

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125521Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL OUTCOME ASSESSMENT REVIEW

<b>CLINICAL OUTCOME ASSESSMENT (COA)</b>	At 2015-66
<b>TRACKING NUMBER</b>	
<b>BLA NUMBER</b>	125521
<b>LETTER DATE/SUBMISSION NUMBER</b>	March 23, 2015
<b>PDUFA GOAL DATE</b>	March 23, 2016
<b>DATE OF CONSULT REQUEST</b>	April 14, 2015
<b>REVIEW DIVISION</b>	Division of Dermatology and Dental Products (DDDP)
<b>MEDICAL REVIEWER</b>	Jane Liedtka
<b>REVIEW DIVISION PM</b>	J. Paul Phillips
<b>COA REVIEWER</b>	Yasmin Choudhry
<b>ASSOCIATE DIRECTOR, COA STAFF (ACTING)</b>	Elektra Papadopoulos
<b>REVIEW COMPLETION DATE</b>	January 7, 2016
<b>ESTABLISHED NAME</b>	Ixekizumab subcutaneous injection
<b>TRADE NAME</b>	TALTZ <sup>®</sup>
<b>SPONSOR</b>	Eli Lilly and Company
<b>CLINICAL OUTCOME ASSESSMENT TYPE</b>	Patient-reported outcome
<b>ENDPOINT(S) CONCEPT(S)</b>	Itching related to plaque psoriasis
<b>MEASURE(S)</b>	Itch Numeric Rating Scale
<b>INDICATION</b>	Moderate to severe plaque psoriasis
<b>INTENDED POPULATION(S)</b>	Adult patients with moderate to severe plaque psoriasis

## Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 125521

Ixekizumab (TALTZ<sup>®</sup>)

Itch Numeric Rating Scale (psoriasis-related itch)

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### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding BLA 125521 ixekizumab (an immunoglobulin G subclass 4 (IgG4) monoclonal antibody) subcutaneous injection for the treatment of adult patients with moderate to severe plaque psoriasis.

Eli Lilly utilized the patient-reported outcome (PRO) measure, the Itch Numeric Rating Scale (Itch NRS) to assess itching severity as a secondary endpoint in the ixekizumab phase 3 clinical trials in patients with moderate to severe plaque psoriasis.

The review concludes that Eli Lilly has provided sufficient evidence to support the validity and reliability of the Itch NRS in the context in which it was used to support a labeling claim related to improvement in itch.

### B. STUDY ENDPOINT REVIEW

#### Materials reviewed:

- Eli Lilly's evidence dossier submitted with the original BLA 125521 received March 23, 2015
- DDDP consult dated April 14, 2015
- COA reviews for IND 100834 (Eli Lilly) dated June 10, and November 9 2011; and May 12, 2014
- COA Review for baricitinib (b) (4) (Eli Lilly) dated July 26, 2013

#### Background:

For content validity of the Itch NRS, Eli Lilly partially relied on the Worst Itch NRS data from baricitinib (b) (4) (also an Eli Lilly product). The current PRO dossier (submitted with BLA 125521 ixekizumab) contains information (on the measurement properties of the Itch NRS-11, the responder definition, and the clinical meaningful change over time from the three ixekizumab Phase 3 clinical studies (I1F-MC-RHAZ [RHAZ], I1F-MCRHBA [RHBA], and the baricitinib phase 2 Study JADP.

## 1 CONTEXT OF USE (COU)

### 1.1 Target Study Population and Clinical Setting

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

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### 1.2 Clinical Trial Design

The ixekizumab phase 3 RHAZ study was a multicenter, randomized, double-blind, placebo-controlled and parallel group outpatient study. This study examined the effect of ixekizumab versus placebo in patients with moderate-to-severe plaque psoriasis during an Induction Dosing Period with the primary endpoint at 12 weeks, followed by a randomized Maintenance Dosing Period to Week 60, and a subsequent Long-Term Extension Period.

The study eligibility inclusion and exclusion criteria were as follows:

**Inclusion criteria:** Male or female patients aged 18 years or older with confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months who were candidates for phototherapy and/or systemic therapy with  $\geq 10\%$  body surface area (BSA) involvement, an sPGA (static Physician global Assessment) score of  $\geq 3$ , and a Psoriasis Area and Severity Index (PASI) score  $\geq 12$  at screening and baseline were included in the study.

**Exclusion criteria:** Patients with pustular, erythrodermic, and/or guttate forms of Ps (non-plaque forms of Ps); active vasculitis or uveitis; current or a history of lymphoproliferative disease; and mental disability or significant mental illness were excluded.

Note that the Itch NRS was utilized in this study (and the two additional phase 3 studies) to assess severity of psoriasis-related itch and was assessed at clinic visits at Week 0, 1, 2, 4, 8, 12.

### 1.3 Endpoint Positioning

#### Co-primary Endpoints:

The co-primary endpoints for the all three trials including the RHAZ study were the:

- Proportion of patients with a sPGA (0=Clear or 1=minimal) with at least a 2-point improvement from baseline at Week 12
- Proportion of patients achieving at least a  $\geq 75\%$  improvement from baseline in PASI-75 from baseline at Week 12

#### Secondary Endpoints:

The key secondary endpoints for the three trials were:

- Proportion of patients achieving a sPGA 0 (remission) at Week 12
- Proportion of patients achieving at least a 90% improvement from baseline in PASI score (PASI 90) at Week 12
- Proportion of patients achieving a 100% improvement from baseline in PASI score (PASI 100) at Week 12
- Proportion of patients maintaining an sPGA (0,1) from Week 12 after re-randomization at start of the Maintenance Dosing Period to Week 60

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- Proportion of patients achieving an Itch NRS  $\geq 4$ -point reduction from baseline for patients who had baseline Itch NRS  $\geq 4$
- Change from baseline in dermatology-specific quality of life (Dermatology Life Quality Index [DLQI]) at Week 12
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) score in patients with fingernail involvement at Week 12

The endpoint model (from the evidence dossier) is as follows:

Abbreviat  
Rating  
improv  
a Gated

*Reviewer comment: According to the Medical Officer's review dated November 13, 2015, ixekizumab was statistically superior ( $p$ -values  $< 0.001$ ) to placebo for all the primary and key secondary efficacy endpoints. The Medical Officer concluded that the data provided by the pivotal trials is persuasive and is highly clinically meaningful.*

### 1.4 Labeling or promotional claim(s) based on the COA

The PRO labeling claim sought was:

(b) (4)

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*Reviewer comment: This COA reviewer recommends a minor modification to the labeling to remove [REDACTED] (b) (4). The COA staff defers to the clinical and statistical review teams with regard to whether the claim, [REDACTED] (b) (4) is supported by evidence. It may also be advisable to include the specific attribute of itch assessed (i.e., worst level of itching in the past 24 hours).*

## 2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The conceptual frame work (Figure 8.1, PRO dossier) is as follows:

Please rate  
your psori  
best desc  
in the pa

*Reviewer comment: The study endpoints, the conceptual framework and the proposed labeling claim are appropriate and are in alignment with each other.*

## 3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE

The Itch NRS is a self-administered, single item paper questionnaire with response options from 0=No Itch to 10=Worst itch imaginable (presented below and in Appendix A of this review):

Please rate  
level of itc

0 1

0 = No itch

A higher score on the NRS corresponds to greater itch severity. According to the evidence dossier, ambiguous values (for example, the circle covers more than 1 number or more than 1 number is circled) and ‘no response’ chosen are treated as missing observations.

The instructions for completion are embedded within the questionnaire for patients to read before responding to the item. The Itch NRS training documents provided in the dossier include specific advice for training of patients, investigational sites, and third party organizations on the appropriate use of the instrument.

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## 4 CONTENT VALIDITY

For content validity of the Itch-NRS, Eli Lilly referenced the (b) (4) baricitinib data (also an Eli Lilly drug product in which the identical instrument the “Worst Itch-NRS” was used). According to the PRO evidence dossier, a qualitative study was conducted in 2011 to inform the PRO strategy for the Phase 3 ixekizumab and baricitinib clinical programs.

*Reviewer comment: Note that the baseline study entry criteria for baricitinib (b) (4) and ixekizumab BLA 125521 were not identical, e.g., the baricitinib study required psoriasis involvement of at least 12% of the BSA, and the ixekizumab study required at least 10% involvement of the BSA. The sPGA and the PASI entry-level criteria were identical for the two studies. This difference in the BSA involvement with psoriasis is not significant and is acceptable.*

A summary of Eli Lilly’s methodology and results of content validity are as follows:

### Concept Elicitation:

The qualitative study was conducted by Eli Lilly in accordance with the 2009 PRO Guidance for Industry. After a literature search was conducted and expert input was obtained, concept elicitation interviews were conducted in 12 patients (6 males and 6 females) with moderate (58%) to severe (42%) plaque psoriasis. Majority (92%) of patients was Caucasian, 58% had less than a college degree and 50% were employed or were in school. The average time since psoriasis diagnosis was 18 years, with a minimum of approximately 2 years and a maximum of 52 years. The inclusion/exclusion criteria were similar to those of the phase 3 clinical trial (see Section 1.2 above). The results of this study confirmed that itching was a key and the most bothersome symptom of psoriasis. Patients were probed regarding frequency, duration, severity, itching at its worst and at its mildest, and factors affecting itching. The sensation of itching reported by patients was characterized as follows:

- Most patients with psoriasis reported experiencing or having the sensation of itching every day. Many patients reported they felt a relatively constant itching that varied from a low level of itchiness that they could easily distract themselves from thinking about (that is, “tune out”) to a severe level that they “had to scratch.” This severe level of itching where patients “had to scratch” might be continuous or intermittent, and might occur for periods of varying duration, such as 2 minutes, 2 hours, or for up to a week.
- Itching at its worst was often accompanied by a burning and/or painful sensation, or a feeling of the itch being deep underneath the skin.
- Patients with psoriasis sometimes expressed the degree of itching in terms of how hard they needed to scratch to get relief. For example, patients described the most severe itching as “scratching and scratching but the itching did not go away”. Scratching also might be sufficiently aggressive or prolonged to cause bleeding. In contrast, patients

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described mild itching as “not as intense.” It was rarely reported that the itching would go away completely.

- Saturation of concepts was attained by the 10th interview. See Appendix B of this review.

### Cognitive debriefing:

The results of the cognitive debriefing interviews conducted in the twelve patients demonstrated the following:

Item Content: Study patients reported that itching was a key and relevant symptom of psoriasis. Itching was also described patients as one of the most bothersome symptoms. There was evidence to support that this item was appropriately interpreted as assessing the intensity of itching, as the patients reported no problems making a rating for the worst level of itch in the past 24 hours.

Item  
generation  
Item  
debriefing  
Item  
modificati  
Abbreviatio  
Ps = pso

Recall Period: The recall period of 24 hours was considered appropriate the patients. Patients were able to make ratings based strictly on this recall period, reported no difficulty in remembering their experiences over that period, and there was no evidence of any patient going beyond this period.

*Reviewer comment: Cross reference to baricitinib data for the content validity of the Itch NRS is acceptable based on the COA review dated July 26, 2013. The Itch-NRS data for baricitinib demonstrated that the concept of itching is a prevalent and an important concept for patients with psoriasis.*

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### 5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Eli Lilly provided combined results of psychometric properties from all four clinical trials:

- The Study JADP for baricitinib (b) (4) - Worst Itch-NRS.
- Three phase 3 clinical trials (RHAZ, RHBA, and RHBC) of ixekizumab – Itch NRS

Note that the baricitinib JADP study's context of use (disease definition, target population, clinical trial design, endpoint positioning, and targeted labeling concepts) was largely similar to that of the ixekizumab Phase 3 studies.

The table below summarizes patient demographics for the four studies:

BMI (kg/m <sup>2</sup> )
Psoriasis Durat Years
Abbreviations

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The patient baseline instrument scores from the four studies are shown in Table 10.2 below:

symptoms  
DLQI score  
higher score  
PATGA = F  
Item Short I  
better health

The distribution of Itch NRS scores at baseline for the four studies is shown in Table 10.3 below:

Abbreviations: :

*Reviewer comment: The demographic characteristics represent the plaque psoriasis patient population generally studied in clinical trials. The distribution of Itch NRS scores at baseline*

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*was comparable across the four studies. Within the individual studies, the distribution of Itch NRS at baseline was also very similar with >80% of patients with a baseline score of  $\geq 4$  points with the mean score ranging from 6.3 to 7.3 across the 4 studies. Approximately 2% of the sample had a score of 0 points, while approximately 12.8% had a score of 10 points at baseline across the Phase 3 studies.*

The methodology and results of the psychometric evaluation for all four studies (one study for baricitinib and three studies for ixekizumab) are as follows:

### **Reliability (test-retest):**

The test-retest of an instrument determines reproducibility and refers to an instrument's ability to reproduce identical measurements between testing when no change has occurred in the underlying concept.

*Methodology:* Test-retest reliability of the Itch NRS was assessed in stable patients during the interval between screening (Visit 1) and baseline (Visit 2) in Studies JADP (baricitinib) and RHAZ (ixekizumab). Stable patients were defined as those with the same sPGA ratings between screening and baseline. The intra-class correlation coefficient (ICC) and change scores were calculated between the initial and retest scores to evaluate test-retest reliability. An ICC of  $\geq 0.60$  was considered substantial agreement.

However, in Studies RHBA and RHBC, where Itch NRS data was only collected once prior to randomization, an alternative approach to assess the test-retest reliability for Itch NRS was considered. According to the evidence dossier, the key notion of test-retest reliability is to identify a stable subsample that provides a consistent response to Itch NRS; therefore, patients from the placebo arm were considered the stable subsample. The ICC was used to assess the association between Itch NRS at Week 0 (Visit 2) and Week 1 (Visit 3), and an ICC  $> 0.60$  was an indicator of substantial agreement.

*Results:* The test-retest reliability results indicated substantial agreement (ICC ranged from 0.66 to 0.74 across the studies) among stable patients between the first two Itch NRS assessments as shown in Table 10.4 below:

**Table 10.4.**

Abbreviations: IC

<sup>a</sup> An ICC of 0.6

<sup>b</sup> In Studies JAI

<sup>c</sup> In Studies RH

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*Reviewer comment: Utilizing patients from the placebo arm is acceptable as the ICC for test-retest reliability is above the acceptable range.*

### **Convergent and Discriminant Validity:**

Convergent and discriminant validity is determined by evidence that relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient group. And the validity is concluded when the associations between concepts measured by a specified instrument and concepts measured by other instruments are as expected.

*Methodology:* The Itch NRS was compared with the sPGA, the Patient Global Assessment (PATGA), the PASI, and the DLQI. The Short Form 36 (SF-36) was also used in the ixekizumab phase 3 studies.

Convergent validity was assessed by Pearson correlations at baseline and at Week 12 between scores of the Itch NRS, PASI, sPGA, and PATGA. Cohen's conventions were used to interpret the absolute value of the correlation results (i.e., correlation >0.5 is large, 0.3 to 0.5 is moderate, 0.1 to 0.3 is small, and <0.1 is insubstantial). It was hypothesized that small-to-moderate correlations at baseline and moderate-to-large correlations at Week 12 were expected between the Itch NRS, PASI, and sPGA scores, and moderate-to-large correlations with the PATGA and SF-36 PCS scores.

Convergent validity was also assessed by Pearson correlation at baseline and at Week 12 between scores of the Itch NRS and the DLQI Total Score and its six domains: *Symptoms and Feeling, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment*. It was hypothesized that the Itch NRS would correlate higher with the DLQI Total Score and Symptoms and Feeling domain than with the other 5 DLQI domains.

Discriminant validity was assessed by Pearson correlations at baseline and at Week 12 between scores of the Itch NRS and SF-36 MCS scores in the Phase 3 studies, where small correlations were hypothesized.

*Results:* Table 10.5 below shows that correlations between the patient-reported Itch NRS and clinician-reported PASI and sPGA were small at baseline; and became substantially robust at Week 12, ranging from  $0.52 \leq r \leq 0.79$ , reflecting that the Itch NRS measures a key PRO symptom in addition to that measured by the other clinical measures of psoriatic plaque disease.

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Baseline	Itch N
	Itch N
	sPGA
Week 12	Itch N
(LOCF)	Itch N
	sPGA
Abbreviations: I	
sPGA = static	

The Itch NRS also had higher correlations at week 12 for the DLQI Symptoms and Feeling domains ( $0.60 \leq r \leq 0.67$ ) than the other 5 DLQI domains. And moderate-to-large correlations between the Itch NRS and the PATGA at baseline and week 12 were also observed. Similar results were also observed with the SF-36.

*Reviewer comment: The results of the convergent / discriminant validity analyses supported Eli Lilly's a priori hypotheses and showed that the Itch-NRS related to other relevant measures in a predictable way.*

### Known-Groups Validity:

Analyses of known-groups validity assesses the extent to which a measure's scores are linked to variance in individuals' known health states and characterizes the degree to which scores produced by a target questionnaire can distinguish among groups hypothesized *a priori* to be clinically distinct.

*Methodology:* In all four studies, the known-groups validity of the Itch NRS was evaluated using two-sample t-tests to distinguish the Itch NRS scores between subgroups defined on the basis of sPGA score at baseline: sPGA score of 3 or combined 4 and 5.

*Results:* The ability of the Itch NRS to discriminate between subgroups of patients with different underlying disease severity confirmed. Patients were categorized into two subgroups: 1) baseline sPGA score of 3, and 2) baseline sPGA score of 4 & 5. As hypothesized, patients with more severe plaque psoriasis experienced more severe itching. The mean Itch NRS at baseline ranged from 5.9 to 7.0 among patients with sPGA score of 3 at baseline, but the range became 6.8 to 7.7 among patients with sPGA score >3 as shown in the table below.

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RHBC  
RHBA  
Abbreviation  
Assessment

*Reviewer comment: The ability of the Itch NRS to differentiate between each known group was demonstrated in these studies.*

### Ability to detect change:

Eli Lilly evaluated the ability to detect change of the Itch NRS by evaluating correlation of the change of the Itch NRS with that of the PASI and the PATGA (Table 10.8):

Table 10.8

Change in Itch NRS	Change in PASI	Change in PATGA
Change in Itch NRS	Change in PASI	Change in PATGA
Abbreviation	Abbreviation	Abbreviation
Assessment	Assessment	Assessment

The results confirmed Eli Lilly's hypothesis and showed that statistically significant moderate-to-large correlations were observed between changes in Itch NRS scores and changes in PASI and PATGA scores, respectively, from baseline to Week 12. The change score correlation with PATGA scores was the largest in magnitude across the 4 studies.

Results of the ability of the Itch NRS to discriminate between subgroups of patients whose PASI score improved  $\geq 75\%$  versus those whose PASI score improved  $\geq 50\%$  and  $< 75\%$  versus those whose PASI score got worse or improved  $< 50\%$  are presented in Table 10.10 below.

