg/mL) did not result in concentration-dependent reduction in mRNA expression for any of the CYPs evaluated (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5). Detailed study methodologies and results are not further described in this individual study summary.

Reviewer's comments: *There is a potential for psoriasis disease-drug-drug interaction (disease-DDI) based on the current understanding that psoriasis patients have elevated proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon disease improvement following biological treatment [1,2].*

Although the current results from studies "440001024" and "LY2439821-2013IV-Explor" showed that IL-17A induced no or minimal changes in enzyme activities or mRNA expression for majority CYPs in vitro, ixekizumab can have the pharmacodynamic effects of modulating expression levels of other cytokines indirectly through the improvement of disease conditions. Recent studies have also indicated that in vitro or animal studies have limited value in the qualitative and quantitative projection of clinical interactions[3]. As such, a clinical study in the target patient population would be more appropriate for elucidating the effect of ixekizumab treatment on CYP enzyme activity/expression.

Therefore, we continue to recommend that the Applicant conducts a clinical trial to determine the potential for ixekizumab to alter the metabolism of CYP substrates in psoriasis patients. See Clinical Pharmacology Review for additional information.

3. STUDY RHAG (PHASE 1)

Title

- LY2439821 (anti-IL-17 humanized antibody) multiple-dose safety and tolerability study in subjects with psoriasis vulgaris

Study period

- 03 September 2008 (the first subject enrolled) to 20 April 2010 (the last subject completed)

Objectives

The primary objective of this study was to assess the safety and tolerability of multiple doses of LY2439821 compared to placebo in subjects with psoriasis. The secondary objectives of the study included the evaluation of the serum pharmacokinetics and the absolute bioavailability of LY2439821 in subjects with psoriasis.

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[1] *Wang et al.* Biological products for the treatment of psoriasis: therapeutic targets, pharmacodynamics and disease-drug-drug interaction implications. *The AAPS Journal*, 2014, 16(5): 938-947

[2] *Huang et al.* Therapeutic protein-drug interactions and implications for drug development. *Clin Pharmacol Ther*, 2010, 87(4):497-503

[3] Drug interaction studies-study design, data analysis, implications for dosing and labeling recommendations. *FDA Guidance for industry (Draft guidance)*, February 2012

Study design

Study RHAG was a Phase 1, multicenter, randomized, subject- and investigator-blinded, and placebo-controlled dose escalation study. Three doses of LY2439821 were administered at Weeks 0, 2, and 4. A total of 46 subjects were randomized in to 4 subcutaneous (SC) injection groups, 1 intravenous (IV) infusion group, and 1 placebo group, as following:

- Placebo (n=9)
- 5 mg SC q2w×3 (n=8)
- 15 mg SC q2w×3 (n=8)
- 50 mg SC q2w×3 (n=8)
- 150 mg SC q2w×3 (n=8)
- 15 mg IV q2w×3 (n=5)

Study products and dose administration

Ixekizumab for injection was supplied as a [redacted] (b) (4) powder in glass vials (20 mg/vial).

SC dose for 5 mg or 15 mg was administered as 1 SC injection. SC dose for 50 mg was administered as 2 SC injections (25 mg each). SC dose for 150 mg was administered as 4 SC injections (37.5 mg each). IV dose for 15 mg was administered as IV infusion over 60 minutes.

PK and immunogenicity blood sample collection

PK samples were collected at Week 0 (0, 1, 3, 9, 48, 96 hr), Week 1 (Days 8 and 11), Week 2 (pre-dose, Day 15), Week 4 (pre-dose, Day 29), Week 6 (Day 43), and Week 16 (Day 113).

Immunogenicity samples were collected at baseline, Days 43 and 113.

PK results

The non-compartmental PK parameters following the first dose administration of LY2439821 by treatment groups are presented in in Table RHAG.1. The mean concentration-time profiles by treatment groups are shown in Figure RHAG.1. The Cmax and $AUC_{(0\text{-}14days)}$ showed an approximate dose proportionality across SC dose levels from 5 mg to 150 mg. The estimated absolute SC bioavailability of LY2439821 was 54%.

Table RHAG.1. LY2439821 non-compartmental pharmacokinetic parameters following the first dose administration in subjects with psoriasis in Study RHAG. PK parameters for Cmax and AUC are presented as geometric mean with CV%. $AUC_{(0\text{-}14days)}$ is the area under the concentration versus time curve from time zero to Day 14. For $AUC_{(0\text{-}tlast)}$, t is the last time point with a measurable concentration in the first dosing interval. *(Data source: Table RGAG.7.1, I1F-MC-RHAG Clinical Pharmacology Study Report)*

	SC				IV
	5 mg (N=8)	15 mg (N=8)	50 mg (N=8)	150 mg (N=8)	15 mg (N=5)
Cmax (mcg/mL)	0.336 (44%)	0.612 (48%)	3.000 (67%)	8.190 (39%)	3.640 (24%)
$AUC_{(0\text{-}14days)}$ (day*mcg/mL)	3.66 (40%)	6.75 (52%)	32.8 (70%)	95.1 (39%)	21.4 (25%)
$AUC_{(0\text{-}tlast)}$ (day*mcg/mL)	3.72 (41%)	7.01 (49%)	34.0 (70%)	101 (41%)	21.2 (29%)

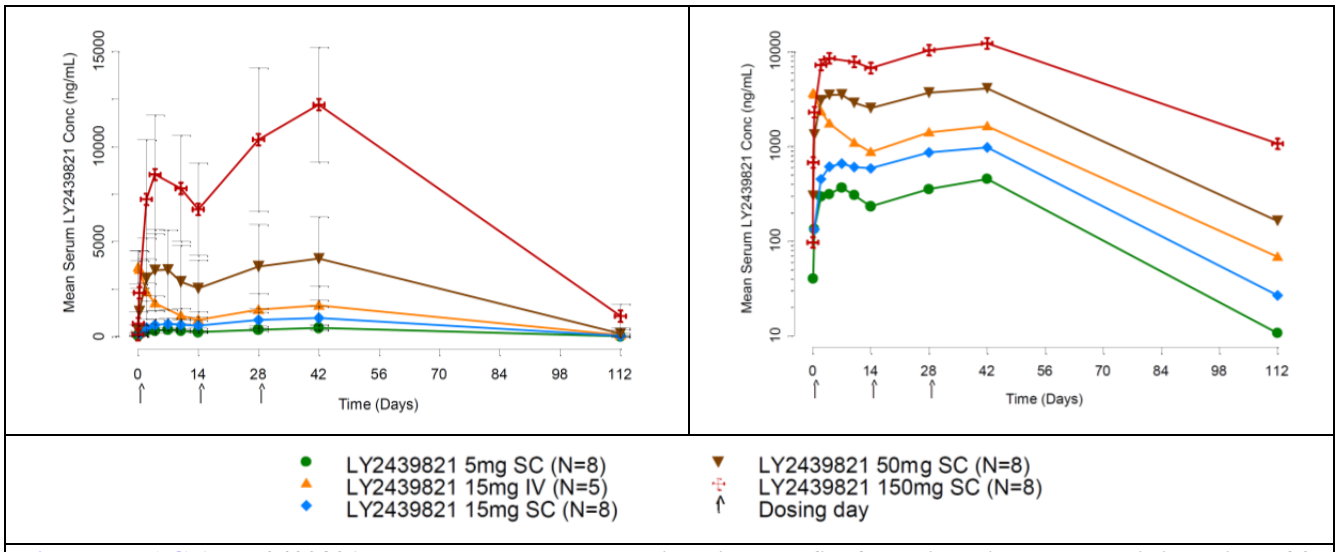

Figure RHAG.1. LY2439821 mean plasma concentration-time profile following biweekly administration of 3 doses of LY2439821 in subjects with psoriasis in Study RHAG. Left panel: linear scale; Right panel: log scale. *(Data source: Figure RGAG.7.1, I1F-MC-RHAG Clinical Pharmacology Study Report)*

Immunogenicity results

The incidence of anti-drug antibodies (ADA) for all evaluable ixekizumab-treated subjects through Week 16 was 58% (21/37). The incidence of treatment-emergent anti-drug antibodies (TE-ADA+) was not provided in the study report.

Table RHAG.2. The incidence of anti-drug antibodies (ADA) by treatment groups in study RHAG. N represents number of evaluable subjects within each treatment group; n represents number of subjects with at least one positive result. (*Data source: Table RHAG.8.3*)

	Placebo (N=9)	Ixekizumab					
		5 mg SC (N=8)	15 mg SC (N=8)	50 mg SC (N=8)	150 mg SC (N=8)	15 mg IV (N=5)	IXE combined (N=37)
ADA+ (n)%	2 (22%)	5 (63%)	6 (75%)	5 (63%)	3 (38%)	2 (40%)	21 (58%)

4. STUDY RHAJ (PHASE 2)

Title

- A dose-ranging and efficacy study of LY2439821 (an anti-IL-17 antibody) in patients with moderate-to-severe Psoriasis

Study period

- 29 April 2010 (the first subject enrolled) to 24 June 2011 (the last subject completed in Part A); Part B of the study ongoing

Objectives

The primary objective was to test the hypothesis that at least one LY2439821 (ixekizumab) treatment group was superior to placebo in the proportion of adult patients with moderate-to-severe chronic

plaque psoriasis who achieved a 75% improvement from baseline to Week 12 in the Psoriasis Area and Severity Index (PASI 75), and to estimate the percentage PASI improvement by treatment using regression techniques.

Study design and methods

Study RHAJ (a Phase 2 study) has 2 parts: Part A was a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging design, and Part B is an optional extension period with an open-label design (Figure RHAJ.1). Part A of the study has been completed and Part B of the study is currently on ongoing.

In Part A, 142 subjects were randomized to 1 of 4 ixekizumab dose groups or to placebo (27 to 30 patients per group). These patients received SC injections of ixekizumab (0 [placebo], 10, 25, 75, or 150 mg) at 0, 2, 4, 8, 12, and 16 weeks. Patients were evaluated at multiple visits for the primary endpoint (PASI 75).

In the currently ongoing Part B of the study, ixekizumab is administered at 80 mg q4w for up to 5 years (240 weeks) after implementation of the protocol amendment, before which ixekizumab was administered at 120 mg ixekizumab q4w.

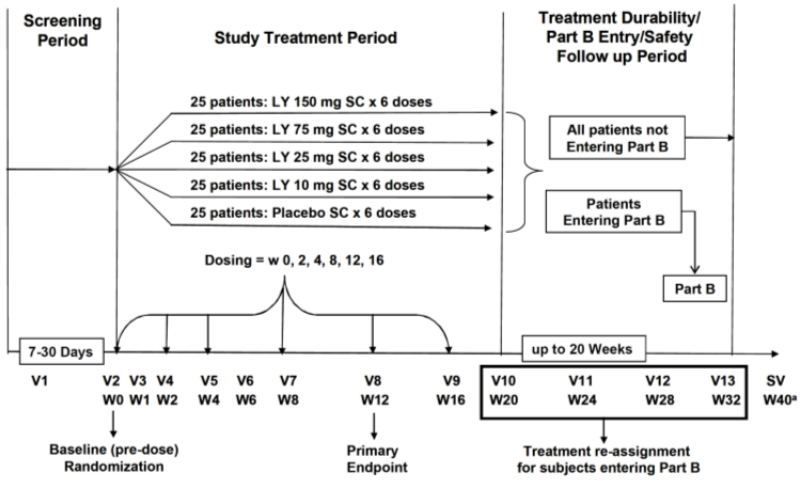

Figure RHAJ.1. Study design for study RHAJ.

Study products

Ixekizumab for injection was supplied as a (b) (4) powder in glass vials (48 mg/vial).

PK and immunogenicity blood sample collection

Two PK sampling schemes were employed in stud RHAJ:

- Scheme 1: Day 7, Week 4 (pre-dose), Week 8 (pre-dose), Week 16 (predose), week 24 and Week 32
- Scheme 2: Week 2 (pre-dose), Week 6 (pre-dose), Week 12 (pre-dose), Week 16 (predose), Week 20 and Week 28

Immunogenicity samples were collected at Weeks 0, 16, and 32.

Efficacy results

The efficacy results demonstrated ixekizumab dose response for PASI 75 and PASI 90 across 10 mg, 25 mg, 75 mg, or 150 mg doses administered at Week 0, 2, 4, 8, 12 and 16 in the double blinded period A (Figure RHAJ.2). The Week 12 PASI 75 response rates (number of subject in each cohort) were 7.7% (n=26), 28.6% (n=28), 76.7% (n=30), 82.8% (n=29), and 82.1% (n=28) for the placebo, 10 mg, 25 mg, 75 mg, and 150 mg dosing regimens, respectively. The Week 12 PASI 90 response rates (number of subject in each cohort) were 0% (n=26), 17.9% (n=28), 50.0% (n=30), 58.6% (n=29), and 71.4% (n=28) for the placebo, 10 mg, 25 mg, 75 mg, and 150 mg dosing regimens, respectively.

Results of this study supported the doses selected for Phase 3 evaluation. In the pivotal Phase 3 studies (RHAZ, RHBA, RHBC) the selected induction dosing regimens (80 mg q4w and 80 mg q2w) were predicted to provide exposure comparable to the ixekizumab dose regimens in this Phase 2 study (75 mg and 150 mg dosing regimens, respectively). A 160-mg starting dose was included for earlier attainment of steady-state concentration. The maintenance dosing period in Phase 3 trials included a dosing regimen of 80 mg q12w to evaluate whether less frequent dosing would maintain clinical responses.

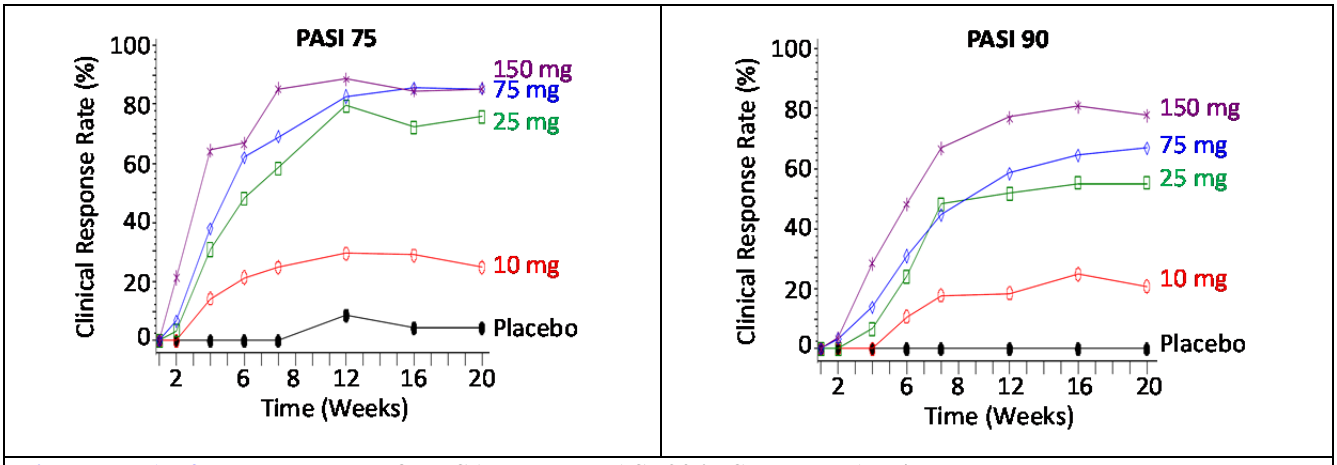

Figure RHAJ.2. Dose-response for PSAI 75 and PASI 90 in Study RHAJ. (*Data source: Figure RHAJ.11.1. and Figure RHAJ.11.3., I1F-MC-RHAJ CSR*)

PK results

The Applicant did not provide a descriptive PK summary in the study report. Refer to the Clinical Pharmacology Review for the population PK results.

Immunogenicity results

The incidence of treatment-emergent anti-drug antibodies (TE-ADA) for all evaluable ixekizumab-treated subjects through Week 16 was 33% (36/110). Patients administered lower doses of ixekizumab (10 mg and 25 mg) were observed to have higher incidences of TE-ADA than in those who received higher doses (75 to 150 mg).

Table RHAJ.1. The incidence of TE-ADA by treatment groups. N represents number of evaluable subjects within each treatment group. (*Data source: Table RHAJ.14.117, I1F-MC-RHAJ CSR*)

	Placebo (N=25)	Ixekizumab SC				
		10 mg (N=24)	25 mg (N=30)	75 mg (N=29)	150 mg (N=27)	IXE combined (N=110)
TE-ADA+ n(%)	1 (4%)	13 (54%)	12 (40%)	5 (17%)	6 (22%)	36 (33%)

5. STUDY RHBL (PHASE 3, PK COMPARABILITY)

Title

- Pharmacokinetic evaluations of ixekizumab following subcutaneous administration using prefilled syringe or auto-injector in patients with moderate-to-severe plaque psoriasis

Study period

- 12 March 2013 (the first subject enrolled) to 25 June 2014 (date of database lock)

Objectives

The primary objective of the study was to evaluate the effect of drug delivery device, either by prefilled syringe (PFS) or by auto-injector (AI), on the PK of ixekizumab after the administration of the starting dose (160 mg SC) in patients with moderate-to-severe plaque psoriasis.

Study design

Study RHBL was a Phase 3, multicenter, randomized, open-label, parallel-group, outpatient, 12-week study examining the effect of the drug delivery device (PFS or AI), the site of injection (arm, thigh, or abdomen), and body weight on the PK of ixekizumab in patients with moderate-to-severe plaque psoriasis (Figure RHBL.1 and Table 1). The study consisted of 4 periods:

- Screening Period
- Treatment Period: occurred from Week 0 to Week 12. A total of 204 patients were randomized at a 1:1 ratio to receive the 160 mg starting dose by PFS and by AI at Week 0. The primary evaluation of ixekizumab PK occurred from Week 0 to Week 2. Patients continued to receive ixekizumab 80 mg q2w treatment with their assigned drug delivery device till Week 12.
- Optional Safety Extension Period: occurred after Week 12 to Week 52 to evaluate long-term safety of ixekizumab. During the Optional Safety Extension Period, all patients were assigned to use a prefilled syringe and were allowed to switch their site of injection. The dosing regimen in the Optional Safety Extension Period was 80 mg every 4 weeks (Q4W)
- Post-Treatment Follow-Up Period

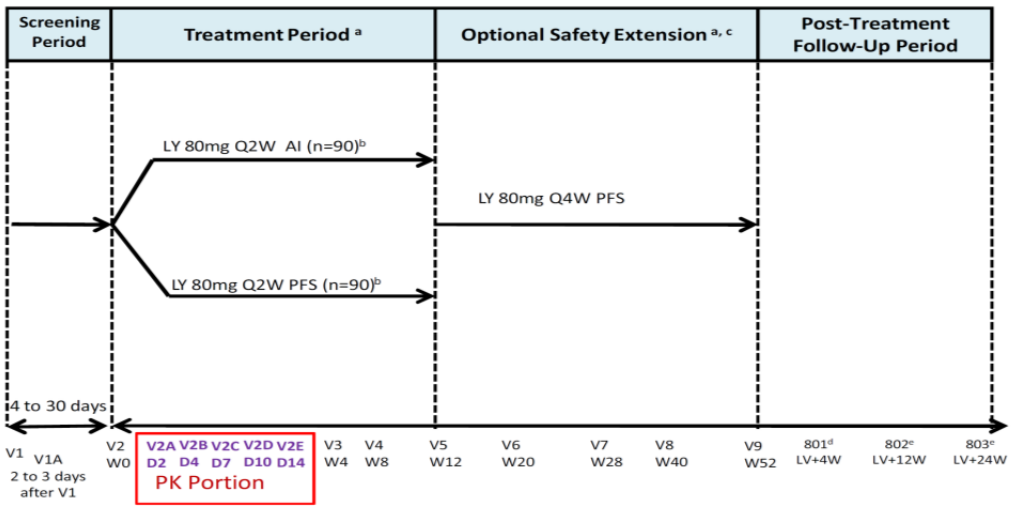

Figure RHBL.1. Study design.

Weight Category (Patients)	Assistance with Injection (Patients)[a,b]	Subcutaneous Injection Location	Delivery Device (Patients)	
Low <80 kg (60 patients[c])	Yes (20 patients)	Arm	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
	No (40 patients)	Abdomen	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
		Thigh	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
Medium 80 kg – 100 kg (60 patients)	Yes (20 patients)	Arm	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
	No (40 patients)	Abdomen	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
		Thigh	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
High >100 kg (60 patients)	Yes (20 patients)	Arm	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
	No (40 patients)	Abdomen	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)
		Thigh	Prefilled syringe	(10 patients)
			Auto-injector	(10 patients)

Table RHBL.1. Subject stratification and randomization chart.