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*Reviewer comment: In all analyses, the Itch NRS was able to differentiate significantly ( $p < .001$ ) between the 3 subgroups. Among the Phase 3 studies, patients who met PASI 75 improvement at Week 12, their Itch NRS improved the most, ranging from 5.1 to 5.9; followed by patients who met PASI 50 but not PASI 75 improvement, ranging from 3.3 to 3.6; and by patients who did not meet PASI 50, ranging from 0.2 to 1. The results indicate that Itch NRS was sensitive to detect change when disease severity improved, especially for the moderate ( $\geq 50\%$  and  $< 75\%$ ) PASI improvement group. There is evidence that the instrument is sensitive to gains and losses in the measurement concept and to change at all points within the entire range expected for the clinical trial population.*

## 6 INTERPRETATION OF SCORES

Eli Lilly proposed a 4-point improvement as representing a clinically important change in itch based on their exploratory quantitative analyses of a previously conducted clinical trial.

*Reviewer comment: Eli Lilly used a ROC analysis using a clinician reported outcome to arrive at a threshold of 4 points. However, it is unclear how a clinician reported outcome could be an appropriate anchor for a symptom such as itch. For this application, qualitative research to determine a specific threshold of change representing meaningful change from the patient perspective may have been more appropriate approach. Regardless of the responder definition, the cumulative distribution function (CDF) curves demonstrate a robust treatment effect.*

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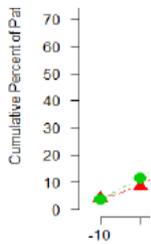
Ixekizumab (TALTZ<sup>®</sup>)

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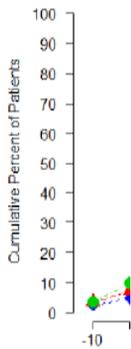
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The cumulative distribution function (CDF) curves of the data from the three ixekizumab studies are shown below and illustrate the cumulative proportion of patients achieving up to a 10-point reduction in Itch NRS from baseline for three studies.

**Figure 11.1. Cumulative distribution curves for Itch NRS change from baseline to Week 12 (LOCF) by treatment group (Study RHAZ).**



**Figure 11.2. Cumulative distribution curves for Itch NRS change from baseline to Week 12 (LOCF) by treatment group (Study RHBC).**



**Figure 11.3. Cumulative distribution curves for Itch NRS change from baseline to Week 12 (LOCF) by treatment group (Study RHBA).**

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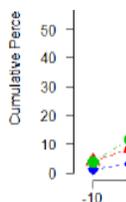
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In all three Phase 3 studies, a higher proportion of ixekizumab-treated patients (approximately 60% to 80%) met the responder definition at Week 12 compared to roughly 10% in the placebo group ( $p < .001$ ). The separations between treatment groups and placebo were greatest at the range of 3-, 4-, and 5-point reductions in Itch NRS in all three of Phase 3 studies respective CDF curves (the same region where the Youden Index was maximized in the baricitinib Phase 2 study (JADP) and the ixekizumab Phase 3 studies).

## 7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Translations and cultural adaptations of the Itch NRS were conducted in accordance with the methods described in the Principles of Good Practice for Translation and Cultural Adaptation, an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report [1]. This included two independent forward translations, one harmonized forward translation, one independent back-translation, reconciliation of back-translation and harmonized translation, review of back-translation by a Survey Research Expert, review of harmonized translation by a clinician reviewer, cognitive debriefing with patients, desktop publishing of validated translation, and proofreading of validated translation in each of the languages and countries shown in Table 12.1 (Source: page 49/381 of the evidence dossier) below.

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1 Wild D et al: Multinational trials-recommendations on the translations, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. *Value Health*. 2009;12(4):430-40.

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United Kingdom

United States

France

Belgium

Canada

Switzerland

Abbreviation: N

## 8 REVIEW USER MANUAL

A user manual was not developed by Eli Lilly for the single-item Itch NRS. Comprehensive investigator training materials provided in the evidence dossier are acceptable.

## 9 PROTOCOL AND ANALYSIS PLAN

Eli Lilly's statistical plan included in the protocol for each of the three ixekizumab studies was reviewed. A gatekeeping testing strategy for the primary and major secondary analyses was implemented to control the overall type I error rate at a 2-sided alpha level of 0.05. This allowed simultaneous inference of all of the primary and major secondary endpoints. The gatekeeping procedure was based on the Bonferroni test and utilizes an intuitive, stepwise testing algorithm. The alpha levels for the p-values associated with the primary and secondary analyses were computed at each step depending on the outcomes of the preceding significance tests.

The responder definition was depicted as a vertical line on the CDF figure. The CDF provides a visual depiction of all patients' change scores and allows for the differentiation in change over time between the treatment and placebo groups across the spectrum of observed change scores. Further to the interpretability analysis, CDF plots were created to illustrate the change from baseline in Itch NRS scores at Week 12 (LOCF) on the X-axis in the PATGA groups, sPGA groups, and PASI groups.

*Reviewer comment: The statistical review dated November 3, 2015 concluded that there were no major statistical issues; the treatment effects were large and consistent across trials and endpoints; and the amount of missing data was relatively small ( $\leq 6\%$ ) at Week 12.*

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**APPENDIX A**

**The Itch Numeric Rating Scale**

Please rate  
level of itch

0      1

0 = No itch

APPEARS THIS WAY ON  
ORIGINAL

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**Appendix B**  
**The Saturation Grid (baricitinib) and**  
**The Item Tracking Matrix for the NRS**

Ps Concept E lesions/patch oozing
Ps Concept E
Ps Concept E lesions/patch

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Ps Concept Eli  
Ps Concept Eli  
Ps Concept Eli  
humiliation/de  
Ps Concept Eli  
humiliation/de

Ps Concept Eli  
Ps Concept Eli  
significant oth  
Ps Concept Eli  
significant oth  
Ps Concept Eli  
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## **Clinical Outcome Assessment Review**

Yasmin Choudhry, M.D.

BLA 125521

Ixekizumab (TALTZ<sup>®</sup>)

Itch Numeric Rating Scale (psoriasis-related itch)

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Abbreviations:  
VAS = Visu

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01/07/2016

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Clinical Review  
Jane Liedtka, MD  
BLA 125521  
Taltz (ixekizumab)

## CLINICAL REVIEW

<b>Application Type</b>	BLA
<b>Application Number(s)</b>	125521
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	March 23, 2015
<b>Received Date(s)</b>	March 23, 2015
<b>PDUFA Goal Date</b>	March 23, 2016
<b>Division/Office</b>	DDDP
<b>Reviewer Name(s)</b>	Jane Liedtka, MD
<b>Review Completion Date</b>	Nov 13, 2015
<b>Established Name</b>	Ixekizumab
<b>(Proposed) Trade Name</b>	Taltz
<b>Applicant</b>	Eli Lilly
<b>Formulation(s)</b>	Solution for sct admin
<b>Dosing Regimen</b>	160 mg at wk 0, followed by 80 mg at wks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 wks
<b>Proposed Indication(s)</b>	moderate-to-severe plaque psoriasis, candidates for systemic therapy or phototherapy
<b>Intended Population(s)</b>	Adults
<b>Recommendation on Regulatory Action Recommended</b>	Approval
<b>Indication(s) (if applicable)</b>	moderate-to-severe plaque psoriasis, candidates for systemic therapy or phototherapy

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## Glossary

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Ab	antibodies
Abnl	abnormal
AC	advisory committee
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
Afib	atrial fibrillation
AI	autoimmune
ANC	absolute neutrophil count
ASA	acetylsalicylic acid
AV	atrio-ventricular
BBB	blood-brain barrier
BLA	biologics license application
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BPH	benign prostatic hypertrophy
BRBPR	bright red blood per rectum
BRF	Benefit Risk Framework
Bx	biopsy
Ca	cancer
CAD	coronary artery disease
CABG	coronary artery bypass graft
Cath	catheterization
CBER	Center for Biologics Evaluation and Research
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDER	Center for Drug Evaluation and Research
C diff	<i>Clostridium difficile</i>
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHF	congestive heart failure
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization

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CRT	clinical review template
CSA	cyclosporine A
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computerized tomography
CVA	cerebrovascular accident
d/c	discontinued
DM	diabetes mellitus
DMC	data monitoring committee
DVT	deep venous thrombosis
Dx	diagnosis
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
Etoh	ethanol (alcohol)
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FH	family history
GCP	good clinical practice
GER	gastroesophageal reflux
GI	gastrointestinal
GRMP	good review management practice
HCTZ	hydrochlorothiazide
Hgb	hemoglobin
h/o	history of
HTN	hypertension
IBS	irritable bowel syndrome
ICH	International Conference on Harmonization
IDP	induction dosing period
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISR	injection site reaction
ISS	integrated summary of safety
ITP	idiopathic thrombocytopenic purpura
ITT	intent to treat
Ixe	Ixekizumab
LE	lower extremity
LTE	long term extension
MDP	maintenance dosing period
Meds	medications

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MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
MRI	magnetic resonance imaging
MTX	methotrexate
MO RV	medical officer review
MRSA	multi-drug resistant staphylococcus aureus
MS	multiple sclerosis
MVP	mitral valve prolapse
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
Neg	negative
NME	new molecular entity
NOS	not otherwise specified
OCP	oral contraceptive
OCS	Office of Computational Science
OLE	open label extension
OPQ	Office of Pharmaceutical Quality
ORIF	open reduction internal fixation
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCP	primary care physician
PD	pharmacodynamics
PE	pulmonary embolus
PFS	prefilled syringe
PI	prescribing information
Pk-yrs	pack-years
PK	pharmacokinetics
Plt	platelet
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PTSD	post-traumatic stress disorder
PUVA	psoralen+ ultra-violet light A
QIDS-SR <sub>16</sub>	quick inventory of depressive symptomatology self- rated (16 question version)
RA	Rheumatoid Arthritis

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REMS	risk evaluation and mitigation strategy
r/o	rule out
Rv	review
Rx	treatment
SAE	serious adverse event
SAP	statistical analysis plan
SCT	subcutaneous
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SOB	shortness of breath
SOC	standard of care, system organ class
s/p	status post
TB	tuberculosis
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TURP	transurethral resection of the prostate
UC	Ulcerative Colitis
UGI	upper gastrointestinal
UTI	urinary tract infection
WNL	within normal limits
X	times

# 1

## 1 Executive Summary

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### 1.1. Product Introduction

Ixekizumab (LY2439821, Ixe) is an immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds (b) (4) to interleukin (IL)--17A, a cytokine. Ixe is a new molecular entity. The pharmacological class for Ixe is an IL-17A antagonist. The proprietary name Taltz has been conditionally accepted in a letter dated June 17, 2015. The proposed dosing regimen is Ixe 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, and then 80 mg every 4 weeks. The proposed dosage forms for Ixe 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 proposed indication is for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted three adequate and well-controlled (placebo and active) clinical trials (RHAZ, RHBA and RHBC) which provided the data that showed substantial evidence of effectiveness of Ixekizumab for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy. The co-primary efficacy endpoints for all three trials were the proportion of subjects achieving a sPGA score of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline at Week 12 and the proportion of subjects achieving a  $\geq 75\%$  improvement in PASI (PASI-75) from baseline at Week 12. Ixekizumab was statistically superior ( $p$ -values  $< 0.001$ ) to placebo for all the primary and key secondary efficacy endpoints. The data provided by the pivotal trials is persuasive and is highly clinically meaningful.

### 1.3. Benefit-Risk Assessment

### Benefit-Risk Summary and Assessment

Ixekizumab (Ixe), a new molecular entity, is a humanized IgG4 monoclonal antibody that selectively binds to the interleukin 17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. Ixekizumab inhibits the release of pro-inflammatory cytokines and chemokines including those implicated in the pathogenesis of psoriasis. With this submission the applicant is seeking claims for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is Ixe 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, and then 80 mg every 4 weeks. Based on evidence from three strongly positive adequate and well-controlled phase III trials, I am recommending approval of this product.

Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations affecting approximately 2-3 % of the US population. Moderate to severe psoriasis is a serious and at times disabling condition that has a substantial impact on patient's lives. There are multiple drugs approved for psoriasis that have an acceptable risk-benefit profile and achieve moderate to high efficacy for the treatment of moderate to severe disease. All of the approved products have significant risks and there is room for both more efficacious and potentially safer products for these patients.

For the induction dose [REDACTED] (b) (4) (Ixe 80mg Q 2 Weeks) the proportion of responders for a sPGA of 0 or 1 were 82%, 83% and 81% and the proportion of PASI 75 responders were 89%, 90% and 87% respectively, for trials RHAZ, RHBA and RHBC. This improvement places Ixe in a "highly efficacious" category which is highly clinically meaningful. From a benefit perspective Ixe should be placed in the category of first line treatments for patients with moderate to severe psoriasis. Exclusion criteria for the pivotal trials included a history of suicide attempt, uncontrolled neuropsychiatric disease or frequent active suicidal ideation which limits the generalizability of the findings to this subpopulation.

The safety profile demonstrated for Ixe is consistent with the known safety profiles of other systemic agents used for the treatment of moderate to severe psoriasis and includes risks of immunosuppression with the associated risk for serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease and hypersensitivity events. Injection site reactions, upper respiratory tract infections, nausea and tinea infections were reported in  $\geq 1\%$  in the pivotal trials.

A detailed safety evaluation focusing on a potential increased risk for suicidal behavior was conducted because of suicidality concerns with another product that blocks IL-17A. At this time, the clinical trials data for Ixe do not support a causal link between Ixe therapy and suicidal events, in my judgment. I recommend ongoing monitoring through pharmacovigilance in the post-market setting as the primary method to

further assess this potential signal.

The safety and efficacy of Ixe in pediatric patients has not been established; however, the pediatric studies are deferred so as not to delay approval in adults.

Approval of Ixe for the treatment of moderate to severe psoriasis in adults is fully supported by the available evidence of efficacy and safety. Although there are a number of approved treatments for this condition, an individual patient may require several trials with different systemic agents before an effective and reasonably-tolerated treatment is identified. Given the clear evidence of benefit and in the context of risks similar to other approved products with similar indications, I recommend approval of this product for the treatment of moderate to severe psoriasis. Ixe represents an important new therapy to address the treatment of moderate to severe plaque psoriasis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>• Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations affecting approximately 2-3 % of the US population. Approximately 80% of those affected with psoriasis have mild to moderate disease, with 20% having moderate to severe psoriasis affecting more than 5% of the body surface area.</li> <li>• Psoriasis is a disabling disease which has important social, psychological and economic consequences. The impact of psoriasis on the quality of life is reported to be comparable with that observed in other chronic medical conditions such as diabetes and depression.</li> <li>• The National Psoriasis Foundation (NPF) conducted a survey in 2014 (811 respondents) which reported the following negative impact on the Quality of Life (QoL) in psoriasis patients: nearly 60% say psoriasis impacts their self-esteem and emotional well-being, more than two-thirds avoid social activities, including dating and intimacy and 51% of patients state that they are un- or undertreated, the top two reasons being fear of side effects and cost or perceived cost of therapy.</li> </ul>	<p>Moderate to severe psoriasis is a serious and at times disabling condition that has a substantial impact on patient’s lives. Safe and effective treatment has the potential to greatly improve the quality of life for a patient with moderate to severe psoriasis.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Current Treatment Options</a></p>	<ul style="list-style-type: none"> <li>• Currently approved drugs for the treatment of moderate to severe psoriasis include the anti-metabolite methotrexate (MTX), tumor necrosis factor (TNF) inhibitors such as etanercept, adalimumab and infliximab, IL-12+23 antagonist ustekinumab, IL-17A antagonist secukinumab, T cell inhibitor cyclosporine (CSA), retinoid soriatane and phosphodiesterase 4 inhibitor apremilast. Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) is also a standard of care treatment for moderate to severe psoriasis patients. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI) with the change from baseline as the most common primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75 ≥ 70%) for cyclosporine, infliximab, adalimumab, ustekinumab and secukinumab to moderately efficacious (PASI 75 ≥ 40%) for methotrexate and etanercept to somewhat efficacious (PASI 75 ≥ 20%) for acitretin and apremilast<sup>1</sup>. Phototherapy is highly efficacious as well<sup>2</sup>.</li> <li>• Significant safety concerns for the moderately and highly efficacious approved products include immunosuppression with the associated risk for serious and in some cases opportunistic or unusual infections, cytopenias, hepatotoxicity and hypersensitivity events. See Table 1 for specifics for each product.</li> </ul>	<p>There are multiple drugs approved that have an acceptable risk-benefit profile for the treatment of moderate to severe psoriasis. All of the approved products have significant risks and there is room for both more efficacious and potentially safer products for these patients.</p>
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>• Trials RHAZ (placebo controlled (PC), induction dosing period(IDP), maintenance dosing period(MDP) and long term extension (LTE) dosing period), RHBA (active and PC, IDP, MDP and LTE period) and RHBC (active and PC, IDP and LTE period) evaluated two dose regimens of Ixe (80mg Q2Weeks (W) +80mgQ4W during IDP and 80mgQ4W+80mgQ12w for MDP). There were 2334 subjects treated with Ixe during the pivotal trials.</li> </ul>	<p>The evidence submitted by the applicant to support the approval of Ixekizumab has met the statutory evidentiary standard for providing substantial</p>

<sup>1</sup> This reviewer has created this efficacy grading system for convenient reference purposes, it is not published.