PK and immunogenicity blood sample collection

Blood samples for PK measurement were collected at baseline, Days 2, 4, 7, 10, and 14 (pre-dose).

Blood samples for immunogenicity testing were collected at Weeks 0, 4, 12, 20, and 52.

PK results

PFS versus AI

Mean (±SD) ixekizumab serum concentration versus time profiles are presented in Figure RHBL.2 by ixekizumab delivery devices (i.e., PFS or AI). A summary of PK parameters are presented in Table RHBL.2. The PK profiles and PK parameters of ixekizumab were following administration of the starting dose (160 mg SC) by PFS and AI presentations. The geometric mean estimates for C_{max} were 15.0 mcg/mL and 14.8 mcg/mL and for AUC were 157 mcg*day/mL and 154 mcg*day/mL, for PFS and AI presentations, respectively. *Refer to the Clinical Pharmacology Review for the PK comparability analysis by the FDA reviewer*.

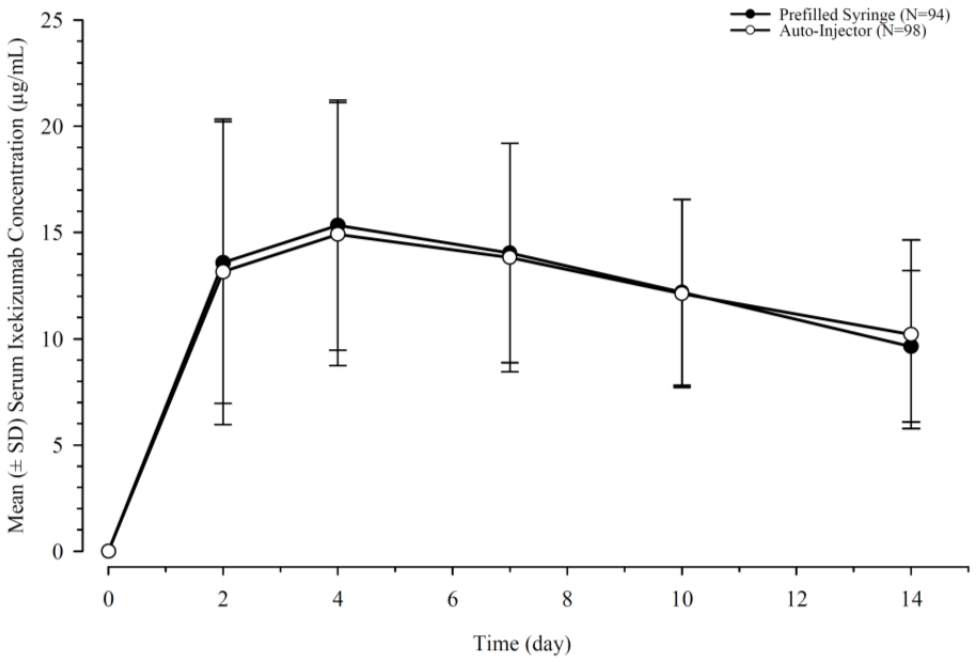

Figure. RHBL.2. Mean (±SD) serum ixekizumab concentrations versus time profiles following a 160-mg subcutaneous dose using either PFS or AI in patients with moderate-to-severe plaque psoriasis. *(Data source: Figure RHBL.11.2, I1F-MC-RHBL CSR)*

Table RHBL.2. Summary of ixekizumab PK parameters following a 160-mg SC dose using either PFS or AI. PK parameters are presented as geometric mean and 90% confidence interval. *(Data source: Table RHBL.11.3, I1F-MC-RHBL CSR)*

PK Parameters	PFS (N=94)	AI (N=98)
C_{max} (mcg/mL)	15.0 (13.9-16.1)	14.8 (13.8-15.9)
$AUC_{(0-t)}$ (mcg*day/mL)	157 (147-168)	154 (144-165)

Effect of body weight on ixekizumab PK

Body weight (BW) was categorized in 3 groups: Low (BW <80 kg), Medium (80 kg ≤BW≤ 100 kg), and High (BW >100 kg). Mean (±SD) ixekizumab serum concentration versus time profiles by body weight groups are presented in Figure RHBL.3. A summary of PK parameters are presented in Table RHBL.3. The PK results showed that ixekizumab exposure was lowest for High body weight category and highest for Low body weight category. Relative to the High body weight category, the mean AUC was 27% and 58% higher for the Medium and Low weight categories, respectively.

Table RHBL.3. Summary of ixekizumab PK parameters following a 160-mg SC dose stratified by body weight categories. PK parameters are presented as geometric mean and 90% confidence interval. *(Data source: Table RHBL.11.4, I1F-MC-RHBL CSR)*

PK Parameters	Body weight <80kg (N=68)	80 kg ≤Body weight≤ 100 kg (N=64)	Body weight >100 kg (N=60)
C_{max} (mcg/mL)	18.2 (16.9-19.5)	15.1 (13.8-16.5)	11.7 (10.8-12.7)
$AUC_{(0-t)}$ (mcg*day/mL)	193 (181-205)	155 (143-168)	122 (113-132)

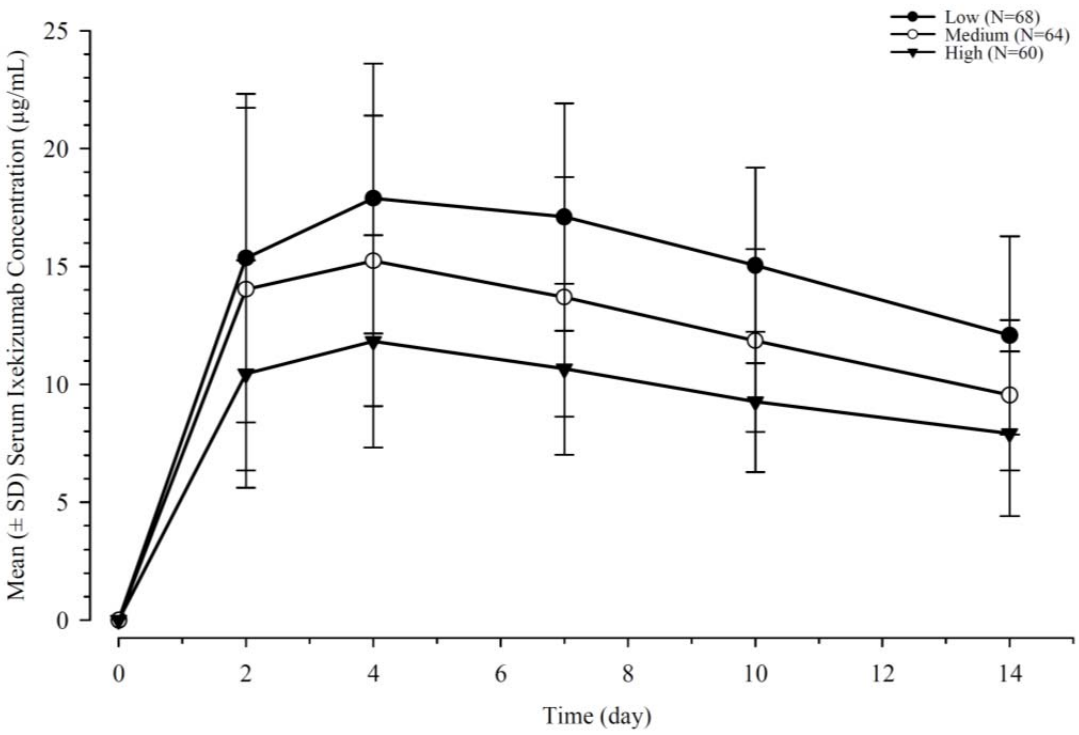

Figure. RHBL.3. Mean (±SD) serum ixekizumab concentrations versus time profiles following a 160-mg subcutaneous dose in patients with moderate-to-severe plaque psoriasis, stratified by body weight categories. *(Data source: Figure RHBL.11.5, I1F-MC-RHBL CSR)*

Effect of injection site on ixekizumab PK: PFS

Three sites for administration were evaluated in Study RHBL: arm, abdomen, and thigh. Mean (±SD) ixekizumab serum concentration versus time profiles by injection site using PFS are presented in Figure RHBL.4. A summary of PK parameters are presented in Table RHBL.4. The exposure was the highest when ixekizumab was administered in the thigh. The geometric mean AUC was 21% and 30% lower when ixekizumab was injected in the arm and abdomen, respectively, compared with the thigh injection.

Table RHBL.4. Summary of ixekizumab PK parameters following a 160-mg SC dose using PFS stratified by injection sites in study RHBL. PK parameters are presented as geometric mean and 90% confidence interval. *(Data source: Table RHBL.11.6, I1F-MC-RHBL CSR)*

PK Parameters	Arm (N=30)	Abdomen (N=34)	Thigh (N=28)
C_{max} (mcg/mL)	14.4 (12.4-16.8)	12.7 (11.3-14.2)	18.5 (17.0-20.1)
$AUC_{(0-t)}$ (mcg*day/mL)	151 (131-173)	135 (122-150)	190 (176-206)

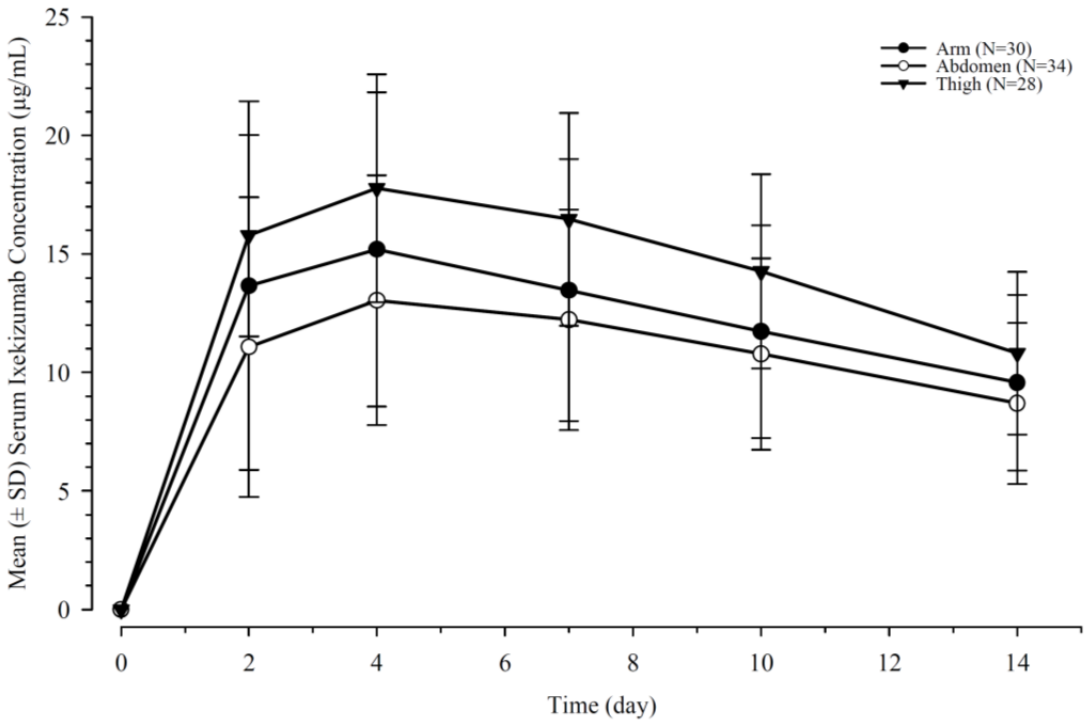

Figure. RHBL.4. Mean (±SD) serum ixekizumab concentrations versus time profiles following a 160-mg subcutaneous dose using PFS in patients with moderate-to-severe plaque psoriasis, stratified by injection sites. *(Data source: Figure RHBL.11.9, I1F-MC-RHBL CSR)*

Effect of injection site on ixekizumab PK: AI

A summary of PK parameters are presented in Table RHBL.5. Mean (±SD) ixekizumab serum concentration versus time profiles by injection site using AI are presented in Figure RHBL.5. The geometric mean $AUC_{(0-t)}$ was 30% and 11% lower when ixekizumab was injected via arm and abdomen, respectively, compared with when ixekizumab was injected via the thigh.

The collective PFS and AI data overall supported that ixekizumab exposure was higher when ixekizumab was administered in the thigh compared to other injection sites including arm and abdomen regardless of delivery device (Figure RHBL.6).

Table RHBL.5. Summary of ixekizumab PK parameters following a 160-mg SC dose using AI stratified by injection site in study RHBL. PK parameters are presented as geometric mean and 90% confidence interval. *(Data source: Table RHBL.11.6, CSR, I1F-MC-RHBL)*

PK Parameters	Arm (N=29)	Abdomen (N=32)	Thigh (N=37)
C_{max} (mcg/mL)	11.5 (10.1-13.0)	15.4 (13.5-17.5)	17.6 (16.0-19.4)
$AUC_{(0-t)}$ (mcg*day/mL)	124 (109-142)	159 (140-180)	178 (163-194)

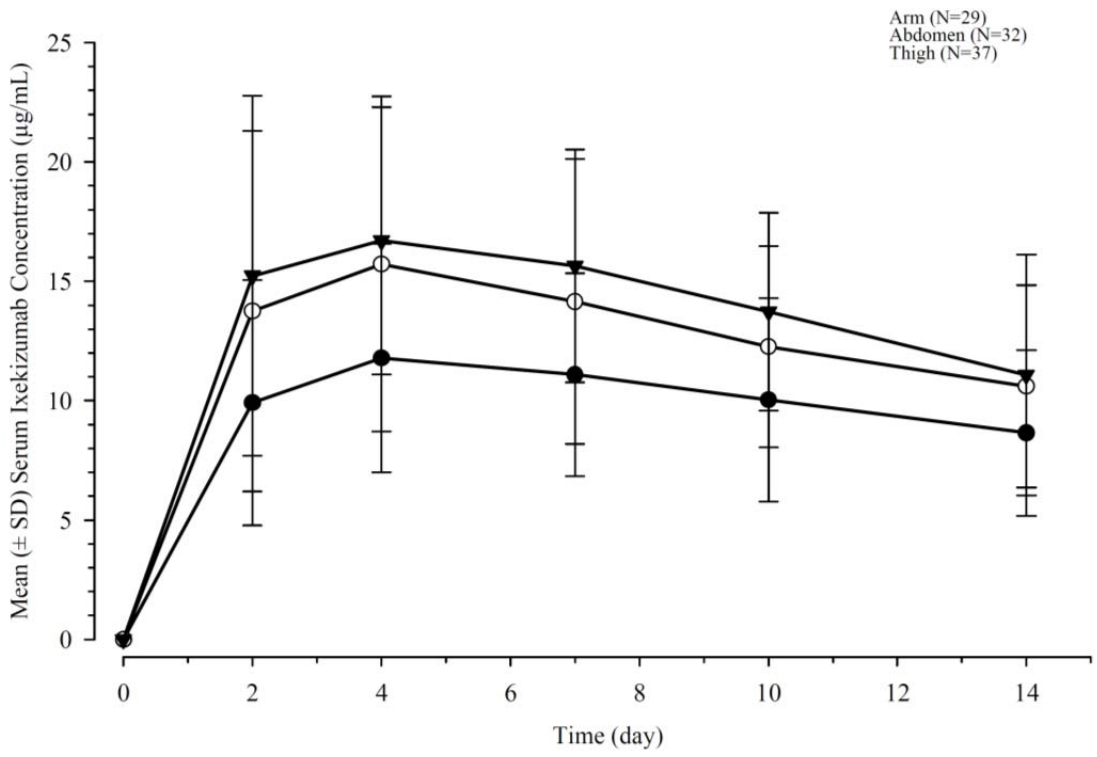

Figure. RHBL.5. Mean (±SD) serum ixekizumab concentrations versus time profiles following a 160-mg subcutaneous dose using AI in patients with moderate-to-severe plaque psoriasis, stratified by injection sites. *(Data source: Figure RHBL.11.12, I1F-MC-RHBL CSR)*

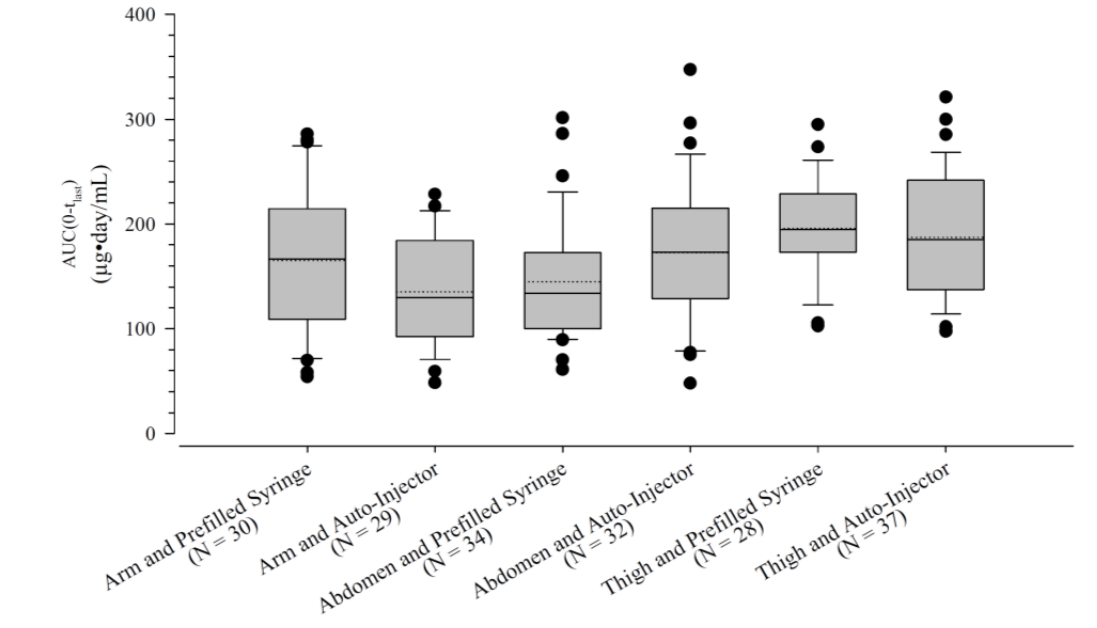

Figure. RHBL.6. Ixekizumab $AUC_{(0-t)}$ following a 160-mg subcutaneous dose in patients with moderate-to-severe plaque psoriasis, stratified by injection site and device type. *(Data source: Figure RHBL.11.16, I1F-MC-RHBL CSR)*

Efficacy results

Patients receiving ixekizumab treatment via PFS appeared to have numerically higher percentages of sPGA 0/1 (80% *versus* 74%) and PASI 75 (88% *versus* 78%) response compared to AI at Week 12 in Study RHBL (Table RHBL.6). Of note, mean PASI scores at baseline were higher in the PFS group (21.1 *versus* 17.8) than the AI group. The Applicant's *post-hoc* analyses on the percent improvement in PASI score adjusted for the baseline imbalances demonstrated no apparent differences between the device groups over the 12-week treatment period (Figure RHBL.6). PASI score change from baseline values corresponded to approximately 89% (PFS) and 87% (AI) improvements at Week 12.