<sup>2</sup> Henry W. Lim, MD et al. Phototherapy in dermatology: A call for action. JAAD. Vol # 72: 6, June 2015, Pages 1078–1080

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>The co-primary efficacy endpoints were the proportion of subjects achieving a sPGA score of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline at Week 12 and the proportion of subjects achieving a <math>\geq 75\%</math> improvement in PASI (PASI-75) from baseline at Week 12.</li> <li>Key secondary endpoints included the proportion of subjects with PASI-90 and PASI-100.</li> <li>For all three trials, both dose regimens of Ixe were statistically superior (p-values <math>&lt; 0.001</math>) to placebo for all primary and key secondary efficacy endpoints. For the induction dose proposed for marketing (Ixe 80mg Q2Weeks) the proportion of responders for a sPGA of 0 or 1 were 82%, 83% and 81% and the proportion of PASI 75 responders were 89%, 90% and 87% respectively for trials RHAZ, RHBA and RHBC. For the induction dose proposed for marketing the proportion of PASI 90 responders were 71%, 71% and 68% respectively for trials RHAZ, RHBA and RHBC. For the induction dose proposed for marketing the proportion of PASI 100 responders were 35%, 40% and 38% respectively for trials RHAZ, RHBA and RHBC.</li> <li>The data provided by the pivotal trials is persuasive and is highly clinically meaningful. The design of the trials was in accord with FDA’s advice during development (with a few exceptions noted in this review). The endpoints were appropriate, clinically relevant and similar to endpoints for previously approved products for this indication. The treatment effect was large and consistent across trials and within subgroups. The duration of the effect was adequate.</li> <li>The proportion of responders with a high degree of improvement indicates that Ixe is a highly efficacious product and the findings are of great relevance to patients and prescribers.</li> <li>The only limitation noted for the Ixekizumab development program was in study design and was the exclusion of subjects with a history of uncontrolled neuropsychiatric conditions, suicide attempts or a current score of <math>\geq 3</math> on item #12 of the QIDS which indicated active suicidal ideation or a past suicide attempt. This may limit the generalizability of the results with regard to safety in this subpopulation in the post-marketing setting.</li> </ul>	<p>evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. For the induction dose proposed for marketing (Ixe 80mg Q2Weeks) the proportion of responders for a sPGA of 0 or 1 were 82%, 83% and 81% and the proportion of PASI 75 responders were 89%, 90% and 87% respectively for trials RHAZ, RHBA and RHBC. The improvement seen with treatment with Ixe places this product in the “highly efficacious” category and is highly clinically meaningful.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk</u></p>	<ul style="list-style-type: none"> <li>• The safety database for Ixe includes all patients from the 3 pivotal trials RHAZ, RHBA and RHBC, supportive data from 4 additional trials in psoriasis patients and 1 trial in rheumatoid arthritis patients. The drug exposure data is considered adequate.</li> <li>• The safety profile demonstrated for Ixe is consistent with the known safety profiles of other systemic agents used for the treatment of moderate to severe psoriasis and includes risks of immunosuppression with the associated risk for serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease and hypersensitivity events.</li> <li>• Injection site reactions, upper respiratory tract infections, nausea and tinea infections were reported in ≥ 1% in the pivotal trials.</li> <li>• A detailed safety evaluation focusing on a potential increased risk for suicidal behavior was conducted because of suicidality concerns with another product that blocks IL-17A. At this time, the clinical trials data for Ixe do not support a causal link between Ixe therapy and suicidal events, in my judgment. I recommend ongoing monitoring through pharmacovigilance in the post-market setting as the primary method to further assess this potential signal.</li> </ul>	<p>The safety profile for Ixe is consistent with the known safety profiles of other systemic agents used for the treatment of psoriasis and includes risks of immunosuppression with serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease and hypersensitivity events. A safety evaluation of a potential increased risk for suicidality was conducted because of concerns with another product that blocks IL-17A. The clinical trials data for Ixe do not, however support a causal link between Ixe therapy and suicidal events, in my judgment.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>• The safety concerns associated with the use of Ixe for moderate to severe psoriasis are well documented. Healthcare providers are familiar with treatment regimens that include immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including IL-17A inhibitors.</li> <li>• Exclusion criteria for the pivotal trials included a history of suicide attempt, uncontrolled neuropsychiatric disease or frequent active suicidal ideation which limits the generalizability of the findings to this subpopulation.</li> <li>• The safety and efficacy of Ixe in pediatric patients have not been studied. The Applicant requested a waiver of pediatric studies in patients less than 7 years old, and a deferral in patients' ≥7 to &lt; 18 years of age. <ul style="list-style-type: none"> <li>○ The prevalence of moderate to severe psoriasis in infants and young children is low. The necessary studies in this population would be impossible or highly impractical.</li> <li>○ The Applicant plans to evaluate Ixe in patients ≥7 to &lt;18 with moderate to severe psoriasis. Details of the revised pediatric plan are under discussion at the time of this review closure.</li> </ul> </li> <li>• The risks associated with this drug can be adequately managed via the product labeling, a medication guide and pharmacovigilance in the post-marketing setting.</li> </ul>	<p>Labelling indicates that approval is only for adults. Studies in children &lt; 7 years of age are waived. Studies in children age <sup>(b)</sup><sub>(4)</sub> are deferred so as not to delay approval in adults. A medication guide will be included in labeling for this product. No REMS is required. No additional risk management interventions beyond professional labeling, a medication guide and pharmacovigilance are required.</p>

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Psoriasis is a common, genetically determined, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2-3 % of the US population. Onset occurs most commonly in the 20s with a second peak of incidence in the 50-60s. Chronic stable plaque psoriasis (psoriasis vulgaris) is the commonest form of the disease, accounting for 85-90 % of cases. The circumscribed infiltrated skin lesions are scaly and erythematous and often symmetrically distributed over the body. The clinical course is unpredictable but in the majority of cases psoriasis is a chronically remitting and relapsing disease.

Epidemiological studies indicate that some diseases (e.g. arthritis, colitis) are quite frequently associated with psoriasis. Younger ages of onset and positive family history have been associated with more widespread and recurrent disease. Psoriasis can be highly variable in morphology, distribution, and severity. Approximately 80% of those affected with psoriasis have mild to moderate disease, with 20% having moderate to severe psoriasis affecting more than 5% of the body surface area. Psoriasis affects men and women equally but has decreased incidence in Native Americans, Asians and African Americans. The diagnosis of psoriasis is based on clinical presentation but skin biopsy can provide supportive information in cases with unusual presentations.

Psoriasis is a disabling disease which has important social, psychological and economic consequences. The impact of psoriasis on the quality of life is reported to be comparable with that observed in other chronic medical conditions such as diabetes and depression. Psychological stress can also lead to depression and anxiety. The prevalence of suicidal ideation and depression in patients with psoriasis is higher than that reported in other medical conditions and in the general population.

Therapeutic choices for chronic plaque psoriasis are typically based on the extent of the disease. Individuals with conditions that limit their activities, including painful palmoplantar involvement and psoriatic arthritis, may require more potent treatments irrespective of the extent of affected body surface area. Likewise, psychological issues and the impact on quality of life should be taken into consideration.

The National Psoriasis Foundation (NPF) conducted a survey in 2014 (811 respondents) which reported the following negative impact on the Quality of Life (QoL) in psoriasis patients

- Nearly 60% say psoriasis impacts their self-esteem and emotional well-being

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- Almost half are uncomfortable in public
- More than two-thirds avoid social activities, including dating and intimacy
- Over half report difficulty on the job
- Nearly two-thirds report significant itching and irritation
- About half have serious pain
- 41% consider their psoriasis disfiguring
- Almost two-thirds feel self-consciousness and embarrassed
- 51% of patients state that they are un- or undertreated, the top two reasons being fear of side effects and cost or perceived cost of therapy

Of the 811 respondents to the NPF 2014 survey, most had moderate psoriasis (57%) defined as 3-10 palms of their body surface area affected, 9% had extensive psoriasis (defined as 11-20 palms of their body surface area affected) and 8% had very extensive psoriasis (defined as > 20 palms of their body surface area affected).

In conclusion, moderate to severe psoriasis is a serious and at times disabling condition that has a substantial impact on patient's lives. Safe and effective treatment has the potential to greatly improve the quality of life for a patient with moderate to severe psoriasis.

## 2.2. **Analysis of Current Treatment Options**

The proposed indication for Ixe is for patients with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Moderate-to-severe psoriasis is typically defined as involvement of more than 5 to 10 percent of the body surface area or involvement of the face, palm or sole, or disease that is otherwise disabling. Patients with more than 5 to 10 percent body surface area affected are generally candidates for systemic therapy, since application of topical agents to a large area is not usually practical, cost-effective or acceptable for most patients. Attempts to treat extensive disease with topical agents are often met with failure and lead to frustration in the patient-clinician relationship. A recommendation for systemic therapy or phototherapy is based on clinical judgment and the decision to proceed is one made between patient and physician with careful attention to risk-benefit considerations, since all of the systemic therapies carry significant risk.

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Currently approved drugs for the treatment of moderate to severe psoriasis include the antimetabolite methotrexate, tumor necrosis factor inhibitors such as etanercept, adalimumab, infliximab, IL-12+23 antagonist ustekinumab, IL-17A antagonist secukinumab, T cell inhibitor cyclosporine, retinoid soriatane and phosphodiesterase 4 inhibitor apremilast. In addition, phototherapy, either UVA light combined with the psoralen methoxsalen or UVB light therapy (narrow or broadband) is a standard of care treatment for moderate to severe psoriasis patients.

The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI) with the change from baseline as the most common primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75  $\geq$  70%) for cyclosporine, infliximab, adalimumab, ustekinumab and secukinumab to moderately efficacious (PASI 75  $\geq$  40%) for methotrexate and etanercept to somewhat efficacious (PASI 75  $\geq$  20%) for acitretin and apremilast. Phototherapy is highly efficacious as well.<sup>3</sup>

In 2008-2009, the Journal of the American Academy of Dermatology (JAAD) published guidelines for the management of psoriasis and psoriatic arthritis<sup>4</sup>. These guidelines were divided into 5 sections and covered topical and systemic therapies including phototherapy with an “emphasis on decision-making criteria that enable the clinician to individualize therapy based on disease type, extent, response to previous treatments, quality-of-life issues, and comorbidities”.

In Section 1 of the JAAD guidelines, the overview, the following recommendations and comments are made. This reviewer has added additional information in *italics* where appropriate to try to present a balanced picture of the risk-benefit profile for each therapy. More specific information regarding these therapies including efficacy findings from the clinical studies section of labeling are presented in Table 1 that follows.

- UVB is safe and effective. However, 20-25 narrowband UVB treatments, given 2-3 times per week are usually required for significant improvement. *This can mean significant out of pocket costs for the patient for visit copays as well as time lost from work. UVB may not be available in all locations.*
- PUVA therapy is very effective in the majority of patients, with potential for long remissions. However, long-term PUVA treatment in Caucasians is associated with an increased risk of squamous cell carcinoma and possibly malignant melanoma. *In addition, PUVA has the*

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<sup>3</sup> Henry W. Lim, MD et al. Phototherapy in dermatology: A call for action. JAAD. Vol # 72: 6, June 2015, Pages 1078–1080

<sup>4</sup> Menter, A et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. JAAD 2008; 58: 826-850.

*same disadvantages regarding time lost and cost as stated above for UVB, is associated with skin aging changes and is contraindicated in pregnancy.*

- Methotrexate, although effective in the majority of patients, has the potential for hepatotoxicity and is contraindicated in the following clinical scenarios: pregnancy; individuals with renal impairment, hepatitis, or cirrhosis; alcoholics; unreliable patients...drug interactions are common...bone-marrow suppression a concern... may induce pneumonitis...is a teratogen, an abortifacient, and decreases sperm count. Prior guidelines suggest a liver biopsy after 1.5-g cumulative dose.
- Cyclosporine (CSA)...works rapidly and is effective in the majority of patients. However, impaired renal function, hypertension, concerns about lymphoma, and a potential increase in cutaneous malignancies are known adverse effects after long-term treatment...best used... in short-term courses of 3 to 4 months...numerous potential drug interactions...guidelines exist for reducing the CSA dose in patients who develop hypertension or elevations in creatinine.
- Acitretin is an effective systemic agent for the treatment of psoriasis that is not immunosuppressive. Because it is teratogenic and should not be used in women who are pregnant, breast-feeding, or may become pregnant within 3 years of discontinuing acitretin, its use is substantially limited in female patients...mucocutaneous side effects are frequent... dyslipidemia may require dose reduction or treatment with lipid-lowering agents... hepatotoxicity is rare.
- The TNF inhibitors (etanercept, adalimumab, infliximab) are effective (see Table \*\* for details)... Pregnancy category B.

All of the TNF inhibitors carry the following warnings and precautions:

- Increased risk of infection (upper respiratory tract infections being the most common)
- Serious infections - uncommon (underlying predisposing medical conditions -more at risk)
- Rare opportunistic infections (histoplasmosis, listeriosis, coccidioidomycosis, cryptococcosis, aspergillosis, candidiasis, and pneumocystis) more often- infliximab or adalimumab than etanercept
- Reactivation of TB, higher risk for developing TB, increased incidence of extra-pulmonary or disseminated cases of TB
- Hepatitis B reactivation
- Peripheral and central demyelinating disorders, including MS... to develop but also to worsen... Congestive heart failure (CHF) – controversial-avoid in NYHA Class III or up
- Drug-induced lupus-like syndromes
- Hepatic disease – infliximab
- Lymphoma – controversial – anecdotal- positive dechallenge cases
- Cutaneous malignancies – increased risk
- Cytopenias-individual case reports
- Anaphylaxis-serious allergic reactions-Injection site reactions-infusion reactions
- Development of antibodies

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- Hepatosplenic T-Cell lymphomas – infliximab and adalimumab with concomitant immunosuppressives – Crohns or UC adolescent males

Ustekinumab (2009) had just been approved at the time of publication of the JAAD guidelines and is only briefly mentioned. Secukinumab (approved in 2015) and apremilast (approved in 2014) were not included in the JAAD guidelines.

Safety concerns for ustekinumab stated in the label include serious infections, malignancies, anaphylaxis, and reversible posterior leukoencephalopathy syndrome. In 2015 Leonardi published a review of biologic use for psoriasis<sup>5</sup> and reported on ustekinumab treatment in 800 patients (517 completers) over 5 years. He stated “through 5 years of continuous treatment, ustekinumab maintained a stable effectiveness and safety profile in patients with psoriasis that was consistent with the observations seen in the shorter-term pivotal trials used for product registration”.

Safety concerns for secukinumab stated in the label include serious infections, Crohn’s disease and hypersensitivity reactions. There is limited available data on the long term safety of secukinumab.

There is ample evidence of efficacy for the systemic biologic therapies; however, high cost prohibiting or limiting their use is a major consideration with these agents. A drug use consult was obtained from the Division of Epidemiology II (DEPII) in an attempt to present some estimates of which of the above mentioned agents are used most commonly by practitioners. The consult provided the “nationally estimated number of times a product was reported (i.e. drug use mentions) for the treatment of psoriasis (ICD-9 696.x), stratified by patient age, as reported by U.S. office-based physician surveys, January 1, 2009 to June 30, 2015, cumulative. For adults 18 years or older, etanercept and methotrexate were the most commonly reported products associated with a diagnosis of psoriasis; each accounted for 30% of the total share (1.8 million mentions each), respectively. Adalimumab and ustekinumab accounted for ≈ 21% (1.3 million mentions) and 8% (528,000 mentions) of the total share, respectively. Apremilast and acitretin, each accounted for ≈ 4% of the total share (235,000 mentions and 238,000 mentions), respectively. Finally, infliximab accounted for approximately 2% of the total share (112,000 mentions). Cyclosporine, secukinumab (approved 1/21/15), methoxsalen, and hydroxyurea were below the acceptable count (<100,000 mentions) to provide a reliable national estimate of use.

In summary, there are multiple drugs approved that have an acceptable reasonable risk-benefit profile for the treatment of moderate to severe psoriasis. That being said, all of the approved

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<sup>5</sup> Craig L. Leonardi, MD. Et al. Ten Years On The Impact of Biologics on the Practice of Dermatology. *Dermatol Clin* 33 (2015) 111–125.

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products have significant risks and there is room for both more efficacious and potentially safer products for these patients.

**Table 1: Summary of Treatment Armamentarium for Moderate to Severe Psoriasis**

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
<b>FDA Approved Treatments</b>					
<b>Antimetabolite/ Immunosuppressant</b>					
Methotrexate 1972	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy	Psoriasis: Starting Dose Schedules 1. Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved. 2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/wk should not ordinarily be exceeded.	No efficacy information for psoriasis in the label.  AAD guidelines <sup>6-3</sup> trials quoted Heydendael et al <sup>7</sup> : Mtx vs CSA (no placebo arm), PASI 75 at 16 weeks 60%-mtx vs 71% CSA (no statistically significant difference) Flytstrom et al <sup>8</sup> Mtx vs CSA (no placebo arm), mean PASI change from baseline 58%-mtx vs 72%-CSA Saurat et al <sup>9</sup> DB,PC mtx vs adalimumab vs placebo PASI 75 at 16 weeks Mtx-36% vs adalimumab- 80% vs placebo-19%	Boxed Warning (BW)- potentially fatal toxic reactions including hepatotoxicity, bone marrow suppression, aplastic anemia, gastrointestinal toxicity, pulmonary toxicity and opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies “should not be used in pregnant women with psoriasis”	Major AE derm dosing: ↑LFT’s stomatitis, diarrhea, nausea and vomiting, lymphopro- liferative disorders  Pregnancy: X
<b>Tumor Necrosis Factor Inhibitors</b>					
Infliximab (Remicade)	Chronic severe	5 mg/kg at 0, 2 and 6 weeks, then	From the label: 3 R,DB,PC <sup>10</sup> trials	BW: risk of serious infections (bacterial	Pregnancy: B

<sup>6</sup> Menter, A et al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. JAAD 2009; 61 #3:451-485.

<sup>7</sup> Heydendael VM et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003; 349:658-65.

<sup>8</sup> Flytstrom I et al, Methotrexate vs cyclosporin in psoriasis: effectiveness, quality of life and safety. a randomized controlled trial. Br J Dermatol 2008; 158:116-21.

<sup>9</sup> Saurat JH et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008; 158:558-66.