Table RHBL.6. IGA 0/1 and PASI 75 response rates at Week 12 by delivery device. (*Data source: Tables RHBL.11.1, RHBL.11.9, and RHBL.11.10, I1F-MC-RHBL CSR*)

		PFS (N=102)	AI (N=102)	Total (N=204)
Efficacy results	**sPGA 0/1 responders% (n)**	80.4% (n=82)	73.5% (n=75)	77.0% (n=157)
	PASI 75 responders% (n)	88.2% (n=90)	78.4% (n=80)	83.3% (n=170)
Patients demographics and baseline characteristics	**Body Weight (kg, mean±SD)**	92.4±25.2	95.6±27.7	94.0±26.5
	Baseline PASI (mean±SD)	21.1±9.4	17.8±6.1	19.4±8.1

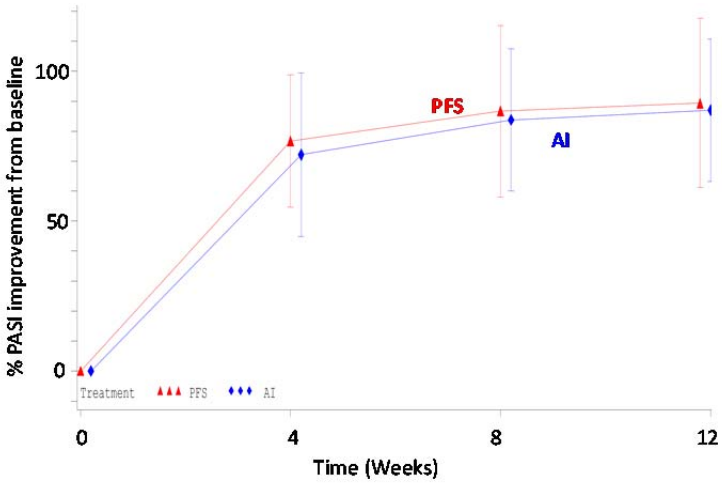

Figure. RHBL.6. Mean (±SD) % PASI score change from baseline. *(Data source: Figure RHBL.11.17, I1F-MC-RHBL CSR)*

Immunogenicity results:

The overall incidence for TE-ADA in Study RHBL was 10% (20/204) through Week 12 (Figure RHBL.7).

Table RHBL.7. The incidence of treatment-emergent anti-drug antibodies (TE-ADA) by treatment groups in study RHBL. N represents number of evaluable subjects within each treatment group. (*Data source: Table RHBL.12.18, I1F-MC-RHBL CSR*)!

	PFS (N=102)	AI (N=102)	Combined (N=204)
TE-ADA+ incidence n (%)	12 (12%)	8 (8%)	20 (10%)

6. STUDY RHAZ (PHASE 3, PIVOTAL)

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 period

- 06 December 2011 (the first subject randomized) to 24 June 2014 (last patient visit for 60-week data analysis)

Objectives

The co-primary objectives of the study are to assess whether ixekizumab 80 mg every 2 weeks (q2w) or 80 mg every 4 weeks (q4w) is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis as measured by:

- Proportion of patients with a static Physician Global Assessment (sPGA) (0,1) with at least a 2-point improvement from baseline
- Proportion of patients achieving at least a 75% improvement from baseline in Psoriasis Area and Severity Index (PASI 75) from baseline.

Study design

Study RHAZ is an ongoing, Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the effect of ixekizumab versus placebo in patients with moderate-to-severe plaque psoriasis during an Induction Dosing Period with the co-primary endpoints at Week 12, followed by a randomized Maintenance Dosing Period to Week 60, and a subsequent Long-Term Extension Period. In addition, longer-term efficacy and safety will be evaluated for up to a total of 5 years in the Long-Term Extension Period for patients who participate through the entire study.

The study consists of 5 periods (Figure RHAZ.1):

- **Screening Period** (Period 1). The purpose of the screening period was to assess patient eligibility.
- **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 primary efficacy endpoints of the study were evaluated at Week 12.
- **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, relapse or rebound following treatment withdrawal, and response to re-treatment with ixekizumab following relapse in a re-randomized patient population.
- **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.

- **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 (ETV) up to a minimum of 12 weeks after that visit.

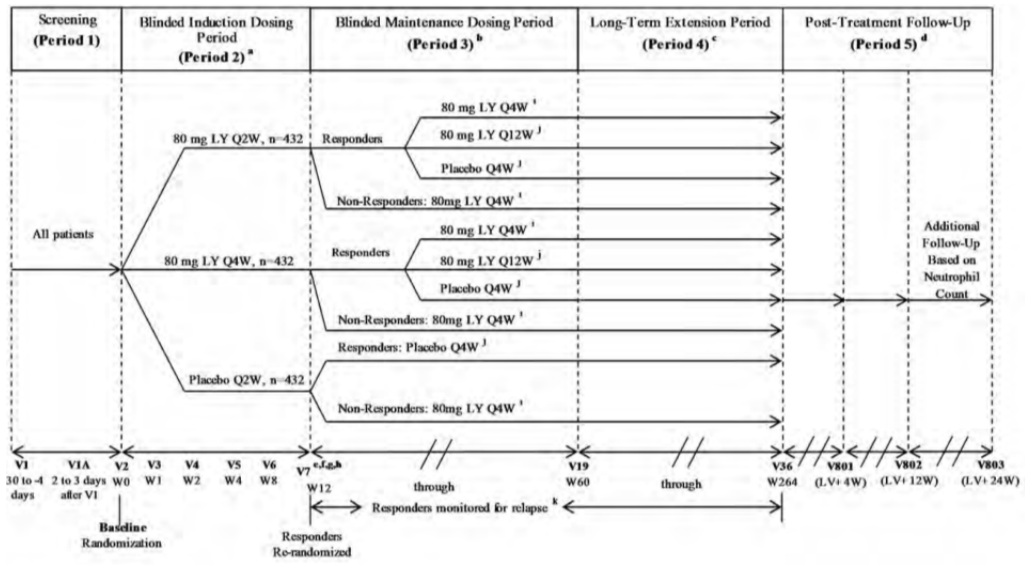

Figure RHAZ.1. Study Design

Investigational Product

Ixekizumab (80 mg) were supplied as an injectable solution in a 1-mL, single-dose, prefilled, disposable manual syringe.

Dosing regimen

During the Induction Dosing Period, patients were administered 1 of 3 regimens:

- **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 at Week 0 followed by placebo q2w (Weeks 2, 4, 6, 8, and 10)

During the Maintenance Dosing Period (Week 12 to Week 60) and the Long-Term Extension Period (Week 60 to Week 264), patients were administered 1 of 3 dosing regimens:

- **80 mg ixekizumab q4w:** A dose of 80 mg given as 1 SC injection plus a placebo injection at Week 12; 80 mg given as 1 SC injection q4w thereafter. Following relapse, a dosage regimen of 80 mg q4w (1 SC injection) was administered for the remainder of the study to maintain the study blind and to see if study response could be regained with continued treatment.
- **80 mg ixekizumab q12w:** A dose of 80 mg given as 1 SC injection plus a placebo injection at Week 12; 80 mg given as 1 SC injection q12w thereafter. To maintain blinding with q4w dosage regimen, placebo was given as 1 SC injection at Weeks 16, 20, 28, 32, 40, 44, 52, 56,

and so on, until the study was unblinded. Following relapse, a dosage regimen of 80 mg q4w (1 SC injection) was administered for the remainder of the study to evaluate whether the response observed earlier could be regained on treatment with a higher dose.

- **Placebo:** Placebo given as 2 SC injections at Week 12 followed by placebo given as 1 SC injection q4w thereafter until unblinding of the study occurred. Following relapse, a dosage regimen of 80 mg q4w (1 SC injection) was administered for the remainder of the study.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Weeks 0 (baseline), 4, 12, 24, 36, 48, and 60 during the induction and maintenance periods up to Week 60. Immunogenicity sampling after Week 60 is not further described in this summary.

Pharmacokinetics

Blood samples for PK assessment were collected in four study cohorts based on the following sampling schedule:

- Cohort 1: Weeks 1, 8, 24, 42.
- Cohort 2: Weeks 2, 12, 30, 44.
- Cohort 3: Weeks 4, 16, 34, 48
- Cohort 4: Weeks 12, 20, 36, 50

Efficacy results

Week 12 efficacy

For the primary analysis variables sPGA (0,1) and PASI 75, both ixekizumab 80 mg q4w and ixekizumab 80 mg q2w treatment groups showed a statistically significant therapeutic advantage over placebo. The sPGA (0,1) response rates for the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups were 81.8%, 76.4%, and 3.2%, respectively. The PASI 75 response rates for the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo groups were 89.1%, 82.6%, and 3.9%, respectively. Table RHAZ.1 also additionally summarizes Week 12 response rates for other efficacy endpoints including sPGA (0), PASI 90, and PASI 100.

Table RHAZ.1. Week 12 efficacy results. *$p<0.001$ versus placebo. *(Data source: Tables RHAZ.11.3., RHAZ.11.4, RHAZ.11.5, RHAZ11.6, RHAZ.11.8, RHAZ.11.9, I1F-MC-RHAZ Clinical Study Report)*

Endpoints	Week 12 clinical response rate, n (%)		
	Placebo (N=431)	Ixekizumab 80 mg q4w (N=432)	Ixekizumab 80 mg q2w (N=433)
sPGA (0,1)	14 (3.2%)	330 (76.4%)*	354 (81.8%)*
PASI 75	17 (3.9%)	357 (82.6%)*	386 (89.1%)*
sPGA (0)	0 (0%)	149 (34.5%)*	160 (37.0%)*
PASI 90	2 (0.5%)	279 (64.6%)*	307 (70.9%)*
PASI 100	0 (0%)	145 (33.6%)*	153 (35.3%)*

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Week 60 efficacy

At Week 60, both ixekizumab 80 mg q4w and ixekizumab 80 mg q12w treatment groups, regardless of the induction dosing regimen, showed a statistically significant therapeutic advantage over placebo, as measured by the proportion of patients maintaining sPGA (0,1) at Week 60 (Table RHAZ.2). Results are first presented with stratification by both the induction and maintenance dosing regimen (Table RHAZ.2), then by maintenance dosing regimen alone (Table RHAZ.3).

- For the Week 12 responders who had received ixekizumab 80 mg q2w during the Induction Dosing Period, sPGA (0,1) response rates at Week 60 were 74.8%, 41.0%, and 7.7% among those re-randomized to ixekizumab 80 mg q4w, ixekizumab 80 mg q12w, and placebo, respectively.
- For the Week 12 responders who had received ixekizumab 80 mg q4w during the Induction Dosing Period, sPGA (0,1) response rates at Week 60 were 70.9%, 33.6%, and 7.3% among those re-randomized to ixekizumab 80 mg q4w, ixekizumab 80 mg q12w, and placebo, respectively
- When data were pooled by maintenance dosing regimen, at Week 60 the response rates for the ixekizumab 80-mg q4w, ixekizumab 80-mg q12w, and placebo groups were 72.9%, 37.4%, and 7.5%, respectively (Table RHAZ.3).

In addition to sPGA (0,1), Table RHAZ.2 and Table RHAZ.3 also present the efficacy results based on sPGA (0).

Table RHAZ.2. Week 60 efficacy results stratified by both induction and maintenance dosing regimens. IXE, ixekizumab. *p<0.001 versus placebo. (*Data source: Table RHZA.11.11, I1F-MC-RHAZ Clinical Study Report*)!

	Week 60 Clinical Response rate, n (%)					
	IXEq4w /PBO (N=109)	**IXEq4w /IXEq12w (N=110)**	**IXEq4w /IXEq4w (N=110)**	**IXEq2w /PBO (N=117)**	**IXEq2w /IXEq12w (N=117)**	**IXEq2w /IXEq4w (N=119)**
sPGA (0,1)	8 (7.3%)	37 (33.6%)*	78 (70.9%)*	9 (7.7%)	48 (41.0%)*	89 (74.8%)*
sPGA (0)	2 (1.8%)	21 (19.1%)*	57 (51.8%)*	4 (3.4%)	25 (21.4%)*	65 (54.6%)*

Table RHAZ.3. Week 60 efficacy results stratified by maintenance dosing regimens. IXE, ixekizumab. *p<0.001 versus placebo. (*Data source: Table RHZA.11.11, I1F-MC-RHAZ Clinical Study Report*)!

	Week 60 Clinical Response rate, n (%)		
	IXE /PBO (N=226)	**IXE /IXEq12w (N=227)**	**IXE /IXE q4w (N=229)**
sPGA (0,1)	17 (7.5%)	85 (37.4%)*	167 (72.9%)*
sPGA (0)	6 (2.7%)	46 (20.3%)*	122 (53.3%)*

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Pharmacokinetics results

In the induction dosing period, steady-state concentrations were achieved by Week 8. At Weeks 8 and 12, geometric mean trough concentrations were 6.56 mcg/mL (N=67) and 7.73 mcg/mL (N=192) for the q2w regimen and 2.50 mcg/mL (N=93) and 2.94 mcg/mL (N=215) for the q4w dosing regimens, respectively (Table RHAZ.4).

Table RHAZ.4. Summary descriptive statistics of ixekizumab trough serum concentrations at Week 8 and Week 12 by dosing regimens during inducting dosing period. (Data source: Table RHAZ.11.17, *I1F-MC-RHAZ Clinical Study Report*)

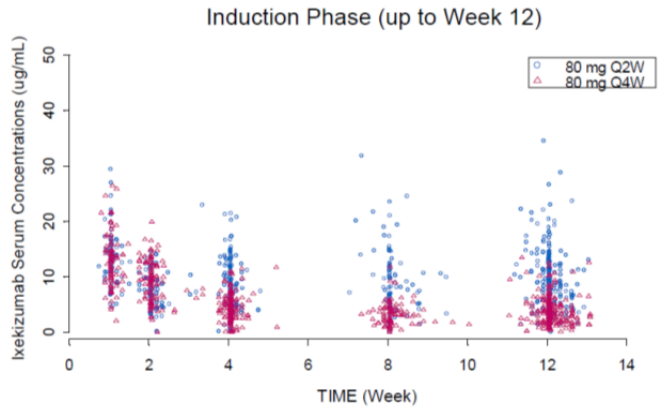
	Week 8 Trough (µg/mL)		Week 12 Trough (µg/mL)	
	Q2W	**Q4W**	**Q2W**	**Q4W**
N	67	93	192	215
Median	7.53	3.10	8.51	3.28
Minimum	0.0260	0.027	0.0765	0.081
Maximum	23.50	11.75	34.5	13.45
Geometric mean	6.56	2.50	7.73	2.94
Geometric %CV	118	97	79	89

For those patients who remained on their assigned dosing regimen for the duration of the maintenance phase, geometric mean trough concentrations ranged from 2.36 to 2.70 mcg/mL for the q4w dosing regimen and ranged from 0.195 to 0.281 mcg/mL for the q12w dosing regimen (Table RHAZ.5).

Table RHAZ.5. Summary descriptive statistics of ixekizumab trough serum concentrations by dosing regimens during maintenance dosing period. (*Data source: Table RHAZ.11.18, I1F-MC-RHAZ Clinical Study Report*)

	Week 24 Trough		Week 36 Trough		Week 48 Trough	
	Q4W	Q12W	Q4W	Q12W	Q4W	Q12W
N	223	60	262	55	227	38
Median	2.63	0.32	3.08	0.22	3.188	0.28
Minimum	0.0145	0.0165	0.0255	0.0185	0.010	0.0215
Maximum	15.60	2.83	14.6	1.325	21.50	7.5
Geometric mean	2.36	0.281	2.68	0.195	2.70	0.259
Geometric %CV	111	175	114	114	123	152

Figure RHAZ.2 shows all observed concentration time data for the ixekizumab 80 mg q2w and 80 mg q4w dosing regimens up to Week 12 (upper panel) and ixekizumab 80 mg q4w and 80-mg q12w dosing regimens up to Week 60 (lower panel).



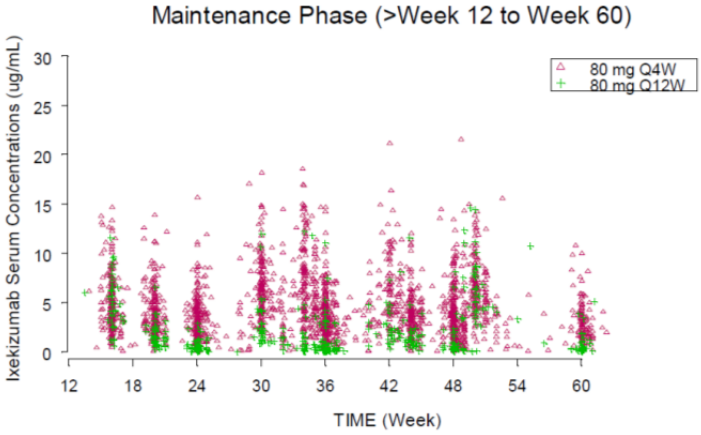


Figure RHAZ.2. Observed ixekizumab serum concentration over time during the induction dosing period (up to Week 12) and maintenance dosing period (up to Week 60) by dosing regimen groups. (*Data source: Figure RHAZ.11.19, Figure RHAZ.11.23, I1F-MC-RHAZ Clinical Study Report*)

Immunogenicity results

Data up to Week 12

During the induction dosing period up to Week 12, the incidences for TE-ADA formation were 10.3%, 12.5%, and 0.5% in of ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups, respectively. NAb was observed in 4.5% and 15.1% among positive TE-ADA patients receiving ixekizumab 80 mg q2w and ixekizumab 80 mg q4w dosing regimens, respectively (Table RHAZ.6).

Table RHAZ.6. Immunogenicity incidence up to Week 12. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. IXE, ixekizumab. (*Data source: Table RHAZ.12.78, I1F-MC-RHAZ Clinical Study Report*)

	Placebo (N=425)	IXEq4w (N=425)	IXEq2w (N=426)	IXE combined (N=851)
TE-ADA	2 (0.5%)	53 (12.5%)	44 (10.3%)	97 (11.4%)
NAb	0	8 (15.1%)	2 (4.5%)	10 (10.3%)

Data up to Week 60

In the maintenance dosing period up to Week 60, positive TE-ADA was observed at any time post-baseline in 16.4%, 25.4%, and 24.5% of patients in the pooled ixekizumab/ixekizumab 80mg q4w, ixekizumab/ixekizumab 80 mg q12w, and ixekizumab/placebo groups, respectively, or 22.0% overall. Among patients with positive TE-ADA, NAb was observed in 2.8%, 3.7%, and 6.4% of patients in the pooled ixekizumab/ixekizumab 80 mg q4w, ixekizumab/ixekizumab 80 mg q12w, and ixekizumab/placebo groups, respectively, or 4.4% overall (Table RHAZ.7).

Week 60 immunogenicity results stratified by both induction and maintenance dosing regimens are presented in Table RHAZ.8.

Table RHAZ.7. Week 60 immunogenicity results stratified by maintenance dosing regimens. IXE, ixekizumab. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. (*Data source: Table RHZA.12.81, I1F-MC-RHAZ Clinical Study Report*)!

	IXE/Placebo (N=192)	IXE/IXEq12w (N=213)	IXE/IXEq4w (N=219)	IXE/IXE Combined (N=432)	TOTAL (N=682)
TE-ADA	47 (24.5%)	54 (25.4%)	36 (16.4%)	90 (20.8%)	137 (22.0%)
NAb	3 (6.4%)	2 (3.7%)	1 (2.8%)	3 (3.3%)	6 (4.4%)

Table RHAZ.8. Week 60 immunogenicity results stratified by both induction and maintenance dosing regimens. IXE, ixekizumab. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. (*Data source: Table RHZA.12.81, I1F-MC-RHAZ Clinical Study Report*)!

	IXEq4w /PBO (N=90)	IXEq4w /IXEq12w (N=105)	IXEq4w /IXEq4w (N=107)	IXEq2w /PBO (N=102)	IXEq2w /IXEq12w (N=108)	IXEq2w /IXEq4w (N=112)
TE-ADA	12 (13.3%)	20 (19.0%)	17 (15.9%)	35 (34.3%)	34 (31.5%)	19 (17.0%)
NAb	0	1 (5%)	1 (5.9%)	3 (8.6%)	1 (2.9%)	0

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7. STUDY RHBA (PHASE 3, PIVOTAL)

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 period

- 30 May 2012 (the first subject randomized) to 11 Sept 2014 (last patient visit for 36-week data analysis)

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 static Physician Global Assessment (sPGA) (0,1) with at least a 2-point improvement from baseline and the proportion of patients achieving a ≥75% improvement in Psoriasis Area and Severity Index (PASI 75) from baseline.
- Noninferior to etanercept at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis as measured by the proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline and the proportion of patients achieving a PASI 75 from baseline.
- Superior to etanercept at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis as measured by the proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline and the proportion of patients achieving a PASI 75 from baseline.

Study design

Study RHBA is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, active comparator, parallel-group study examining the effect on primary efficacy endpoint measures at 12 weeks of 2 dose regimens of ixekizumab 80 mg (q2w or q4w; each with a starting dose of 160 mg) versus placebo and versus etanercept (50 mg twice weekly) in patients with moderate-to-severe plaque psoriasis. All investigational products are administered subcutaneously.