<sup>10</sup> R=randomized, DB=double-blind, PC= placebo-controlled

2006	(extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy	every 8 weeks	PASI75 at week 10 1-Inflix <sup>11</sup> (5mg/kg)-80% vs 3% placebo 2- Inflix (5mg/kg)-75% vs 2% placebo 3- Inflix (5mg/kg)-88% vs Inflix (3mg/kg) 72% vs 6% placebo	sepsis, TB, invasive fungal and opportunistic), Hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy	
Adalimumab (Humira) 2008	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	80 mg initial dose, followed by 40 mg every other week starting one week after initial dose	From the label: 2 R, DB, PC <sup>5</sup> trials PASI75 at week 16 1-Ada <sup>12</sup> -71% vs 7% placebo 2- Ada-78% vs 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), Warnings: hypersensitivity reactions, Hep B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome	Pregnancy: B
Etanercept (Enbrel) 2004	Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy	50 mg twice weekly for 3 months, followed by 50 mg once weekly	From the label: 2 R, DB, PC5 trials PASI75 at 3 months 1-Etan <sup>13</sup> -47% vs 4% placebo 2-Etan-46% vs 3% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, pancytopenia, malignancy, Hep B reactivation	Pregnancy: B
<b>IL- 12 +23 antagonist</b>					
Ustekinumab (Stelara)	Moderate to severe	For patients weighing <100 kg	From the label: 2 R, DB, PC trials	Warnings and Precautions (W&Ps):	Pregnancy: B

<sup>11</sup> Inflix=infliximab  
<sup>12</sup> Ada=adalimumab  
<sup>13</sup> Etan= etanrecept

2009	psoriasis, candidates for phototherapy or systemic therapy	:45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks For patients weighing >100 kg: 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks	PASI75 at week 12 1-uste <sup>14</sup> (90mg)-66% vs uste(45mg)-67% vs 3% placebo 2-uste (90mg)-76% vs uste(45mg)-67% vs 4% placebo	Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	
<b>IL- 17A antagonist</b>					
Secukinumab (Cosentyx) 2015	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From the label: 4 R, DB, PC trials PASI75 at week 12 1-sec <sup>15</sup> (300mg)-82% vs sec (150mg)-71% vs 4% placebo 2-sec (300mg)-76% vs sec (150mg)-67% vs 5% placebo 3-sec (300mg)-75% vs sec (150mg)-69% vs 0% placebo 4-sec (300mg)-87% vs sec (150mg)-70% vs 3% placebo	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB.	Pregnancy: B
<b>T-Cell Inhibitor/ Immunosuppressant</b>					
Cyclosporine 1997	Severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.	From the label: PASI75 - 51% at 8 weeks, 79% at 16 weeks	BW-Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx-	Pregnancy Category C

<sup>14</sup> Uste=ustekinumab

<sup>15</sup> Sec= secukinumab

					↑ risk of skin malignancies	
<b>Retinoid</b>						
Acitretin (Soriatane) 1996	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments		Starting dose: 25 to 50 mg per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	From the label: 2 DB, PC trials- Mean change in PGA at 8 weeks A-Acitretin(50mg)-2 vs -0.29 on placebo B- Acitretin (50mg)-1.57 vs Acitretin (25 mg)-1.06 vs -0.06 on placebo (no multiplicity adjustment for trial B)	BW-pregnancy must be prevented during Rx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @ FDA for details. Patients cannot donate blood for 3 years post Rx, See label for data on pregnancies in partners of male patients on acitretin	W&P: hepatotoxicity, skeletal abnormalities, lipids↑, Cardiovascular risk ↑, Ophthalmologic effects, Pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression  Pregnancy category X
<b>Phosphodiesterase 4 (PDE4) inhibitor</b>						
Apremilast (Otezla) 2014	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy		To reduce risk of gastroin-testinal symptoms, titrate to recommended dose of 30 mg twice daily	From the label: 2 R, DB, PC trials PASI75 at 16 weeks 1- aprem <sup>16</sup> 33% vs 5% in placebo 2- aprem 28.8% vs 5.8% in placebo	W&P: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine, phenytoin)	Diarrhea, nausea, URI, headache  Pregnancy Category C
<b>Phototherapy</b>						
PUVA-8-MOP (methoxsalen) + UVA therapy ? year approved	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy		20 -70 mg (based on weight) taken 2-4 hours before exposure to UVA light	No efficacy information for psoriasis in the label.  AAD Guidelines: 2 systematic reviews: 70-100% of patients achieved skin clearing	BW: Should only be used by MDs who have special competence in psoriasis management, serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion

<sup>16</sup> aprem=apremilast

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						Pregnancy category C
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### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Ixe is a new molecular entity and is not currently marketed. Ixe is being developed for psoriasis under IND 100834 (b) (4)

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

The psoriasis program was conducted under IND 100834. The initial IND was submitted on Nov 1, 2007. The FDA has issued 15 Advice/Information request letters for this program from May 2008 through September of 2014. In addition, the FDA has provided feedback to the sponsor in 8 Guidance meetings and 1 Pre-BLA meeting. Of note, the sponsor did not have an EOP2 meeting or SPA with the FDA. Key Presubmission regulatory activities included the following:

- A teleconference was held on Jan 29, 2008 to discuss a phase 1 study that was placed on hold due to the death of monkey (due to unknown cause) who was treated with 5 mg/kg/wk in a nonclinical study. The event was investigated, a safety update on ongoing clinical studies outside the US (OUS) was provided, the phase 1 study stopping criteria were revised and a complete response to clinical hold was submitted on Feb 6, 2008. The hold was removed on May 2, 2008.
- On June 22, 2011 a guidance meeting (originally requested as an EOP2 meeting) was held. Additional phase 2 dose-ranging, evaluation of dosing for maintenance treatment (including retreatment upon relapse) and investigation of weight based dosing were recommended. A 5 grade PGA was recommended as the primary endpoint measure. The sponsor was advised that “Trials utilizing comparator products should use the U.S. approved drug/biological product according to the approved labeled directions. Information should be provided to the IND related to the source and manufacturing facility for comparator products”. The Agency acknowledged the importance of “itching” as a relevant concept for psoriasis trials, provided general advice on itch assessment and recommended an 11 point numerical rating scale (NRS). The Agency stated that “routine ECG monitoring in Phase 3 should be sufficient to detect significant cardiovascular effects for this new molecular entity”. Comments were also conveyed regarding autoinjector performance, biocompatibility studies and human factors studies.
- Comments regarding phase 3 protocols were conveyed on Feb 7, 2012, May 30, 2012, July 9, 2012, July 18, 2012, April 9, 2013 and April 17, 2013. These included additional advice

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regarding the source of etanercept and the fact that the acceptability of the sponsor's approach to support comparative labeling claims would be a review issue.

- Comments regarding the human factors studies and autoinjector evaluation were conveyed in Advice letters sent on May 22, 2014, June 13, 2013 and Sept 25, 2014. In addition a guidance meeting was held on Nov 7, 2012 to discuss drug delivery devices including performance, stability testing and human factors studies. Two written response only meetings to further discuss delivery devices were granted and the letters conveying the written responses were dated Sept 4, 2013 and Nov 1, 2013.
- A written response only meeting to discuss the logistical and formatting aspects of the planned BLA prior to the pre-BLA meeting was granted and the letter conveying the written response was dated Jan 28, 2014. This included the following comments
  - You have recently identified allergy/hypersensitivity as potential risk associated with Ixe administration. In order to fully understand the spectrum and nature of these reactions, we recommend that events for allergic reactions/hypersensitivities include both moderate and severe reactions.
  - You propose five integrated analysis datasets for safety:
    - 1. Integrated RHAZ, RHBA, and RHBC dataset (Induction Dosing Period)
    - 2. Integrated RHBA and RHBC dataset (Induction Dosing Period)
    - 3. Integrated RHAZ and RHBA dataset (Maintenance Dosing Period)
    - 4. Integrated RHAG, RHAJ, RHAZ, RHBA, RHBC, RHAT, and RHBL dataset (All Study Periods)
    - 5. All Rheumatoid Arthritis (RA) Ixe Exposures Integrated Analysis Set

Your proposal is acceptable.

- The impact of weight should be assessed according to earlier recommended weight categories for RHBL study: <80 kg, 80 to 100 kg and >100 kg.
- In addition to infections, allergic reactions/hypersensitivities, and injection site reactions you have identified hepatic AEs, cytopenias, CV AEs, malignancies and depression as adverse events of special interest (AESI)s. Based upon our current understanding of Ixe safety profile, the listing is adequate.
- An advice letter containing an agreed upon PSP was sent on March 10, 2014. This letter contained the following statements

We have completed our review of the submission and acknowledge your plan to request a waiver for subjects 0 to 6 years old and to defer your pediatric study plan (PSP) in subjects (b) (4) years old until such time as adult safety experience can be evaluated. We also acknowledge your intent to conduct trials in pediatric subjects outside the United States (US) to satisfy regulatory requirements for non-US jurisdictions. The adequacy of these trial(s) to address the US regulatory requirements for pediatric safety and efficacy data (i.e., PREA) cannot be determined at this time, as safety and efficacy for adults has not yet been evaluated by the Agency.

- A guidance meeting was held on April 30, 2014 to discuss the Itch NRS responder definition and strategy for analyzing and reporting Itch NRS data in the (Ixe) Phase 3 psoriasis clinical program. Some of the comments conveyed at that meeting included
  - Additional information will be necessary to evaluate who might be clinically meaningful responders for this patient reported outcome, particularly since you did not establish inclusion criteria with respect to the Itch NRS in the phase 3 protocols.
  - The selection of clinically meaningful responders needs to take into consideration that, for example, the clinical implications of a subject with a baseline Itch NRS of 4 who would be a “responder” might be different that subjects who have a baseline Itch NRS of 10 and demonstrate the same numerical decrease on the Itch NRS.
  - Placebo success rates for PRO are often high and responder cutoff of 3 points on itch NSR is difficult to accept as clinically meaningful in the absence of placebo data for comparison.
  - You should propose a higher cutoff point for the success criterion on the itch NRS scale.
  - Subjects who are “clear” on the sPGA are expected to have no itch. You might consider an approach based on the subset of subjects who were clear on the sPGA scale.
- A CMC guidance meeting was held on July 30, 2014 to discuss minimum required dilution (MRD) data, approaches to cut point determination, assay sensitivity to detect anti-drug antibodies (ADA) and determining treatment emergence.
- A guidance meeting to discuss the bridge between US and EU etanercept was scheduled for Sept 17, 2014. The sponsor withdrew their meeting request on Aug 26, 2014 stating that “Based on these findings, [that results from RHBA and RHBC showed Ixe was superior to etanercept in the overall study population and in the US-only population] coupled with the robust bridging package which provides our scientific justification for inclusion of the EU-approved etanercept data from Studies RHBA and RHBC, Lilly will provide compelling evidence to support a labeling claim for superiority of Ixe to etanercept in the BLA. As a result, Lilly respectfully withdrawals its request for the scheduled Type C meeting on 17 September 2014 to discuss its plans to bridge between US- and EU-sourced etanercept.” The OND Therapeutic Biologics and Biosimilars Team (TBBT), when informed of the cancellation advised DDDP “please note that the bridging strategy they outlined in the meeting briefing is concerning and will need to be discussed once Lilly does submit”.
- A Pre-BLA meeting was held on Oct 29, 2014. Some of the comments conveyed at that meeting included
  - Based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.
  - Overall your application appears adequate for filing.
  - We recommend that you conduct a clinical trial (can be done as a post-approval

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study) to assess whether Ixe alters the metabolism or pharmacokinetics of CYP substrates in the target psoriasis patient population treated with Ixe.

### 3.3. Foreign Regulatory Actions and Marketing History

This section is not applicable as Taltz is not approved in any other jurisdiction at the time of this review.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

Three sites were chosen for inspection for the following reasons:

- Dr. Blauvelt’s site was selected because of its participation in two trials (RHAZ and RHBC) and because the results were not consistent across trials (Ixe 80 mg Q2W: 93% vs 79% / Ixe 80 mg Q4W: 86% vs. 56%).
- Dr. Bukhalo’s site was selected for inspection because of its participation in two trials (RHAZ and RHBC) and because the results for etanercept (an approved product for this indication) were very low (i.e., 8% for success on sPGA). In addition, the results for the Ixe treatment arms were also much lower than the overall average.
- Dr. Birbara’s site was selected for Trial RHBA because the results for all three active treatment arms were very low, especially for etanercept (i.e., 9% for success on sPGA).

**Table 2: Results of Inspections by Site**

	Protocol #/ #Subjects	Inspection Dates	Final Classification
Blauvelt, Andrew Portland, OR Site #102	I1F-MC-RHBC- 52 enrolled I1F-MC-RHAZ- 40 enrolled	14 Jul-10 Aug 2015	VAI**
Bukhalo, Michael Arlington Heights, IL Site# 103	I1F-MC-RHBC- 44 enrolled I1F-MC-RHAZ- 36 enrolled	26 Jun-21 Jul 2015	NAI*
Birbara, Charles Worcester, MA Site# 102	I1F-MC-RHBA- 38 enrolled	8-15 Jun 2015	VAI**

\*NAI = No deviation from regulations, \*\*VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Source: OSI Review-Clinical Inspection Summary Pg.4 (modified)

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The OSI reviewer's conclusions were as follows:

The clinical sites of Drs. Blauvelt, Bukhalo, and Birbara were inspected in support of this NDA.

Dr. Blauvelt was issued a Form FDA 483 for a number of protocol deficiencies; however, Dr. Blauvelt's written response appeared adequate. In addition, a statistical reevaluation of the data resulting from the site's use of a different sPGA form demonstrated that there was no significant change to overall findings. The final classification of this inspection was Voluntary Action Indicated (VAI).

Dr. Bukhalo was not issued a Form FDA 483, and the final classification of the inspection was No Action Indicated (NAI).

Dr. Birbara was issued a Form FDA 483 for a protocol deviation involving treatment of a subject with a protocol-excluded medication. Other than this discrepancy, the study appears to have been conducted adequately and the final classification of the inspection was Voluntary Action Indicated (VAI).

In summary, the clinical sites of Drs. Blauvelt, Bukhalo, and Birbara appear to have conducted the studies adequately, and the data generated by these sites appear acceptable in support of the respective indication.

## 4.2. Product Quality

### Product Description

Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) with neutralizing activity against IL-17A. Ixekizumab is produced by recombinant DNA technology in a recombinant mammalian cell line and purified using standard technology for bioprocessing. 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, and has a molecular weight of 146,158 Daltons for the protein backbone of the molecule.

See Subsection 4.5.1 **Mechanism of Action** under Section 4.5 **Clinical Pharmacology** for the established mechanism of action for Ixe.

Ixe injection is sterile, preservative free, colorless to yellowish (b) (4) solution for subcutaneous use available as: 80 mg of ixekizumab in a 1 mL single-dose prefilled autoinjector or a

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single-dose prefilled syringe. The autoinjector and prefilled syringe each contain a 1 mL glass syringe with a fixed 27 gauge ½ inch needle. The Ixe 80 mg autoinjector and prefilled syringe are manufactured to deliver 80 mg of Ixe. Each mL is composed of Ixe (80 mg), Citric Acid Anhydrous, USP, (0.51 mg); Polysorbate 80, USP (0.3 mg); Sodium Chloride, USP (11.69 mg); Sodium Citrate Dihydrate, USP (5.11 mg); and Water for Injection, USP. The Ixe solution has a pH of 5.3 – 6.1.

### Drug Substance Review

According to the Drug Substance CMC reviewer

We recommend approval of this BLA from a drug substance perspective, pending an acceptable response from the Sponsor for an FDA's information request (IR) that will be sent to the Sponsor in the near future. The sponsor's response to the FDA IR will be assessed in an addendum to this review. This review covers the information provided in sections 3.2.S Drug Substance, 3.2.A.2 Adventitious Agents Safety Evaluation and 3.2.A.2, Regional Information. There are no issues identified so far in the reviewed sections that would preclude approval of this application, and it is anticipated that sponsor will be able to adequately address all items of the drug substance IR.

The data reviewed support the conclusion that the manufacture of ixekizumab drug substance is well controlled and leads to a product that is pure and potent. The drug substance is free of adventitious infectious agents, the conditions used in manufacturing have been sufficiently validated, and a consistent drug substance has been manufactured from multiple production runs.

The Sponsor provided 36 months real time stability data for ixekizumab drug substance to support their proposed 3 years expiry for the drug substance. No significant deficiencies have been identified at this time in the drug substance or adventitious agents sections of BLA 125521.

See Drug Substance CMC Review and addendum for details on the specifics of the IR, the response and the Agency's assessment of the response.

### Drug Product Review

According to the product quality drug product reviewer

We recommend approval of the ixekizumab BLA125521 from the drug product quality perspective, pending an acceptable response from the sponsor for a FDA

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information request (IR). The IR will be sent to the sponsor in the near future. The sponsor's response to the FDA IR will be evaluated and this review will be amended.

Overall the ixekizumab drug product process produces a monoclonal antibody that is well characterized and the manufacturing process is adequately controlled. The sponsor has provided two years of real time stability results for the semi-finished syringe that support the sponsor's proposed two year expiry for the prefilled syringe and auto injector. At this time no significant deficiencies have been identified with the drug product quality section of BLA 125521. However, there are some outstanding items that need to be addressed by the sponsor.

The quantity and composition of the drug substance and the drug product are identical except for (b) (4) (b) (4) (b) (4) ... The excipients are appropriate and of compendial grade. There is no concern with the excipients.

Ixekizumab drug product had three formulations during the clinical development. The Phase 1 and 2 clinical trials were conducted using (b) (4) (b) (4), respectively, as shown in Table 3.2.P.2.2.1.1-2. The Phase 3 and limited Phase 2 trials were conducted using a solution formulation at 80 mg/vial. The (b) (4) DP is provided in a Type I glass container with an (b) (4) closure and has a proposed 24 months shelf life when stored at 2-8°C. The container closure for DP solution is the prefilled syringe or auto injector.

(b) (4) (b) (4) injector) is more convenient for patient self-administration. Adjustment of the (b) (4) during the development transition appear appropriate and standard for this product class.

See Drug Product CMC Review and addendum for details on the specifics of the IR, the response and the Agency's assessment of the response.

#### Product Quality Microbiology Review

According to the product quality microbiology reviewer

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The drug substance part of this BLA is recommended for approval from a product quality microbiology perspective, pending the review of drug substance endotoxin spiking and hold study data. The pending data will be reviewed in an addendum to this review memo.

### Product Quality Immunogenicity Review

According to the product quality immunogenicity reviewer

The assays to detect anti-ixekizumab antibodies are suitable for use in clinical studies. Overall, the data from the pivotal trials show that development of ADA does not raise safety concerns...Approximately 20% of patients treated with ixekizumab across the phase 3 clinical studies developed anti-drug antibodies (ADA). This incidence includes all different dose schemes tested. Specifically, for patients dosed with the recommended commercial dose of 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection every 2 weeks for 12 weeks followed by 80 mg every 4 weeks, the incidence of ADA was approximately 20%. Overall, the data from the pivotal trials show that development of ADA was not associated with serious adverse events but was associated with reduced ixekizumab serum concentrations, especially in patients with higher ADA titers and neutralizing activity. Moreover, development of high ADA titers and antibody responses with neutralizing activity resulted in decreased or loss of efficacy as measured by sPGA and PASI75.

It is important to mention that the assay to test for the presence of neutralizing antibodies is sensitive to expected concentrations of ixekizumab in serum samples. Therefore, there is a possibility that the number of anti-ixekizumab neutralizing samples is under reported and some patients are false negatives. The Sponsor acknowledges the limited tolerance of the assay and therefore, classifies those patients with levels of drug that can cause interference in the assay as inconclusive.

Some minor issues were identified during the review of the immunogenicity assays and immunogenicity data that were not addressed before the internal due date for this review. Specifically, regarding the assays, the sponsor did not justify their selection of system suitability criteria for the screening and neutralizing assays. In addition, the sponsor did not discuss whether Neutralizing Antibody assay cut point data were normally distributed, although they used a cut point calculation that assumes data are normally distributed. Regarding the clinical data, the sponsor groups their analyses by titer  $\leq 1:160$  and titer  $\geq 1:160$ . The rationale for grouping data based on those titers was not provided. The

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sponsor notes that ~4.5% of subjects screened positive at baseline, but did not attempt to explain the specificity or source of those antibodies. An information request will be sent requesting the Sponsor to clarify these issues. The responses to our information requests will be discussed in an addendum to this review memo.