An ongoing blinded Maintenance Dosing Period followed the Induction Dosing Period and will evaluate the maintenance of response at Week 60 with 2 different dosing intervals of ixekizumab 80 mg (q4w or q12w), as well as relapse or rebound following treatment withdrawal, and response to re-treatment with ixekizumab following relapse. Long-term efficacy and safety of ixekizumab will be evaluated for up to a total of 5 years in patients who participate through the entire study.

The study consists of 5 periods:

1. **Screening Period** (Period 1).
2. **Blinded Induction Dosing Period** (Period 2) was a double-blind treatment period from Week 0 to Week 12.
3. **Blinded Maintenance Dosing Period** (Period 3) is an ongoing double-blind treatment period from Week 12 to Week 60. The Maintenance Dosing Period has 3 patient populations:
   - Primary Population (defined as patients randomized to ixekizumab in Period 2 who achieved an sPGA (0,1) and were re-randomized at Week 12).

- Secondary Population (defined as ixekizumab patients who were not re-randomized at Week 12 or patients who were randomized to placebo or etanercept at Week 0 who received at least 1 dose of study treatment during Period 3).
- Relapse Population (defined as all patients who were responders at Week 12 who first experienced a relapse (sPGA ≥3) at any point during Period 3).

4. **Long-Term Extension Period** (Period 4) is an ongoing treatment period from Week 60 up to Week 264.
5. **Post-Treatment Follow-Up Period** (Period 5) takes place from a patient's last treatment period visit or Early Termination Visit (ETV) up to a minimum of 12 weeks after that visit.

The Maintenance Dosing, Long-Term Extension, and Post-Treatment Follow-Up Periods are ongoing at the time of the database lock for this report.

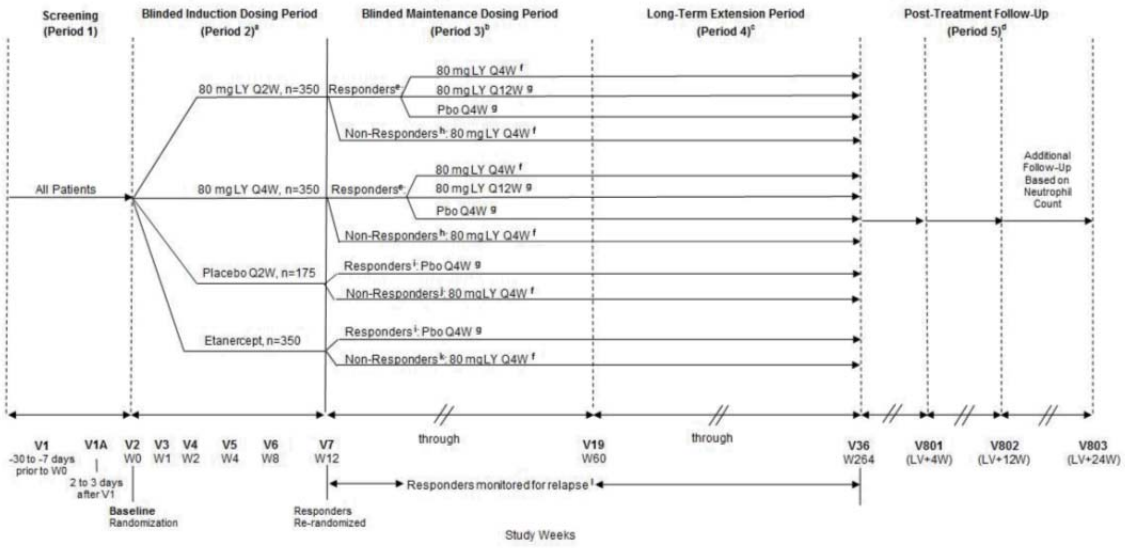

Figure RHBA.1. Study design.

Investigational Product

Ixekizumab (80 mg) were supplied as an injectable solution in a 1-mL, single-dose, prefilled, disposable manual syringe.

Commercially purchased etanercept (Enbrel®, 50 mg) were supplied as an injectable solution in a single-dose, prefilled disposable manual syringe. Two sources of etanercept were used in the study: US-approved etanercept for all US study sites and EU-approved etanercept for study sites in other countries.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Weeks 0 (baseline), 4, 12, 24, 36, 48, and 60 during the induction and maintenance periods up to Week 60. Immunogenicity sampling after Week 60 is not further described in this summary.

Pharmacokinetics

This study did not collect blood samples for PK assessment.

Efficacy results

Week 12 efficacy

For the primary analysis variables [sPGA (0,1) and PASI 75], both ixekizumab 80 mg q4w and ixekizumab 80 mg q2w treatment groups showed a statistically significant therapeutic advantage over placebo. The sPGA (0,1) response rates for the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups were 83.2%, 72.9%, and 2.4%, respectively. The PASI 75 response rates for the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo groups were 89.7%, 77.5%, and 2.4%, respectively. Table RHBA.1 also additionally summarizes Week 12 response rates for other efficacy endpoints including sPGA (0), PASI 90, and PASI 100.

Table RHBA.2 summarizes the efficacy results based on data from US study sites for comparison with the efficacy data for US approved-etanercept. *Refer to the Biostatistics review regarding the non-inferiority and superiority statistical comparison to etanercept.*

Table RHBA.1. Week 12 efficacy results (overall). *$p<0.001$ *versus* placebo. *(Data source: Tables RHBA.11.4, RHBA.11.5, RHBA.11.15, RHBA.11.16, RHBA.11.17, I1F-MC-RHBA Clinical Study Report)*

Endpoints	Week 12 clinical response rate, n (%)		
	Placebo (N=168)	IXE 80 mg q4w (N=347)	IXE 80 mg q2w (N=351)
sPGA (0,1)	4 (2.4%)	253 (72.9%)*	292 (83.2%)*
PASI 75	4 (2.4%)	269 (77.5%)*	315 (89.7%)*
sPGA (0)	1 (0.6%)	112 (32.3%)*	147 (41.9%)*
PASI 90	1 (0.6%)	207 (59.7%)*	248 (70.7%)*
PASI 100	1 (0.6%)	107 (30.8%)*	142 (40.5%)*

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Table RHBA.2. Week 12 efficacy results (US-data only). *$p<0.001$ *versus* placebo. *(Data source: Tables RHBA.11.7, RHBA.11.9, I1F-MC-RHBA Clinical Study Report)*

Endpoints	Week 12 clinical response rate, n (%)			
	Placebo (N=49)	Etanercept (N=111)	IXE 80 mg q4w (N=105)	IXE 80 mg q2w (N=104)
sPGA (0,1)	0	24 (21.6%)	64 (61.0%)*	73 (70.2%)*
PASI 75	0	36 (32.4%)	71 (67.6%)*	89 (85.6%)*

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Week 60 efficacy

At Week 60, both ixekizumab 80 mg q4w and ixekizumab 80 mg q12w treatment groups, regardless of the induction dosing regimen, showed a statistically significant therapeutic advantage over placebo, as measured by the proportion of patients maintaining sPGA (0,1) at Week 60 (Table RHBA.3). Results are first presented with stratification by both the induction and maintenance dosing regimen (Table RHAZ.3), then by maintenance dosing regimen alone (Table RHAZ.4).

- For the Week 12 responders who had received ixekizumab 80 mg q2w during the Induction Dosing Period, sPGA (0,1) response rates at Week 60 were 75.8%, 29.9%, and 7.0% among those re-randomized to ixekizumab 80 mg q4w, ixekizumab 80 mg q12w, and placebo, respectively.
- For the Week 12 responders who had received ixekizumab 80 mg q4w during the Induction Dosing Period, sPGA (0,1) response rates at Week 60 were 59.6%, 34.4%, and 4.2% among those re-randomized to ixekizumab 80 mg q4w, ixekizumab 80 mg q12w, and placebo, respectively

- When data were pooled by maintenance dosing regimen, at Week 60 the response rates for the ixekizumab 80-mg q4w, ixekizumab 80-mg q12w, and placebo groups were 68.1%, 32.0%, and 5.7%, respectively (Table RHBA.4).

In addition to sPGA (0,1), Table RHBA.3 and Table RHBA.4 also present the efficacy results based on sPGA (0).

Table RHBA.3. Week 60 efficacy results stratified by both induction and maintenance dosing regimens. IXE, ixekizumab. *p<0.001, #p<0.01, §p<0.05, *versus* placebo. (*Data source: Table RHBA.11.18, I1F-MC-RHBA Clinical Study Report*)!

	Week 60 Clinical Response rate, n (%)					
	IXE80q4w /PBO (N=72)	**IXE80q4w /IXE80q12w (N=61)**	**IXE80q4w /IXE80q4w (N=57)**	**IXE80q2w /PBO (N=86)**	**IXE80q2w /IXE80q12w (N=67)**	**IXE80q2w /IXE80q4w (N=62)**
sPGA (0,1)	3 (4.2%)	21 (34.4%)*	34 (59.6%)*	6 (7.0%)	20 (29.9%)*	47 (75.8%)*
sPGA (0)	0	8 (13.1%)#	24 (42.1%)*	2 (2.3%)	8 (11.9%)§	35 (56.5%)*

Table RHBA.4. Week 60 efficacy results stratified by maintenance dosing regimens. IXE, ixekizumab. *p<0.001 versus placebo. (*Data source: Table RHZA.11.18, I1F-MC-RHBA Clinical Study Report*)!

	Week 60 Clinical Response rate, n (%)		
	IXE/PBO (N=158)	**IXE/Ixe80q12w (N=128)**	**IXE/Ixe80q4w (N=119)**
sPGA (0,1)	9 (5.7%)	41 (32.0%)*	81 (68.1%)*
sPGA (0)	2 (1.3%)	16 (12.5%)*	59 (49.6%)*

Immunogenicity results

Data up to Week 12

The incidences for TE-ADA formation were 10.4%, 14.1%, and 0% in ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups, respectively. NAb was observed in 5.6% and 12.5% among positive TE-ADA patients receiving ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W dosing regimens, respectively (Table RHBA.5).

Table RHBA.5. Immunogenicity incidence up to Week 12. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. IXE, ixekizumab. (*Data source: Table RHBA.12.52, I1F-MC-RHBA Clinical Study Report*)

	Placebo (N=165)	**IXE 80 mg q4w (N=340)**	**IXE 80 mg q2w (N=346)**	**IXE combined (N=686)**
TE-ADA	0	48 (14.1%)	36 (10.4%)	84 (12.2%)
NAb	0	6 (12.5%)	2 (5.6%)	8 (9.5%)

Data up to Week 60

In the maintenance dosing period up to Week 60, positive TE-ADA was observed in 14.6%, 24.9%, and 21.8% of patients in the pooled ixekizumab/ixekizumab 80mg q4w, ixekizumab/ixekizumab 80 mg q12w, and ixekizumab/placebo groups, respectively, or 20.3% overall. Among patients with positive TE-ADA, NAb was observed in 0%, 9.5%, and 2.9% of patients in the pooled ixekizumab/ixekizumab 80 mg q4w, ixekizumab/ixekizumab 80 mg q12w, and ixekizumab/placebo groups, respectively, or 4.9% overall (Table RHBA.6).

Week 60 immunogenicity results stratified by both induction and maintenance dosing regimens are presented in Table RHBA.7.

Table RHBA.6. Week 60 immunogenicity results stratified by maintenance dosing regimens. IXE, ixekizumab. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. (*Data source: Table RHBA.12.55, I1F-MC-RHBA Clinical Study Report*)!

	IXE/Placebo (N=156)	IXE/IXEq12w (N=169)	IXE/IXEq4w (N=178)	IXE/IXE Combined (N=347)	TOTAL (N=503)
TE-ADA	34 (21.8%)	42 (24.9%)	26 (14.6%)	68 (19.6%)	102 (20.3%)
NAb	1 (2.9%)	4 (9.5%)	0	4 (5.9%)	5 (4.9%)

Table RHBA.7. Week 60 immunogenicity results stratified by both induction and maintenance dosing regimens. IXE, ixekizumab. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. (*Data source: Table RHBA.12.55, I1F-MC-RHBA Clinical Study Report*)!

	IXEq4w /PBO (N=69)	IXEq4w /IXEq12w (N=79)	IXEq4w /IXEq4w (N=79)	IXEq2w /PBO (N=87)	IXEq2w /IXEq12w (N=90)	IXEq2w /IXEq4w (N=99)
TE-ADA	14 (20.3%)	21 (26.6%)	13 (16.5%)	20 (23.0%)	21 (23.3%)	13 (13.1%)
NAb	1 (7.1%)	3 (14.3%)	0	0	1 (4.8%)	0

8. STUDY RHBC (PHASE 3, PIVOTAL)

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 period

- 11 August 2012 (the first subject enrolled) to 14 July 2014 (date of data cutoff)

Objectives

The primary objective was to assess whether 80 mg ixekizumab q2w or q4w is superior to placebo, noninferior to etanercept, and/or superior to etanercept in the treatment of patients with moderate-to-severe plaque psoriasis at Week 12 as measured by the proportion of patients with a Static Physician Global Assessment (sPGA) with at least a 2-point improvement from baseline (sPGA [0,1]) and the proportion of patients achieving a ≥75% improvement in Psoriasis Area and Severity Index from baseline (PASI 75).

Study design

Study RHBC is an ongoing, Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study examining the effect on primary efficacy endpoints measured at 12 weeks of 2 dosage regimens of 80 mg ixekizumab (q2w or q4w; each with a starting dose of 160 mg) versus placebo and versus etanercept (50 mg twice weekly) in patients with moderate-to-severe plaque psoriasis. Long-term safety and efficacy of 80 mg ixekizumab q4w will be evaluated in an extension phase for up to a total of 5 years.

The study consists of 4 periods (Figure RHBC.1):

1. **Screening Period** (Period 1)

2. **Blinded Induction Dosing Period** (Period 2): From Week 0 (baseline) up to Week 12. The purpose of Period 2 was to compare the safety and efficacy of ixekizumab versus etanercept and versus placebo. The primary efficacy endpoints of the study were evaluated at Week 12.
3. **Long-Term Extension Period** (Period 3): From Week 12 up to Week 264. The purpose of Period 3 is for continued, longer-term evaluation of safety and efficacy parameters of ixekizumab 80 mg Q4W treatment in participating patients.
4. **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. The purpose of Period 4 is for safety monitoring following treatment discontinuation.

The Long-Term Extension Period is ongoing at time of this report.

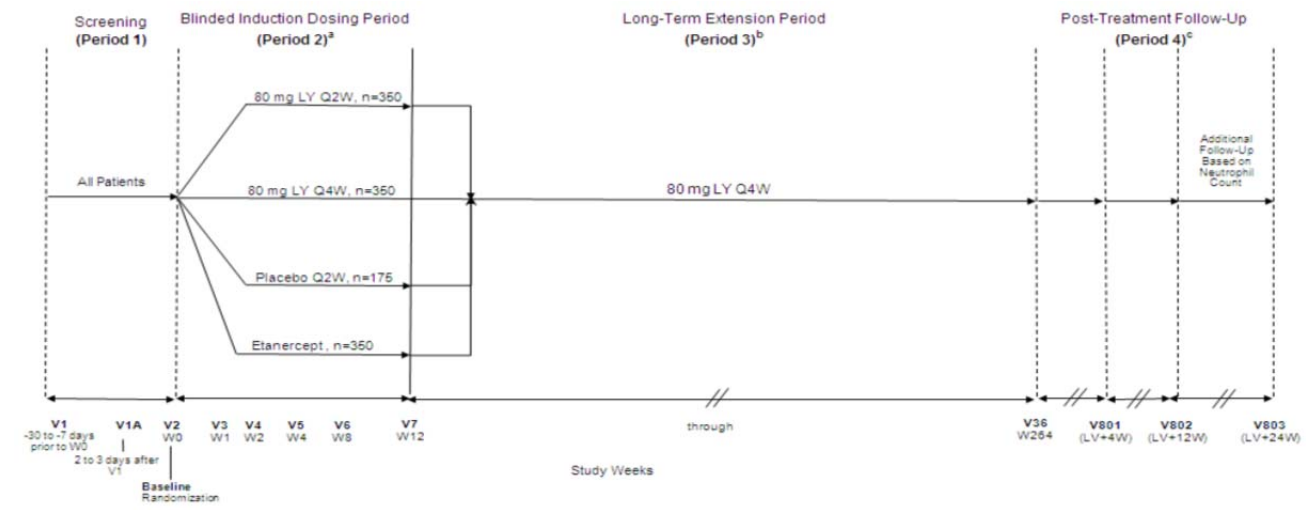

Figure RHBC.1. Study design.

Investigational Product

Ixekizumab (80 mg) were supplied as an injectable solution in a 1-mL, single-dose, prefilled, disposable manual syringe.

Commercially purchased etanercept (Enbrel®, 50 mg) were supplied as an injectable solution in a single-dose, prefilled disposable manual syringe. Two sources of etanercept were used in the study: source of US-approved etanercept for all US study sites and source of EU-approved etanercept for study sites in other countries.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Weeks 0 (baseline), 4, and 12 during the induction dosing period. Immunogenicity sampling after Week 12 is not further described in this summary.

Pharmacokinetics

This study did not collect blood samples for PK assessment.

Efficacy results

Week 12 efficacy

For the primary analysis variables, sPGA (0,1) and PASI 75, both ixekizumab 80 mg q4w and ixekizumab 80 mg q2w treatment groups showed a statistically significant therapeutic advantage over placebo. The sPGA (0,1) response rates for the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups were 80.5%, 75.4%, and 6.7%, respectively. The PASI 75 response rates for the ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo groups were 87.3%, 84.2%, and 7.3%, respectively. Table RHBC.1 also additionally summarizes Week 12 response rates for other efficacy endpoints including sPGA (0), PASI 90, and PASI 100.

Table RHBC.2 summarizes the efficacy results based on data from US study sites for comparison with the efficacy data for US approved-etanercept. *Refer to the Biostatistics review regarding the non-inferiority and superiority statistical comparison to etanercept.*

Table RHBC.1. Week 12 efficacy results (overall). *$p<0.001$ *versus* placebo. *(Data source: Tables RHBC.11.3, RHBC.11.4, RHBC.11.12, RHBC.11.3, RHBC.11.14, I1F-MC-RHBC Clinical Study Report)*

Endpoints	Week 12 clinical response rate, n (%)		
	Placebo (N=193)	IXE 80 mg q4w (N=386)	IXE 80 mg q2w (N=385)
sPGA (0,1)	13 (6.7%)	291 (75.4%)*	310 (80.5%)*
PASI 75	14 (7.3%)	325 (84.2%)*	336 (87.3%)*
sPGA (0)	0	139 (36.0%)*	155 (40.3%)*
PASI 90	6 (3.1%)	252 (65.3%)*	262 (68.1%)*
PASI 100	0	135 (35.0%)*	145 (37.7%)*

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Table RHBC.2. Week 12 efficacy results (US-only). *$p<0.001$ *versus* placebo. *(Data source: Tables RHBC.11.6, RHBC.11.8, I1F-MC-RHBC Clinical Study Report)*

Endpoints	Week 12 clinical response rate, n (%)			
	Placebo (N=69)	Etanercept (N=146)	IXE 80 mg q4w (N=147)	IXE 80 mg q2w (N=141)
sPGA (0,1)	4 (5.8%)	46 (31.5%)	96 (65.3%)*	105 (74.5%)*
PASI 75	6 (8.7%)	68 (46.6%)	118 (80.3%)*	141 (87.9%)*

Immunogenicity results

Data up to Week 12

During the induction dosing period up to Week 12, the incidences for TE-ADA formation were 6.1%, 13.8%, and 1.0% in ixekizumab 80 mg q2w, ixekizumab 80 mg q4w, and placebo treatment groups, respectively. NAb was observed in 4.3% and 9.6% among positive TE-ADA patients receiving ixekizumab 80 mg q2w and ixekizumab 80 mg q4w dosing regimens, respectively (Table RHBC.3).

Table RHBC.3. Immunogenicity incidences during induction dosing period up to Week 12. The incidence of TE-ADA is calculated based on the number of evaluable patients in each treatment group. The incidence of NAb is calculated based on the number of TE-ADA positive subjects. IXE, ixekizumab. (*Data source: Table RHBC.12.40, I1F-MC-RHBC Clinical Study Report*)

	Placebo (N=191)	IXE 80 mg q4w (N=378)	IXE 80 mg q2w (N=378)	IXE combined (N=756)
TE-ADA	2 (1.0%)	52 (13.8%)	23 (6.1%)	75 (9.9%)
NAb	1 (50%)	5 (9.6%)	1 (4.3%)	6 (8.0%)

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