See Section 8.4.10 **Immunogenicity** for discussion of wording for the immunogenicity section of labeling.

*Reviewer Comment:*

*An addendum to the clinical review will be added after receiving all the addendums from the CMC reviewers.*

Facility Review

According to the OPQ/OPF/DIA reviewer

The subject BLA proposes manufacture of TALTZ™ (ixekizumab) Drug Substance (DS) and DP, respectively, at Eli Lilly S.A. – Irish Branch, Kinsale, Ireland (FEI: 3002806888) and Eli Lilly and Company, Indianapolis, IN (FEI 1819470). The storage facility for the master and working cell bank will occur at (b) (4) (b) (4). Cell based potency assay for the (b) (4) drug substance will occur at (b) (4) (b) (4). Mycoplasma and virus release assays (b) (4) will occur at (b) (4) (b) (4). ... The facilities for manufacture, storage, release and stability testing for ixekizumab DS are adequately described... The facility and equipment/product/personnel/waste flow and cleaning strategy used for ixekizumab DS manufacture are adequately described and were assessed during inspection... The procedures for cross contamination control used for ixekizumab DS manufacture are adequately described and were confirmed during inspection... The compliance status of the facilities associated with the manufacturer of ixekizumab DP is adequate.

The OPQ/OPF/DIA reviewer recommends this application for approval from a facility review perspective.

**4.3. Clinical Microbiology**

Not applicable.

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#### 4.4. Nonclinical Pharmacology/Toxicology

Dr. Jill Merrill finds BLA 125504 is approvable from a pharmacology/toxicology perspective (see review dated Nov 2, 2015 in DARRTS).

The pharmacology-toxicology reviewer had the following comments:

TALTZ™ (ixekizumab) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin 17A (IL-17A, also known as IL-17). LY2439821 was developed by humanization and optimization of mouse anti-human IL-17 antibody. It (b) (4) (b) (4) neutralizes the activity of both human and monkey IL-17. It has high specificity to IL-17A and no cross reactivity to other IL-17 family members (IL-17B through IL-17F).

Ixekizumab cross-reacts with cynomolgus monkey IL-17A, but not with the rodent IL-17A, making the cynomolgus monkey the most appropriate nonclinical species. Repeat-dose toxicity, fertility, embryofetal development and peri- and postnatal development studies have been conducted with the cynomolgus monkey.

In a 9-month toxicity study in cynomolgus monkeys subcutaneous injections of ixekizumab (0, 0.5, 5, 50 mg/kg/week) caused no adverse compound-related clinical signs at ≤5 mg/kg/week. A dose of 50 mg/kg/week exceeded the maximum-tolerated dose for one animal due to injection site reactions resulting in suspension of dosing, but was otherwise well tolerated. One male given 5 mg/kg/week was found dead 6 days after the 20th weekly injection (Day 140). Although the cause of death could not be determined, it was not considered compound-related.<sup>17</sup> Ixekizumab administration did not produce any remarkable changes in the peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, total B cells, natural killer cells, and helper-to-cytotoxic T cell ratio) or natural killer cell assay data. Based on the injection site reactions requiring dose suspension, the NOAEL for this 9-month study was 5 mg/kg/week.

Safety pharmacology evaluations incorporated within the 8-week and 9-month repeat-dose toxicity studies indicated that ixekizumab did not affect

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<sup>17</sup> Since no deaths occurred in the higher dose group and no compound-related adverse effects were noted at this dose level or higher that could account for the death, this death was not attributed to the test article. Source: Pharmacology-Toxicology Review pg. 20

cardiovascular, respiratory or central nervous system functions.

Fertility, embryofetal development and peri- and postnatal development studies have been conducted with ixekizumab in cynomolgus monkeys treated by subcutaneous injection with up to 50 mg/kg/week. No treatment-related effects were observed during these studies. Neonatal deaths occurred in the infants of two monkeys administered ixekizumab at 5 mg/kg/week and two monkeys administered ixekizumab at 50 mg/kg/week. The cause and/or clinical significance of these findings is unknown.

#### 4.5. **Clinical Pharmacology**

According to the clinical pharmacology reviewer, 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.

In addition the clinical pharmacology reviewer had the following comments:

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(0-14days) and Cmax were 0.99 [0.89, 1.10] and 0.98 [0.89, 1.10], respectively, all within the [0.8, 1.25] bioequivalence boundaries.

The following table summarizes the clinical trials containing clinical pharmacology assessments relevant to the proposed indication and labeling.

**Table 3: Clinical Trials and their Utilities to Support Clinical Pharmacology Assessments of Ixekizumab for the treatment of psoriasis.**

<b>Clinical Trials</b>	<b>Study design</b>	<b>Ixekizumab Dosing regimen</b> (number of subjects randomized)	<b>Formulation</b>	<b>Main Clinical Pharmacology data</b>
<b>RHAG</b>	Phase 1 dose escalation for assessment of safety and PK	<ul style="list-style-type: none"> <li>- Placebo (n=9)</li> <li>- 5 mg SC q2w×3 (n=8)</li> <li>- 15 mg SC q2w×3 (n=8)</li> <li>- 50 mg SC q2w×3 (n=8)</li> <li>- 150 mg SC q2w×3 (n=8)</li> <li>- 15 mg IV q2w×3 (n=5)</li> </ul>	LYO	<ul style="list-style-type: none"> <li>- Descriptive PK</li> <li>- SC bioavailability</li> <li>- Population PK</li> </ul>
<b>RHAJ</b>	Phase 2 dose-ranging	Part A: SC at Weeks 0, 2, 4, 8, 12, and 16 (n=27-30 per group) <ul style="list-style-type: none"> <li>- Placebo</li> <li>- 10 mg</li> <li>- 25 mg</li> <li>- 75 mg</li> <li>- 150 mg</li> </ul> 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)	<ul style="list-style-type: none"> <li>- Descriptive PK</li> <li>- Population PK</li> <li>- Dose-ranging for efficacy/safety</li> </ul>
<b>RHBL</b>	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) <ul style="list-style-type: none"> <li>- PFS (n=102)</li> <li>- AI (n=102)</li> </ul>	PFS AI	<ul style="list-style-type: none"> <li>- Descriptive PK</li> <li>- PK comparability between PFS and AI</li> <li>- Impact of injection site on PK</li> <li>- Impact of body weight on PK</li> <li>- Population PK</li> </ul>
<b>RHAZ</b>	Phase 3 randomized, double-blind, placebo-controlled, efficacy/safety trial	Induction to Week 12: <ul style="list-style-type: none"> <li>- Placebo (n=431)</li> <li>- SC 80 mg q4w, 160 mg at Week 0 (n=432)</li> <li>- SC 80 mg q2w, 160 mg at Week 0 (n=433)</li> </ul> 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	<ul style="list-style-type: none"> <li>- Immunogenicity</li> <li>- Descriptive PK</li> <li>- Population PK</li> <li>- E-R analysis for efficacy/safety</li> </ul>

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<b>RHBA</b>	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.
<b>RHBC</b>	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.

Source: Clinical Pharmacology Review pg. 8-9

#### 4.5.1. Mechanism of Action

From the draft labeling for Ixe:

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds to the interleukin 17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab inhibits the release of pro-inflammatory cytokines and chemokines.

#### 4.5.2. Pharmacodynamics

From the draft labeling for Ixe:

No formal pharmacodynamic studies have been conducted with TALTZ.

#### 4.5.3. Pharmacokinetics

From the draft labeling for Ixe:

##### Absorption

Following a single subcutaneous dose of 160 mg in subjects with plaque psoriasis, ixekizumab reached peak mean (±SD) serum concentrations (C<sub>max</sub>) of (b) (4) mcg/mL by approximately 4

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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; (b) (4)

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.

### Distribution

The mean (geometric CV%) volume of distribution at steady-state was 7.11 L (29%) in subjects with plaque psoriasis.

### Elimination

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 (b) (4) systemic clearance was 0.39 L/day (37%) and the mean (b) (4) (b) (4) half-life was 13 days (40%) in subjects with plaque psoriasis.

### Weight

Ixekizumab clearance and volume of distribution increase as body weight increases.

### Dose Linearity

Ixekizumab exhibited dose-proportional pharmacokinetics in subjects with plaque psoriasis over a dose range from 5 mg (not the recommended dose) to 160 mg following subcutaneous administration.

### Specific Populations

#### *Age: Geriatric Population*

Population pharmacokinetic analysis indicated that age did not significantly influence the

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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.

#### Drug Interaction Studies

Drug interaction studies have not been conducted with TALTZ.

(b) (4)

## **Devices and Companion Diagnostic Issues**

### Center for Devices and Radiological Health (CDRH), Office of Compliance Consult

DDDP consulted the CDRH Office of Compliance asking for a determination as to whether a device related inspection is required for this product which comes in either a pre-filled syringe (PFS) or an auto-injector (AI). A response was received dated Oct 7, 2015 which stated the following:

The Office of Compliance (OC) at CDRH has completed the evaluation of application BLA 125521 and has the following recommendations:

1. CDRH, OC recommends BLA 125521 filable.
2. CDRH, OC recommends that in the next inspection, this facility be considered for device inspection.
3. Application BLA 125521 approvable.

### CDRH-Biocompatibility Consult Review for the Prefilled Syringe (PFS) and the Auto-injector (AI)

The CDRH/ General Hospital Devices Branch/DAGRID reviewer had the following comments:

- The biocompatibility test reports (for the PFS) have been reviewed. All testing is deemed

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acceptable. I have no question regarding the biocompatibility of the external components of the PFS.

- The biocompatibility test reports (for the AI) have been reviewed. Please see the recommended deficiencies below.

1. To demonstrate biocompatibility of the auto-injector, you have provided testing of *in vitro* cytotoxicity, irritation, and sensitization using a test device identified (b) (4). However, you do not provide a clear and detailed description (b) (4) and do not justify how the test device represented the final finished subject auto-injector. To determine if the testing provided is appropriate and adequate to support the biocompatibility of the subject device, please provide a valid justification for the test device. Alternatively, please provide revised test reports for each of the biocompatibility testing based on the final finished subject device. Please ensure that all patient contacting device components contained in the subject auto-injector were evaluated for biocompatibility.

2. The test extracts used in the *in vitro* cytotoxicity testing (b) (4) may invalidate the test results. Without an appropriate justification, it is not acceptable by the FDA. To demonstrate that the cytotoxicity test results are valid, please provide chemical analytical testing data to support (b) (4) the test samples (b) (4). Alternatively please provide the cytotoxicity testing (b) (4).

Eli Lilly provided a response on Oct 16, 2015 via a 22 page PDF document (See CDRH/ General Hospital Devices Branch/DAGRID RV dated 11/3/15 for details of the response). The CDRH/ General Hospital Devices Branch/DAGRID reviewer concluded that

The information provided in the BLA122521-ICC1500161-S002 response is deemed adequate to address the biocompatibility concerns raised in my email dated 9/23/2015. There are no pending biocompatibility deficiencies for the Prefilled Syringe (PFS) and the Auto-injector proposed in ICC1500161 (BLA 125521).

CDRH posed additional questions to the applicant. In May of 2015 the applicant responded to these additional questions. (See CDRH/ General Hospital Devices Branch/DAGRID RV dated 11/3/15 for the questions and detailed responses). The CDRH/ General Hospital Devices Branch/DAGRID reviewer concluded that

Eli Lilly has provided adequate device performance data for the PFS and AI constituent of the combination product to show that the device can deliver accurate volume of the drug under the specified injection time (labeling specified

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10seconds, actual time is less than 5 seconds). The sponsor provided adequate responses to the device deficiencies. No further device issues.

#### 4.7. **Consumer Study Reviews**

Not applicable

## **5 Sources of Clinical Data and Review Strategy**

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### 5.1. **Table of Clinical Studies**

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**Table 4: Listing of Clinical Trials Relevant to BLA 125521**

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Countries and sites
<b>Controlled Studies to Support Efficacy and Safety in Psoriasis</b>							
I1F-MC-RHAG  Completed  PK and Tolerability-Safety	Phase 1, multi-center (MC), randomized (R), double-blind (DB), placebo-controlled (PC), dose-escalation trial	Ixe (Ixe) 5, 15, 50, 150 mg by Subcutaneous (SC) injection; 15 mg IV or placebo given q 2 wks X 3 doses	Safety	4 weeks (wks)	46 37- Ixe 9-placebo	Chronic plaque psoriasis, adults, BSA ≥ 15%, PASI≥13, BMI 18-40 kg/m <sup>2</sup>	US-9
I1F-MC-RHAZ  LTE-ongoing  Pivotal-Safety and Efficacy	Phase 3, MC,R,DB, PC, parallel group (PG) induction trial (12 weeks) followed by a randomized maintenance period (48 weeks) then a long term extension (LTE) period	Ixe SC starting dose of 160 mg Ixe SC 80 mg Q2W or Q4W or placebo up to 12 weeks (Induction) Ixe SC 80 mg Q4W or Q12W or placebo Week 12 to Week 60 (Maintenance)	1° efficacy at 12 weeks  1. Proportion of patients with a static Physician Global Assessment (sPGA) (0,1) with at least a 2-point improvement from baseline 2. Proportion of patients achieving at least a 75% improvement from baseline in Psoriasis Area and Severity Index (PASI) score (PASI 75) from baseline	Induction-12 wks Maintenance-48 wks LTE-up to 5 years (yrs)	1296-R 865-Ixe 431-placebo	Chronic plaque psoriasis, adults, BSA ≥ 10%, PASI≥12, PGA≥3	105 sites US-33 Canada-14 Germany-17 Poland-9 Romania-4 Denmark-2 Italy-2 UK-4 Australia-6 Hungary-7 Japan-10

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I1F-MC-RHBA  LTE-ongoing  Pivotal-Safety and Efficacy	Phase 3, S&E, MC, R, DB, PC, active comparator (AC), PG induction trial (12 weeks) followed by a R maintenance period (48 weeks) then a LTE period	Ixe SC Starting Dose of 160 mg Ixe SC 80 mg Q2W or Q4W up to Week 12 (Induction)  Ixe SC 80 mg Q4W or Q12W up to Week 60 (Maintenance)  Long-Term Extension Period Doses: Ixe 80 mg Q4W, 80 mg Q12W or placebo by SC injection	1 <sup>o</sup> efficacy at 12 weeks  1. Proportion of patients with a sPGA (0,1) with at least a 2-point improvement from baseline  2. Proportion of patients achieving at least a PASI	Induction-12 wks Maintenance-48 wks LTE-up to 5 years (yrs)	Total R = 1224 697-Ixe 357-etanercept 167-placebo	Chronic plaque psoriasis, adults, BSA ≥ 10%, PASI≥12, PGA≥3	121 sites US-41 sites Canada-17 sites Germany-13 sites Poland-7 sites Romania-6 sites UK-7 sites Australia-8 sites France-8 sites Netherlands -3 sites Austria-4 sites Czech Republic-3 sites Spain-10 sites
I1F-MC-RHBC	Phase 3, S&E, MC, R, DB, PC, AC, PG induction trial (12 weeks) followed by a	Ixe SC Starting Dose of 160 mg S Ixe C 80 mg Q2W or Q4W up to Week 12 (Induction)	1 <sup>o</sup> efficacy at 12 weeks  1. Proportion of patients with a sPGA (0,1) with at least a 2-point improvement from baseline	Induction-12 weeks LTE- up to 204 weeks	Total R = 1346 766-Ixe 382-etanercept 193-	Chronic plaque psoriasis, adults, BSA ≥ 10%, PASI≥12,	119 sites US-45 sites Canada-11 sites Germany-34 sites

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	LTE period		2. Proportion of patients achieving at least a PASI		placebo	PGA≥3	Bulgaria-5 sites Poland-3 sites Mexico-2 sites Hungary-12 sites Russia-9 sites Chile-2 sites
<b>Studies to Support Safety-Psoriasis</b>							
I1F-JE-RHAT  Ongoing  Japanese subjects	Phase 3, MC, single-arm, open-label, long term trial	Induction Dosing Period Doses: Ixe at Week 0 starting dose of 160 mg by SC injection; thereafter, 80 mg Q2W by SC injection Maintenance Dosing and Retreatment Periods Dose: 80 mg Q4W by SC injection	Treatment response in Japanese subjects via PASI 75	Induction-12 wks Maintenance-40 wks drug-free wks 52 thru 100 Re-Rx period- Up to 192 wks starting at wk 100	91 enrolled and exposed to Ixe	Chronic plaque psoriasis (BSA ≥10%, sPGA ≥3, and PASI ≥12); pustular psoriasis or erythro-dermic psoriasis (BSA ≥80%)	Japan-28 sites
<b>Studies to Support Safety-Rheumatoid arthritis</b>							
I1F-MC-RHAF  Completed	Phase 1-2 part, MC, R, DB, PC, dose-escalation trial	Part A: Ixe at single IV doses: placebo, 0.06, 0.2, 0.6, 2 mg/kg Part B: Ixe Q2W x 5 IV	Safety and tolerability in patient with RA taking ≥1 DMARDs, and possibly NSAIDs and/or	Part A: Single IV dose Part B: 10 weeks	Part A: 20 R, 16 - Ixe; 4 - placebo	Part A: active RA on background oral	Australia-2 sites  Belgium-11

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		doses: placebo, 0.2, 0.6, 2 mg/kg	glucocorticoid(s)		Part B: 77 R, 59 -Ixe 18-placebo	DMARDs Part B: active RA on background oral DMARDs; an insufficient response	sites  Romania-4 sites
I1F-JE-RHAL  Completed	Phase 1, MC, R, DB, PC, dose escalation trial	First 3 Cohorts: Ixe given at Wks 0, 1, 2, 4, 6, 8 +10 Doses: 30, 80, and 180 mg by SC injection or placebo by SC injection  Last Cohort: Ixe given at Wk 0 (240 mg starting dose), followed by 120 mg Q1W (Wks 1 -10) or placebo by SC injection	To evaluate the safety and tolerability of multiple doses in Japanese patients with RA	12 wks	32 R; 24 - Ixe 8-placebo	Diagnosed RA on concomitant MTX	Japan- 7 sites
I1F-JE-RHAM  Completed	Phase 1, MC, open label trial	Ixe given at 30 or 80 mg Q1W for first 3 doses, then Q2W by SC injection Ixe given at 160 mg Q4W by SC injection after the safety of study drug was confirmed at 180 mg from Study RHAL	To evaluate the safety and tolerability of Ixe SCT administered for 48 wks in Japanese patients with RA who have completed RHAL	First injection at Wk 0 and last dose at Wk 44 48-wk treatment period	28 enrolled exposed to Ixe	Diagnosed RA on concomitant MTX who have completed Study RHAL	Japan- 7 sites
<b>Studies to Support Safety-Psoriatic Arthritis</b>							
I1F-MC-RHAP	Phase 3, MC, DB, active and	DB Period Doses: Ixe by SC injection at Wk 0	To assess whether Ixe 80 mg Q2W or 80 mg Q4W is	DB-Rx Period: Wk 0 - Wk 24	416 R; exposures	Psoriatic arthritis	US- 35 sites Belgium-1

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Completed	PC, PG design followed by a LTE	starting dose of 160 mg; thereafter, 80 mg Q2W or 80 mg Q4W; at Wk 16, IRs will receive rescue Rx and continue 80 mg Q2W or 80 mg Q4W to Wk 24 Placebo and adalimumab (40 mg Q2W) doses by SC injection; at Wk 16, IRs will receive rescue Rx and be re-randomized to Ixe 80 mg Q2W or 80 mg Q4W to Wk 24 Extended and Long-Term Rx Periods: Ixe 80 mg Q2W or Q4W	superior to placebo in the Rx of bDMARD-naïve patients with active PsA, as measured by the proportion of patients achieving ACR20 response at Wk 24	Extension Treatment Period: Wk 24 - Wk 52 Long-Term Extension Rx Period: Wk 52- Wk 156	by Rx group not available due to blinding of ongoing study	And bDMARD-naïve	site Bulgaria-6 sites Canada- 4 sites Estonia- 4 sites Poland-10 sites UK-7 sites France-3 sites Japan- 6 sites Mexico- 5 sites Netherlands -1 site Czech Republic-12 sites Russia- 5 sites Spain-9 sites Ukraine-6 sites
<b><i>Other studies pertinent to the review of efficacy or safety in Psoriasis and Rheumatoid Arthritis (e.g., clinical pharmacological studies)</i></b>							
Ongoing	I1F-MC-RHBL Phase3, MC, R, PG, open-label trial	Ixe SC 160 mg starting dose; thereafter, 80 mg Q2W by prefilled Syringe(PFS) or auto-	To evaluate drug delivery device	12 weeks Optional extension: 40	204 R and exposed to Ixe	Chronic plaque psoriasis, adults,	US-26 sites

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Extrinsic factor PK-Safety and Efficacy		injector (AI)  Optional Safety Extension Period: 80 mg Q4W by prefilled syringe		weeks		BSA ≥ 10%, PASI≥12, PGA≥3	
I1F-MC-RHAJ  A-Completed B-ongoing  Population PK/PD-Safety and Efficacy	Phase 2, MC  Part A- R, DB, PC, PG, dose-ranging trial  Part B-optional open-label extension	Ixe or placebo by SC injection at Weeks 0, 2, 4, 8, 12, and 16 (Part A only) Doses: 10, 25, 75, and 150 mg  Part B: Ixe 120 mg Q4W by SC injection until implementation of amendment (c); thereafter, 80 mg Q4W for up to Week 240 (5 years)	PK characterization – sparsely sampled Ixe concentrations via a population approach  Total PASI score was evaluated as clinical PD efficacy endpoint for exposure-response relationship	16 weeks  (20 weeks; A-B transition) Part B: for up to 240 weeks	Patients in final PK dataset: 114-Ixe 27-placebo Part B- 120 Ixe	Chronic plaque psoriasis, adults, BSA ≥ 10%, PASI≥12, PGA≥3	Denmark- 1 site US-22 sites
I1F-MC-RHAK  Completed  Dose-ranging for RA	Phase 2, MC  Part A- R, DB, PC, PG, dose-ranging trial  Part B: optional open-label extension design	Part A: Ixe given by SC injection at Wks 0, 1, 2, 4, 6, 8, 10; doses for bDMARD-naive population: placebo, 3, 10, 30, 80, 180 mg; doses for TNFα -IR population: Placebo, 80, 180 mg Part B: Ixe given by SC injection at Wks 16, 18,	To determine the dose-response relationship of Ixe at Wk 12, as measured by the proportion of ACR20 responders in the bDMARD-naive population	Part A: 12 wks (16 wks including the A->B transition) Part B: 48 wks Wk 16->Wk 60 (16, 18, 20 wks, then Q4W to Wk	448 R: Part A: 330 - Ixe; 118 - placebo Part B: 390 - Ixe	TNFα-IR or bDMARD-naive patients on concomitant DMARDs. RA patients	Argentina- 3 sites Chile-2 sites Germany-3 sites India-6 sites Korea-5 sites Peru- 4 sites Poland-9 sites

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		20, and Q4W through Wk 60; all patients received 160 mg		60)			Romania- 6 sites Russia-2 sites Taiwan-5 sites US-40 sites
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Source: Clinical Reviewer's Table

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## 5.2. Review Strategy

This review will focus primarily on evaluation of efficacy from the induction and maintenance dosing periods for the 3 pivotal trials RHAZ, RHBA and RHBC. In trials RHBA and RHBC an active comparator arm was included. US-sourced etanercept was used in the trials conducted in the US. For the most part, EU-sourced etanercept was used in the trials conducted outside the US. Only data pertaining to the US-sourced etanercept will be included in this review.

The majority of the analyses presented were performed by the statistical reviewer with occasional supplementation from the sponsor's analyses.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. I1F-MC-RHAZ (b)

Protocol I1F-MC-RHAZ(b): 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 Ixe in Patients with Moderate-to-Severe Plaque Psoriasis (RHAZ)

#### 6.1.1. Study Design

##### Overview and Objective

The co-primary objectives of the study were to assess whether Ixe 80 mg Q2W or 80 mg Q4W was superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque Ps as measured by: (1) Proportion of patients with a sPGA (0, 1) with at least a 2-point improvement from baseline and (2) Proportion of patients achieving a  $\geq 75\%$  improvement in PASI (PASI 75) from baseline.

##### Trial Design

RHAZ is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, outpatient study examining the effect of Ixe versus placebo in patients with moderate-to-severe plaque Psoriasis (PS) during an Induction Dosing Period (IDP) with the primary endpoint at 12 weeks, followed by a randomized Maintenance Dosing Period (MDP) to Week 60, and a subsequent Long-Term Extension(LTE) Period.

During the IDP, the study evaluated the efficacy and safety of 2 dose regimens of subcutaneous (SC) Ixe vs placebo. Patients were randomized at a 1:1:1 ratio to 1 of 3 treatment groups: 80 mg

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Ixe Q2W, 80 mg Ixe Q4W, or placebo; each as 1 SC injection. Randomization was via a computer-generated random sequence using an interactive voice response system (IVRS). Patients were stratified by geographic regions, previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥3 conventional systemic therapies), and weight (<100 kg or ≥100 kg).

*Reviewer Comment: In an advice letter dated Feb 7, 2015, DDDP recommended that randomization be stratified by center and Cochran-Mantel-Haenszel (CMH) test controlled for center as the primary analysis method. In a response dated September 12, 2012 the applicant stated that the study was already ongoing so that the randomization plan could not be changed.*

At Week 12 (Visit 7), patients who entered the maintenance period were classified as a responder or nonresponder according to the following criteria:

- Responder = sPGA score of “0” or “1”
- Non-responder = sPGA score of >1.

Responders who received Ixe during the induction period were re-randomized to one of 3 arms (80 mg Q4W, 80 mg Q12W or placebo). Responders who received placebo during the IDP were to continue to receive placebo during the MDP until relapse. Relapse was defined as a loss of response equal to a sPGA score of ≥3. Nonresponders were assigned to the 80 mg Q4W arm.

Patients who were responders at Week 12 were monitored and assessed for relapse at each visit after re-randomization. Patients who relapse were treated as follows:

- Patients receiving 80 mg Ixe Q4W continued on 80 mg Ixe Q4W in order to maintain the study blind and to see if study response could be regained with continued treatment.
- Patients receiving 80 mg Ixe Q12W were switched to 80 mg Ixe Q4W to evaluate whether the response observed earlier could be regained.
- Patients receiving placebo were switched to 80 mg Ixe Q4W.

During the MDP, the study evaluated the maintenance of response/remission with 2 different dose regimens of Ixe (80 mg Q4W or Q12W) vs placebo, the safety of these regimens, as well as relapse or rebound following treatment withdrawal, and response to retreatment following relapse. In addition, longer-term efficacy and safety were evaluated for up to a total of 5 years in the LTE Period for patients who participated through the entire study.

Throughout the trial, to maintain the blind, all patients continued to receive one SC dose Q4W of investigational product (Ixe or placebo) until the study was unblinded. All patients receiving at least one dose of investigational product were entered into the Post-Treatment Follow-Up Period for a minimum of 12 weeks after their last regularly scheduled visit [or the date of their end of treatment visit (ETV)].

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Key Inclusion Criteria: male or female patients aged 18 years or older who have chronic plaque Ps based on a confirmed diagnosis of chronic Ps vulgaris for at least 6 months who are candidates for phototherapy and/or systemic therapy, and who have  $\geq 10\%$  BSA involvement, an sPGA score of  $\geq 3$ , and a PASI score  $\geq 12$  at screening and baseline.

#### Key Exclusion Criteria

- Pustular, erythrodermic or guttate forms of Ps
- Received systemic non-biologic Ps therapy within 4 weeks, biologic Ps therapy within 5 half-lives or topical Ps therapy within 2 weeks of baseline
- Live vaccination within 12 weeks of baseline
- History of malignancy
- Uncontrolled cerebro-cardiovascular (CV) disease (MI, CHF, HTN), respiratory, hepatic, renal, Gastrointestinal (GI), endocrine, hematologic, neurologic or neuropsychiatric disorders (suicide attempt, score of 3 on item 12 of QIDS-SR16), or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data
- Serious Infection including opportunistic infection, varicella (VZV) within 12 weeks of baseline, active or latent TB, HIV infection, HCV, Hep B (see protocol for details)
- Abnormal laboratories considered clinically significant

The following medications were permitted during the course of the study:

Topical Steroids: Topical steroids, class 6 (mild) or 7 (least potent), were permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not have been used within approximately 24 hours prior to study visits requiring sPGA and PASI measures. More potent topical steroids may have been used, as needed, after Week 60 (Visit 19) assessments were completed.

Trial Start Date: Dec 6, 2011

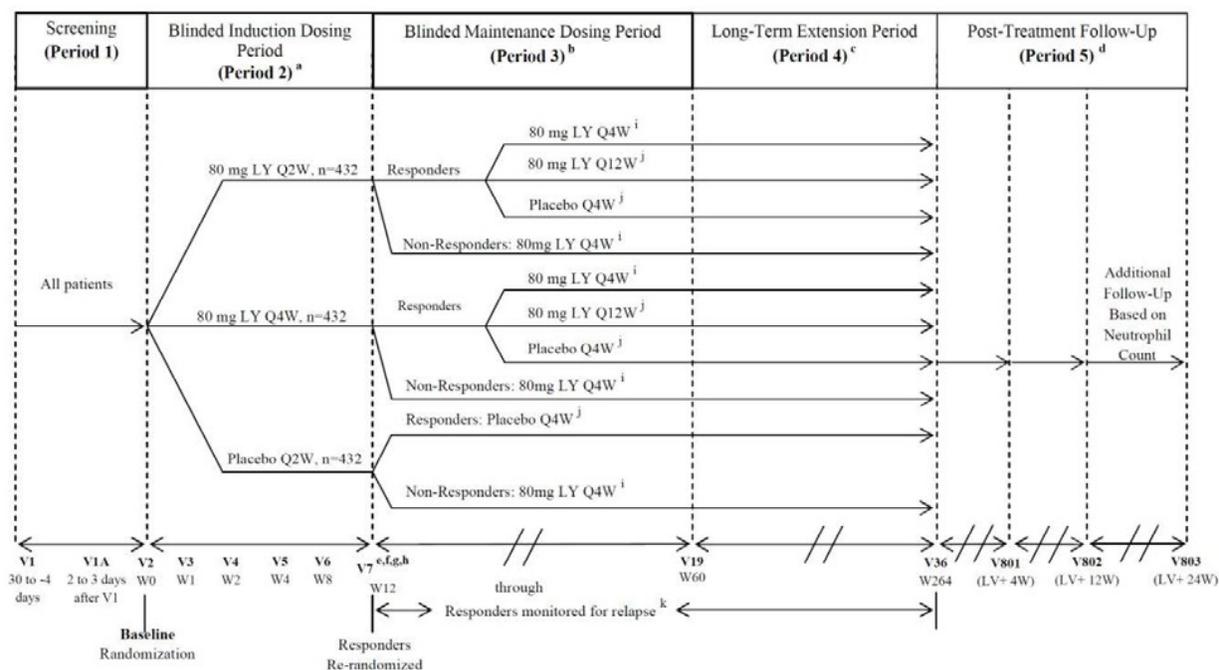
Last patient visit prior to database lock for BLA submission: June 24, 2014

Database lock date for BLA submission: Aug 7, 2014

Trial End Date: ongoing

RHAZ is being conducted at 101 sites in the following countries – US-33 sites, Canada-14 sites, Germany- 17 sites, Poland-9 sites, Romania-4 sites, Denmark-2 sites, Italy-2 sites, UK-4 sites, Australia-6 sites, Hungary-7 sites and Japan-10 sites.

**Figure 1: Trial Design for RHAZ**



**Abbreviations:** LV = date of last visit;

- <sup>a</sup> All patients will receive 2 SC doses of investigational product at Week 0 (Visit 2) and 1 SC dose Q2W from Week 2 (Visit 4) through Week 10.
- <sup>b</sup> All patients will receive 2 SC doses of investigational product at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 60 (Visit 19). Study visits will occur at least Q4W during Period 3.
- <sup>c</sup> Study visits will occur at least Q12W during Period 4. Treatment will remain blinded to investigators, study site personnel, and patients until all patients reach Week 60 (Visit 19) or have discontinued from the study (moved into Period 5).
- <sup>d</sup> All patients receiving investigational product must enter into Period 5 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed.
- <sup>e</sup> Responders to Ixe at Week 12 (Visit 7; responders are defined as achieving an sPGA score of 0 or 1) will be randomly assigned at a 1:1:1 ratio to Ixe 1 Q4W, Q12W, or placebo.
- <sup>f</sup> Non-responders to Ixe at Week 12 (Visit 7; non-responders are defined as having an sPGA score of >1) will receive Ixe 80 mg Q4W.
- <sup>g</sup> Responders to placebo at Week 12 (Visit 7) will receive 2 injections of placebo at Week 12 and will remain on placebo Q4W until relapse.
- <sup>h</sup> Non-responders to placebo at Week 12 (Visit 7) will receive 2 injections of Ixe (starting dose) at Week 12 followed by Ixe 80 mg Q4W.
- <sup>i</sup> Patients who experience loss of treatment efficacy (relapse) during Period 3 will remain on 80 mg Ixe Q4W in order to maintain the blind.
- <sup>j</sup> Patients who experience loss of treatment efficacy (relapse) during Period 3 will be switched to 80 mg Ixe Q4W.
- <sup>k</sup> Relapse occurring after Week 12 (Visit 7) is defined as a loss of response equal to an sPGA score of  $\geq 3$ .

Source: Applicant’s Statistical Analysis Plan (SAP) Amendment 2, Final RHAZ pg. 25

*Reviewer Comment: The overall design of the trial ie MC, R, DB and PC is appropriate. The population studied; subjects with chronic plaque psoriasis with a BSA  $\geq 10\%$ , PASI $\geq 12$  and PGA $\geq 3$  is consistent with the targeted population in the US population for this indication. The protocol however, excluded subjects with depression and with a history of prior suicide attempt which limits our ability to assess the safety of this product in that group. Since moderate to severe psoriasis is known to be associated with an increased risk of depression and suicidal ideation this is an important subgroup to study for systemic psoriasis treatments. It is notable that this protocol was not the subject of either a SPA or EOP2 meeting; therefore no agreements*

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*on inclusion/exclusion criteria were reached. (See Section 3.2 **Summary of Presubmission/Submission Regulatory Activity** for further details).*

*The induction period design was similar to the design used for other biologics approved for psoriasis (See clinical reviews for ustekinumab BLA 125261 dated Nov 19, 2008 and secukinumab BLA 125504 dated Dec 9, 2014).*

*The randomized withdrawal portion of the design during the maintenance period allowed for an assessment of the duration of response after discontinuing Ixe. The duration of the induction period, 12 weeks, was typical of trials for biologics for moderate to severe psoriasis. A long term extension period of 5 years is appropriate for this product.*

### **Study Endpoints**

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

*Reviewer Comment: These primary efficacy endpoints are the same as those used for the recent approval on Jan 21, 2015 of Cosentyx (secukinumab) (See BLA 125504 Clinical Review dated Dec 9, 2014). They are the currently recommended primary efficacy endpoints for moderate to severe psoriasis in the division.*

The key secondary efficacy endpoints included

1. Proportion of Patients with sPGA of 0 at Week 12
2. Proportion of Patients with PASI 90 at Week 12
3. Proportion of Patients with PASI 100 at Week 12
4. Proportion of Patients with sPGA (0,1) at Week 60
5. Change from Baseline in Itch numerical rating score (NRS) score at Week 12
6. Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 12
7. Change from Baseline in Nail Psoriasis Severity Index (NAPSI) at Week 12

*Reviewer Comment:*

*The NRS instrument was the subject of a SEALD consult which was completed on May 12, 2014. The reviewer stated "This review concludes that the Itch NRS is an appropriate measure of severity of itch in the proposed context of use." See Section 3.2 **Summary of Presubmission/Submission Regulatory Activity** for additional comments conveyed regarding the NRS at the April 30, 2014 meeting.*

Other secondary efficacy endpoints included

CDER Clinical Review Template 2015 Edition  
Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

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- To assess the efficacy of Ixe 80 mg Q2W or 80 mg Q4W compared to placebo at Week 12 and over the 12-week study period by evaluating:
  - Time course of response to treatment as measured by the proportion of patients with a sPGA (0,1) with at least a 2-point improvement from baseline.
  - Time course of response to treatment as measured by the proportion of patients with a sPGA (0).
  - Time course of response to treatment as measured by the proportion of patients achieving at least a 50% improvement in PASI score from baseline (PASI 50), PASI 75, PASI 90, and PASI 100.
  - Time course of response to treatment as measured by change and percent improvement of PASI from baseline.
  - Time to sPGA response as measured by an sPGA (0,1).
  - Time to PASI 75 response.
  - Percent of BSA involvement of Ps.
  - Change from baseline in NAPSI score in patients with fingernail involvement.
  - Change from baseline in Ps Scalp Severity Index (PSSI) score in patients with scalp involvement.
  - Change from baseline in other health outcome endpoints: Quick Inventory of Depressive Symptomatology-Self Report (16 items) (QIDS), all scores of the Work Productivity Activity Impairment questionnaire-Ps (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment), Medical Outcomes Study 36-Item Short Form Health Survey, Physical Component Summary and Mental Component Summary scores, and patient's global assessment of disease severity.
  - Change from baseline in itching severity (Itch NRS) score.
  - Change from baseline on DLQI.
  - Change from baseline in Palmoplantar PASI (PPASI) and proportion of patients achieving at least a 50% improvement in PPASI score from baseline (PPASI 50), at least a 75% improvement in PPASI score from baseline (PPASI 75), and a 100% improvement in PPASI score from baseline (PPASI 100) in patients with palmoplantar involvement.
- To assess maintenance of efficacy of Ixe compared to placebo at Week 60 and during the Maintenance Dosing Period among patients who had an sPGA (0,1) at Week 12 and were re-randomized by evaluating:
  - Time to relapse (sPGA  $\geq$ 3).
  - Time course of the loss of response to treatment until relapse as measured by a sPGA  $\geq$ 3.
  - Proportion of patients who maintain or achieve remission (that is, a sPGA (0)).
  - Time course of response to treatment as measured by change from baseline of sPGA score.
  - Time course of response to treatment as measured by the proportion of patients

- who maintain an sPGA (0,1), and by the proportion of patients who maintain an sPGA (0).
- Time course of response to treatment as measured by change from baseline and percent improvement of PASI from baseline.
- Percent of BSA involvement of Ps.
- Incidence of disease rebound within 8 weeks (worsening of Ps severity over baseline sPGA score, or worsening of Ps severity over baseline PASI score by 125% or change in Ps phenotype [for example, from plaque to pustular]) after re-randomization to placebo at Week 12.
- Time course of response to treatment as measured by the proportion of patients who maintain a PASI 75, PASI 90, and PASI 100.
- Change from baseline in NAPSI score in patients with fingernail involvement.
- Change from baseline in PSSI score in patients with scalp involvement.
- Change from baseline in other health outcome endpoints: QIDS-SR16, all scores of the WPAI-PSO (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment), SF-36 PCS and MCS scores, and patient's global assessment of disease severity.
- Change from baseline in itching severity (Itch NRS) score.
- Change from baseline on DLQI.
- Change from baseline in PPASI and proportion of patients achieving at least a 50% improvement in PPASI score from baseline (PPASI 50), at least a 75% improvement in PPASI score from baseline (PPASI 75), and a 100% improvement in PPASI score from baseline (PPASI 100) in patients with palmoplantar involvement.
- To assess the efficacy of Ixe 80 mg Q4W following disease relapse after re-randomization to placebo treatment in the Maintenance Dosing Period by evaluating:
  - Proportion of patients who regain a sPGA (0,1) within 12 weeks after Ixe re-treatment.
  - Proportion of patients who achieve a PASI 75, PASI 90, PASI 100 within 12 weeks after Ixe re-treatment.
- To assess the pharmacokinetic (PK) / pharmacodynamic (PD) relationship and immunogenicity of Ixe throughout the study by:
  - Characterizing the PK of Ixe, determine the magnitude of within- and between-patient variability, and identify the potential intrinsic and extrinsic factors that may have an impact on the PK of Ixe through Week 60.
  - Characterizing the dose-/exposure-response relationships, to describe the time course of efficacy endpoints (sPGA and PASI score), and to identify potential factors that may impact the efficacy endpoints.
  - Evaluating the potential development of anti-Ixe antibodies and its impact on patient safety, efficacy, and PK of Ixe.

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*Reviewer Comment: The Quick Inventory of Depressive Symptomatology-Self Report (16 Items) (QIDS-SR16, from here on abbreviated as QIDS) is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). The reference time period is the last 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation.*

*Subjects were excluded from participation if they had a score of 3 or greater on Item #12 "Thoughts of death or suicide" at screening or baseline. See Section 8.5.1 **Depression and Suicidality** for further discussion of the instrument and this topic.*

Exploratory endpoints included

- To assess the efficacy of Ixe 80 mg Q2W or 80 mg Q4W compared to placebo on joint pain at Week 12 and over the 12-week study period, as well as at Week 60 and during the Maintenance Dosing Period in patients with an sPGA (0,1) at Week 12 and were re-randomized, by evaluating change from baseline in joint pain (Joint Pain visual analog scale [VAS]) score in patients with PsA at baseline.
- To explore the impact of Ixe on change from baseline in measures of health utility (European Quality of Life – 5 Dimensions 5 Level [EQ-5D 5L]), Skin Pain VAS, healthcare resource utilization, and self-reported skin appearance bothersomeness (Ps Skin Appearance Bothersomeness scale [PSAB]) compared to placebo.
- To assess the psychometric properties (including reliability, validity, and responsiveness) of the Itch NRS and PSAB.
- To form and evaluate subgroups that may have different risk for benefit or harm from therapy using the Enterprising Selective Multi-Instrument Blend for Heterogeneity analysis (ENSEMBLE) Minimum Data Set 1.5 (MDS).
- To explore biomarkers of disease, drug activity, or that are predictive of response to Ixe treatment that may be contained in serum, plasma, messenger ribonucleic acid (mRNA), and deoxyribonucleic acid (DNA) samples.
- To explore the impact of Ixe compared to placebo at Weeks 4 and 12 on change from baseline in presence or absence of facial psoriasis (as indicated by the investigator in the eCRF) and measures of quality of life (SF-36 MCS and DLQI) and PSAB in the subgroup of patients with Ps located on the face.

Statistical Analysis Plan

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The primary analysis was based on the ITT population, defined as randomized subjects. In addition, an analysis of the per protocol (PP) population was used to support the primary efficacy analysis. The PP population was defined as all randomized subjects who were compliant with therapy, who did not have significant protocol violations, and whose investigator site did not have significant GCP issues that required a report to the regulatory agencies prior to Week 12. Compliance with therapy was defined to be missing no more than 20% of expected doses and not missing 2 consecutive doses during the period that patients participated in the study and prior to Week 12.

Treatment comparisons between each Ixe dose regimen and placebo in the proportion of patients achieving a sPGA (0,1) response at Week 12 (Visit 7) were analyzed using the logistic regression model. Missing data was imputed using the NRI method. Treatment comparisons between each Ixe dose regimen and placebo in the proportion of patients achieving PASI 75 at Week 12 (Visit 7) was analyzed using the logistic regression model. Missing data was imputed using the NRI method.

### **Protocol Amendments**

There was one protocol amendment approved by the applicant on Mar 15, 2012. The above protocol summary reflects the amended protocol.

### **Data Quality and Integrity: Sponsor's Assurance**

The applicant stated the following:

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by email, mail, telephone, and/or fax.
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

*Reviewer Comment: These measures appear to be adequate.*

### 6.1.2. Study Results

The efficacy analysis will be described under the integrated efficacy analysis section for each pivotal trial to avoid redundancy.

## 6.2. I1F-MC-RHBA (b)

I1F-MC-RHBA (b): A Multicenter, Randomized, Double-Blind, Placebo- Controlled Study Comparing the Efficacy and Safety of Ixe (LY2439821) to Etanercept and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis

### 6.2.1. Study Design

#### Overview and Objective

The primary objectives of the study were to assess whether 80 mg Ixe every 2 weeks (Q2W) or every 4 weeks (Q4W) was:

- Superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque Ps 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 a  $\geq 75\%$  improvement in Psoriasis Areas and Severity Index (PASI 75) from baseline.
- Non-inferior to etanercept at Week 12 in the treatment of patients with moderate-to-severe plaque Ps as measured by:
  - Proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline.
  - Proportion of patients achieving a  $\geq 75\%$  improvement in PASI (PASI 75) from baseline.
- Superior to etanercept at Week 12 in the treatment of patients with moderate-to-severe plaque Ps as measured by:
  - Proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline.

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- Proportion of patients achieving a  $\geq 75\%$  improvement in PASI (PASI 75) from baseline.

### **Trial Design**

RHBA is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study examining the effect on primary efficacy endpoint measures during an induction dosing period (IDP) at 12 weeks of 2 dose regimens of 80 mg Ixe (every 2 weeks [Q2W] or every 4 weeks [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 (Ps). All investigational products were administered subcutaneously. A blinded Maintenance Dosing Period (MDP) followed to evaluate the maintenance of response at Week 60 with 2 different dosing intervals of 80 mg Ixe (every 4 weeks [Q4W] or every 12 weeks [Q12W]), as well as relapse or rebound following treatment withdrawal, and response to retreatment with Ixe following relapse. Long-term efficacy and safety of Ixe were evaluated for up to a total of 5 years in patients who participated through the entire study.

The details of the study design are similar to Trial RHAZ with the exception of the addition of the active comparator etanercept arm. See Trial Design for RHAZ Section 6.1.1 **Study Design** for further details. The following are where the designs differ:

The IDP for RHBA was a double-blind, double-dummy, (both Ixe and etanercept had matching placebos) treatment period. Patients were randomized at a 2:2:2:1 ratio to 1 of 4 treatment groups: 80 mg Ixe Q2W, 80 mg Ixe Q4W, etanercept, or placebo. Patients were stratified by center. All patients receive a total of 31 SC injections during the IDP (24 injections of either etanercept or etanercept placebo and 7 injections of either Ixe or placebo for Ixe).

Patients randomized to placebo or etanercept at Week 0 (IDP) who were responders at Week 12 (Visit 7) received placebo at 4-week intervals during Period 3 until relapse; these patients received 2 SC injections of placebo at Week 12 (Visit 7) in order to maintain the study blind. Patients randomized to etanercept at Week 0 (IDP) who were non-responders at Week 12 (Visit 7) received placebo as 2 SC injections at Week 12 (Visit 7) and then received 80 mg Ixe Q4W during the remainder of the MDP. This ensured a washout period of  $\geq 5$  half-lives ( $>21.5$  days) after the last etanercept injection before receiving Ixe.

See Trial Design for RHAZ Section 6.1.1 Study Design for inclusion and exclusion criteria

#### **Additional Exclusion Criteria**

Prior use of etanercept

*Reviewer Comment: The randomization and stratification scheme for RHBA is different than that used for RHAZ and is in accord with recommendations made by DDDP.*

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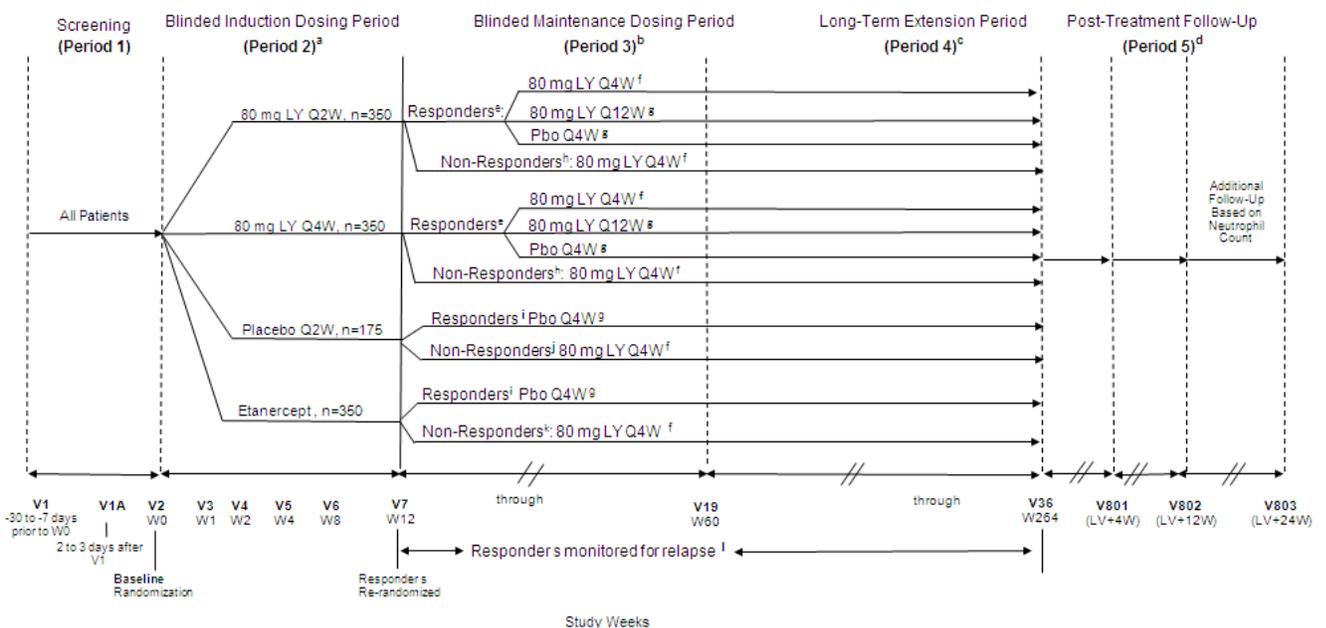
Trial Start Date: May 30, 2012

Last patient completed week 36: Sept 11, 2014 Database lock for this study report: 01 Oct 2014

Trial End Date: ongoing

RHAZ is being conducted at 120 sites in the following countries – US-41 site, Canada-17 sites, Germany- 13 sites, Poland-7 sites, Romania-6 sites, UK-7 sites, Australia-8 sites, France-8 sites, Netherlands-3 sites, Austria-4 sites, Czech Republic-3 sites and Spain-10 sites.

**Figure 2: Trial Design for RHBA**



**Figure RHBA.1. Illustration of study design for Clinical Protocol 11F-MC-RHBA (not to scale).**

**Abbreviations:** LV = date of last visit

<sup>a</sup> All patients will receive SC doses of investigational product (Ixe [Q2W or Q4W], placebo, or etanercept [twice weekly]) starting at Week 0 (Visit 2) up to Week 12 as outlined in [Table RHBA.1](#).

<sup>b</sup> All patients will receive 2 SC doses of investigational product (Ixe or placebo) at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 60 (Visit 19). Study visits will occur at least Q4W during Period 3.

<sup>c</sup> Study visits will occur at least Q12W during Period 4. Treatment (Ixe and placebo) will remain blinded to investigators, study site personnel, and patients until all patients reach Week 60 (Visit 19) or have discontinued from the study (moved into Period 5).

<sup>d</sup> All patients receiving investigational product must enter into Period 5 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed.

<sup>e</sup> Responders to Ixe at Week 12 (Visit 7; responders are defined as achieving an sPGA score of 0 or 1) will be randomly assigned at a 1:1:1 ratio to Ixe (Q4W, Q12W), or to placebo.

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- f Patients who experience loss of treatment efficacy (relapse) during Period 3 will remain on 80 mg Ixe Q4W in order to maintain the blind.
- g Patients who experience loss of treatment efficacy (relapse) during Period 3 will be switched to 80 mg Ixe Q4W.
- h Nonresponders to Ixe at Week 12 (Visit 7; nonresponders are defined as having an sPGA score of >1) will receive Ixe 80 mg Q4W.
- i Responders to placebo or etanercept at Week 12 (Visit 7) will receive 2 injections of placebo at Week 12 followed by placebo Q4W until relapse.
- j Nonresponders to placebo at Week 12 (Visit 7) will receive 2 injections of Ixe (starting dose) at Week 12 followed by Ixe 80 mg Q4W.
- k Non-responders to etanercept at Week 12 (Visit 7) will receive 2 injections of placebo at Week 12 followed by 80 mg Ixe Q4W starting at Week 16.
- l Relapse occurring after Week 12 (Visit 7) is defined as a loss of response equal to an sPGA score of  $\geq 3$ .

Source: Applicant's Protocol RHBA, pg. 33-34

## Study Endpoints

### Primary Analyses

- Proportion of Patients with sPGA (0 or 1) and At Least a 2-Point Improvement from Baseline at Week 12 Compared with Placebo
- Proportion of Patients Achieving PASI 75 at Week 12 Compared with Placebo
- Proportion of Patients with sPGA (0 or 1) at Week 12, Non-Inferiority with Etanercept. This non-inferiority analysis will be conducted only if the Ixe dose is significantly better than placebo and etanercept is significantly better than placebo.
- Proportion of Patients with sPGA (0 or 1) at Week 12, Superiority with Etanercept
- Proportion of Patients with PASI 75 at Week 12, Non-inferiority with Etanercept
- Proportion of Patients with sPGA (0 or 1) at Week 12, Superiority with Etanercept

### Major Secondary Analyses

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

### Other Secondary Analyses

**Table 5: Secondary Efficacy Analyses in the Induction Period**

**Table RHBA.9.8. Secondary Efficacy Analyses in the Induction Dosing Period**

Secondary Efficacy Measure	Variable	Analysis
sPGA	<ol style="list-style-type: none"> <li>sPGA (0,1) and sPGA (0)</li> <li>Time to sPGA (0,1) response: defined as the number of days from initial randomization to the first visit at which the patient had an sPGA (0,1) during Period 2 (Induction Dosing Period).</li> </ol>	<ol style="list-style-type: none"> <li>Logistic regression, Fisher's exact test, categorical MMRM, and pMI approach [sPGA (0,1) only].</li> <li>For patients who discontinued early in Period 2 or who completed Period 2 without meeting the criteria for response, the time-to-first response was censored and defined as the number of days from initial randomization to the patient's last visit during Period 2. Time to first response for each treatment group in Period 2 was estimated using the Kaplan-Meier product limit method. Treatment group comparisons were performed using the log-rank test at the 2-sided 0.05 significance level.</li> </ol>
PASI	<ol style="list-style-type: none"> <li>PASI 50, PASI 75, PASI 90, and PASI 100.</li> <li>Change from baseline, percent improvement.</li> <li>Time to PASI 75 response: defined as the number of days from initial randomization to the first visit at which the patient met the PASI 75 criterion during Period 2 (Induction Dosing Period).</li> </ol>	<ol style="list-style-type: none"> <li>Logistic regression, Fisher's exact test, categorical MMRM.</li> <li>MMRM, ANCOVA LOCF, ANCOVA mBOCF.</li> <li>Kaplan-Meier product limit method, log-rank test.</li> </ol>
NAPSI	<ol style="list-style-type: none"> <li>Change from baseline</li> <li>NAPSI total score =0</li> </ol>	<ol style="list-style-type: none"> <li>MMRM, ANCOVA LOCF, ANCOVA mBOCF</li> <li>Logistic regression, Fisher's exact test, categorical MMRM</li> </ol>
PSSI	<ol style="list-style-type: none"> <li>Change from baseline</li> <li>PSSI total score = 0</li> </ol>	<ol style="list-style-type: none"> <li>MMRM, ANCOVA LOCF, ANCOVA mBOCF</li> <li>Logistic regression, Fisher's exact test, categorical MMRM</li> </ol>
PPASI	<ol style="list-style-type: none"> <li>Change from baseline</li> <li>PPASI 50, PPASI 75, and PPASI 100</li> </ol>	<ol style="list-style-type: none"> <li>MMRM, ANCOVA LOCF, ANCOVA mBOCF</li> <li>Logistic regression, Fisher's exact test, categorical MMRM</li> </ol>
BSA	<ol style="list-style-type: none"> <li>Change from baseline</li> </ol>	<ol style="list-style-type: none"> <li>MMRM, ANCOVA LOCF, ANCOVA mBOCF</li> </ol>
Facial Psoriasis	<ol style="list-style-type: none"> <li>Presence/absence of facial psoriasis</li> </ol>	<ol style="list-style-type: none"> <li>Descriptive statistics, shift table</li> </ol>

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; LOCF = last observation carried forward; mBOCF = modified baseline observation carried forward; MMRM = mixed-effect model of repeated measures; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index; PASI 50= at least 50% improvement in PASI score; PASI 75 = at least 75% improvement in PASI score; PASI 90 = at least 90% improvement in PASI score; PASI 100 = at least 100% improvement in PASI score; pMI = placebo multiple imputation; PPASI = Palmoplantar PASI; PSSI = Psoriasis Scalp Severity Index; sPGA = static Physician Global Assessment.

Source: Applicant's RHBA Clinical Study Report, Pg 191

**Table 6: Secondary Efficacy Analyses in the Maintenance Dosing Period**

Table RHBA.9.9. Secondary Efficacy Analyses in the Maintenance Dosing Period

Secondary Efficacy Measure	Variable	Analysis for Maintenance Dosing Period Primary Population	Analysis for Maintenance Dosing Period Secondary Population	Analysis for Maintenance Dosing Period Relapse Population
sPGA	1. sPGA (0,1) and sPGA (0) 2. Loss of efficacy (sPGA $\geq$ 3)	1. CMH test stratified by pooled center, Fisher's exact test, categorical MMRM and pMI approach (sPGA [0,1] only) 2. Kaplan-Meier product limit method	1. Descriptive statistics 2. NA	1. Descriptive statistics; regain or achieve the response with 12 weeks of retreatment 2. NA
PASI	1. PASI 50, PASI 75, PASI 90, and PASI 100 2. Change from baseline, percent improvement	1. CMH test stratified by pooled center, Fisher's exact test, categorical MMRM 2. MMRM, ANCOVA LOCF, ANCOVA mBOCF	1. Descriptive statistics 2. Descriptive statistics	1. Descriptive statistics; achieve response rates within 12 weeks of re-treatment 2. NA
NAPSI	1. Change from baseline 2. NAPSI total score =0	1. MMRM, ANCOVA LOCF, ANCOVA mBOCF 2. Categorical MMRM	1. Descriptive statistics 2. Descriptive statistics	1. NA 2. Descriptive statistics
PSSI	1. Change from baseline 2. PSSI total score = 0	1. MMRM, ANCOVA LOCF, ANCOVA mBOCF 2. Categorical MMRM	1. Descriptive statistics 2. Descriptive statistics	1. NA 2. Descriptive statistics
PPASI	1. Change from baseline 2. PPASI 50, PPASI 75, and PPASI 100	1. MMRM, ANCOVA LOCF, ANCOVA mBOCF 2. Categorical MMRM	1. Descriptive statistics 2. Descriptive statistics	1. NA 2. Descriptive statistics
BSA	1. Change from baseline	1. MMRM, ANCOVA LOCF, ANCOVA mBOCF	1. Descriptive statistics	1. NA

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; mBOCF = modified baseline observation carried forward; MMRM = mixed-effect model of repeated measures; NA = not applicable; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index; PASI 50 = at least 50% improvement in PASI score; PASI 75 = at least 75% improvement in PASI score; PASI 90 = at least 90% improvement in PASI score; PASI 100 = at least 100% improvement in PASI score; pMI = placebo multiple imputation; PPASI = Palmoplantar PASI; PSSI = Psoriasis Scalp Severity Index; sPGA = static Physician Global Assessment.

Source: Applicant's RHBA Clinical Study Report, Pg 193

### Statistical Analysis Plan

Treatment comparisons between each Ixe dose regimen and placebo in the proportion of patients achieving an sPGA (0,1) response at Week 12 (NRI) were analyzed using CMH test stratified by pooled center. As a sensitivity analysis, the CMH test stratified by pooled center was repeated for the PPS. Missing data were imputed using the NRI method.

Treatment comparisons between each Ixe dose regimen and placebo in the proportion of patients achieving PASI 75 response at Week 12 (NRI) were analyzed using the CMH test stratified by pooled center. As a sensitivity analysis, the CMH test stratified by pooled center was repeated for the PPS. Missing data were imputed using the NRI method described.

The non-inferiority test for each Ixe dose regimen compared to etanercept in the proportion of patients achieving an sPGA (0,1) response at Week 12 (Visit 7) was carried out by a statistical test of the null hypothesis defined in Section 9.7.1.1.2.1.1 (method for FDA) and Section 9.7.1.1.2.1.2 (method for CHMP).

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

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between etanercept and placebo in the proportion of patients achieving an sPGA (0,1) response at Week 12 (Visit 7) were also analyzed using the CMH test stratified by pooled center. Missing data were imputed using the NRI method described in Section 9.7.1.3.1.

The non-inferiority test for each Ixe dose regimen compared to etanercept in the proportion of patients achieving a PASI 75 response at Week 12 (Visit 7) was carried out by a statistical test of the null hypothesis defined in Section 9.7.1.1.2.1.1 (method for FDA) and Section 9.7.1.1.2.1.2 (method for CHMP).

This non-inferiority analysis was conducted only if the Ixe dose was significantly better than placebo, and etanercept was significantly better than placebo. Treatment comparisons between etanercept and placebo in the proportion of patients achieving a PASI 75 response at Week 12 (Visit 7) were also analyzed using the CMH test stratified by pooled center. Missing data were imputed using the NRI method described in Section 9.7.1.3.1.

Superiority testing of each Ixe dose regimen compared to etanercept in the proportion of patients achieving an sPGA (0,1) response at Week 12 (Visit 7) was carried out using the methods defined in Section 9.7.1.1.2.1.1 (method for FDA) and Section 9.7.1.1.2.1.2 (method for CHMP). Missing data were imputed using the NRI method described in Section 9.7.1.3.1.

As sensitivity analyses, the aforementioned analyses was repeated for the PPS. As a sensitivity analysis, the non-inferiority and superiority of Ixe compared to etanercept analysis was repeated using the US-only population.

Superiority testing of each Ixe dose regimen compared to etanercept in the proportion of patients achieving a PASI 75 response at Week 12 (Visit 7) was carried out using the methods defined in Section 9.7.1.1.2.1.1 (method for FDA) and Section 9.7.1.1.2.1.2 (method for CHMP). Missing data were imputed using the NRI method described in Section 9.7.1.3.1.

As sensitivity analyses, the aforementioned analyses was repeated for the PPS. As a sensitivity analysis, the non-inferiority and superiority of Ixe compared to etanercept analysis was repeated using the US-only population.

For Study RHBA, an interim lock occurred after the last patient completed 24 weeks of treatment in the Maintenance Dosing Period to allow for a second, independent assessment of maintenance of effect.

### **Protocol Amendments**

Same as for RHAZ

### **Data Quality and Integrity: Sponsor's Assurance**

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Same as for RHAZ

### 6.2.2. Study Results

The efficacy analysis will be described under the integrated efficacy analysis section for each pivotal trial to avoid redundancy.

### 6.3. I1F-MC-RHBC (b)

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

#### 6.3.1. Study Design

##### Overview and Objective

See Trial Design for RHBA Section 6.2.1 **Study Design** for further details.

##### Trial Design

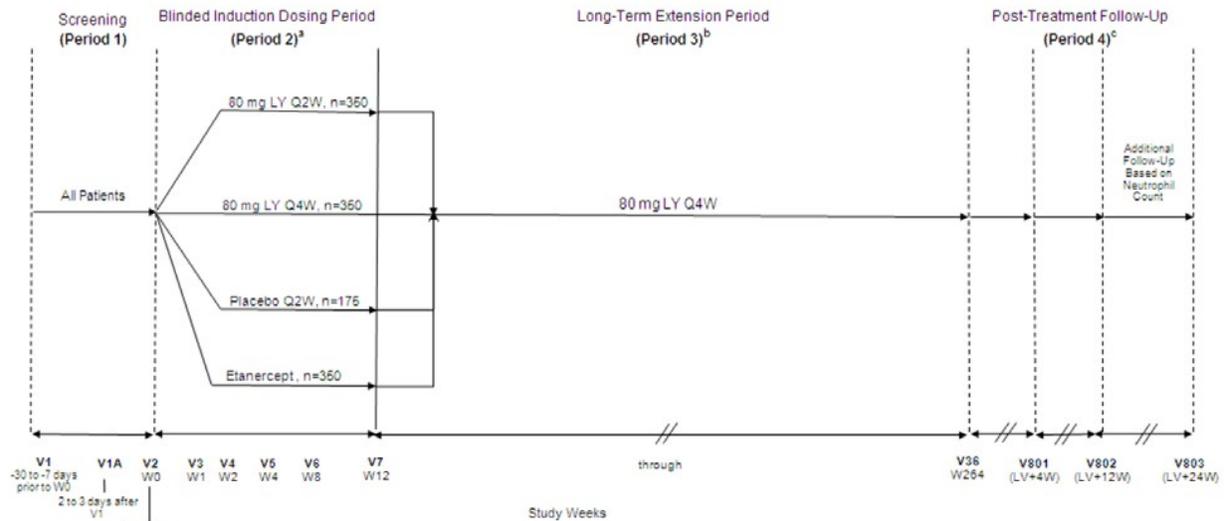
The details of the study design are similar to Trial RHBA with the exception of the lack of a maintenance period. See Trial Design for RHBA Section 6.2.1 **Study Design** for further details.

The following are where the designs differ:

The study will consist of 4 periods:

- Period 1 (Section 7.1.1): Screening Period (Visits 1 and 1A) lasting from 7 to 30 days prior to Period 2 (baseline, Week 0, Visit 2)
- Period 2 (Section 7.1.2): Induction Dosing Period from Week 0 (baseline, Visit 2) up to Week 12 (Visit 7)
- Period 3 (Section 7.1.3): Long-Term Extension Period from Week 12 (Visit 7) up to Week 264 (Visit 36)
- Period 4 (Section 7.1.4): Post-Treatment Follow-Up Period occurring from last treatment period visit or Early Termination Visit (ETV) up to a minimum of 12 weeks following that visit.

**Figure 3: Trial Design for RHBC**



**Abbreviations:** LV = date of last visit;

<sup>a</sup> All patients will receive SC doses of investigational product (Ixe [Q2W or Q4W], placebo, or etanercept [twice weekly]) starting at Week 0 (Visit 2) up to Week 12 as outlined in [Table RHBC.1](#).

<sup>b</sup> All patients will receive 2 SC doses of investigational product (Ixe or placebo) at Week 12 (Visit 7) and 1 SC dose of Ixe Q4W from Week 16 (Visit 8) through Week 264 (Visit 36). Treatment will remain blinded until all patients complete Week 12 (Visit 7) or have discontinued from the study (moved into Period 4).

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

Source: Applicant’s IIF-MC-RHBC (b) Clinical Protocol Page 29

**Study Endpoints**

See Trial Design for RHBA Section 6.2.1 **Study Design** for further details (except for lack of maintenance period analyses).

**Statistical Analysis Plan**

See Trial Design for RHBA Section 6.2.1 **Study Design** for further details (except for lack of maintenance period analyses).

**Protocol Amendments**

Same as RHAZ

**Data Quality and Integrity: Sponsor's Assurance**

Same as RHAZ

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Taltz (ixekizumab)

Trial Start Date: Aug 11, 2012  
Last patient visit prior to database lock for this report: May 22, 2014  
Database lock for this study report: July 14, 2014  
Trial End Date: ongoing

RHBC is being conducted at 123 sites in the following countries – US-45 sites, Canada-11 sites, Germany- 34 sites, Bulgaria- 5 sites, Poland-3 sites, Mexico-2 sites, Hungary-12 sites, Russia-9 sites, Chile-2 sites.

### 6.3.2. Study Results

The efficacy analysis will be described under the integrated efficacy analysis section for each pivotal trial to avoid redundancy.

## 7 Integrated Review of Effectiveness

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The following table displays the basic design features of the pivotal trials and highlights the differences between them.

**Table 7: Design Features of the Pivotal Phase 3 Studies**

**Table 2.7.3.1. Design Features of the Pivotal, Controlled, Randomized, Double-Blind, Phase 3 Studies**

	RHAZ N=1296 Placebo-Controlled, Efficacy and Safety Study with LTE	RHBA N=1224 Active Comparator (Etanercept) and Placebo-Controlled, Efficacy and Safety Study with LTE	RHBC N=1346 Active Comparator (Etanercept) and Placebo-Controlled, Efficacy and Safety Study with LTE
<b>Population</b>	Adults with moderate-to-severe plaque psoriasis; candidates for phototherapy or systemic therapy		
<b>Disease Activity</b>	BSA $\geq$ 10%; PASI $\geq$ 12; sPGA $\geq$ 3		
<b>Induction Treatment Groups (Weeks 0-12)</b>	160-mg starting dose, then 80 mg Q2W 160-mg starting dose, then 80 mg Q4W Placebo (Randomization ratio: 1:1:1)	160-mg starting dose, then 80 mg Q2W 160-mg starting dose, then 80 mg Q4W Placebo Comparator (etanercept) (Randomization ratio: 2:2:1:2)	
<b>Maintenance Treatment Groups: Maintenance Dosing Period Primary Population<sup>a</sup> (Weeks 12-60)</b>	80 mg Q4W 80 mg Q12W Placebo (Randomization ratio: 1:1:1, re-treatment with 80 mg Q4W upon relapse)		NA
<b>Maintenance Treatment Groups: Maintenance Dosing Period Secondary Population<sup>b</sup> (Weeks 12-60)</b>	80 mg Q4W (nonresponders to any treatment at Week 12) Placebo (responders to placebo or etanercept at Week 12, re-treatment with 80mg Q4W upon relapse)		NA
<b>Treatment Groups (LTE Phase)</b>	80 mg Q4W 80 mg Q12W Placebo		80 mg Q4W
<b>Co-Primary Endpoints</b>	PASI 75 and sPGA (0,1) at 12 weeks		
<b>Duration Blinded</b>	60 weeks		12 weeks
<b>Efficacy/Health Outcome Data Included in This Submission<sup>d</sup></b>	All data up to 60 weeks	Data up to 60 weeks (based on an interim analysis performed when the final patient completed 36 weeks)	All data up to 12 weeks

Abbreviations: BSA = body surface area; LTE = long-term extension; NA = not applicable; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; sPGA = static Physician Global Assessment.

<sup>a</sup> Ixekizumab-treated patients who responded to treatment, that is, who achieved sPGA (0,1), during the Induction Dosing Period.

<sup>b</sup> Patients randomized to either placebo or etanercept at Week 0 or ixekizumab-treated patients who did not respond to therapy (achieve sPGA 0,1) during the Induction Dosing Period.

<sup>c</sup> Etanercept nonresponders received placebo for a 4-week washout period, before commencing treatment with ixekizumab 80 mg Q4W at Week 16.

<sup>d</sup> For the Maintenance Dosing Period, efficacy data reported are from patients who completed Week 60, discontinued prior to Week 60, or relapsed prior to Week 60.

Source: Applicant’s Summary of Clinical Efficacy Pg. 16-17.

In addition to the differences displayed in the table above, the trials differed in

- Randomization pattern (RHAZ - 1:1:1 (TATLZ 80 mg Q2W, TATLZ 80 mg Q4W, and placebo), RHBA and RHBC – 2:2:1:2 (TATLZ 80 mg Q2W, TATLZ 80 mg Q4W, placebo, and etanercept)
- Stratification: In Trial RHAZ, randomization at Week 0 was stratified by geographic region (North America or Other), previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or  $\geq$ 3 conventional systemic therapies), and weight (<100 kg or  $\geq$ 100 kg). In Trials RHBA and RHBC, randomization at Week 0 was stratified by center. At Week 12, re-randomization in Trial RHBA was

stratified by induction dosing regimen, while in Trial RHAZ, re-randomization at Week 12 was stratified by induction dosing regimen and weight (<100 kg or ≥100 kg).

- Data included in the BLA submission: For Trial RHAZ, the BLA application contains all data collected through August 7, 2014, which includes all data from the first three periods (i.e., screening period, blinded induction dosing period, and blinded maintenance dosing period) and safety data collected during the long-term extension period and post-treatment follow-up period. For Trial RHBA, the BLA application contains all data collected up to a database lock (October 1, 2014) that occurred after all subjects enrolled completed the Week 36 visit of the maintenance dosing period. For Trial RHBC, the BLA application all data up to Week 12 and all safety data up to the database lock (May 22, 2014).
- Pooling of Centers: For Trials RHBA and RHBC, the protocols specified pooling centers with fewer than 5 subjects per treatment arm (See statistical review for details). Pooling for Trial RHAZ was not specified in the protocol.
- Secondary endpoints

**Table 8: Secondary Efficacy Endpoints Across the Pivotal Trials**

<b>Endpoint</b>	<b>Trial</b>
sPGA of 0 at Week 12	All Three
PASI-90 at Week 12	All Three
PASI-100 at Week 12	All Three
Maintaining sPGA 0 or 1 from Week 12 to Week 60	RHAZ and RHBA
≥ 4-point reduction in Itch NRS from baseline at Week 12	RHAZ and RHBC
Change from baseline in DLQI at Week 12	RHAZ and RHBC
Change from baseline in NAPSI (for fingernails) at Week 12	RHAZ and RHBC

Source: Statistical Review Pg. 9

## 7.1. Assessment of Efficacy Across Trials

### **Indication**

Ixe is indicated for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy.

### **Methods**

The applicant submitted electronic analysis datasets for review which were analyzed by Matt Guerra, the Agency biostatistical reviewer. Pivotal trials were analyzed separately. This reviewer evaluated the statistical reviewer’s analysis, the applicant’s clinical study reports and clinical summaries of efficacy and the proposed labeling.

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**Demographics**

The following tables display the baseline demographics for the three pivotal trials RHAZ, RHBA, RHBC.

**Table 9: Patient Demographic Characteristics at Baseline ITT Population (RHAZ)**

	TALTZ 80 mg		Placebo (N=431)
	Q2W (N=433)	Q4W (N=432)	
<b>Age (years)</b>			
Mean (SD)	45 (12)	46 (13)	46 (13)
Median	45	46	47
Range	17 – 75	18 – 88	18 – 79
<b>Gender</b>			
Male	291 (67%)	289 (67%)	303 (70%)
Female	142 (33%)	143 (33%)	128 (30%)
<b>Race</b>			
White	401 (93%)	397 (92%)	401 (93%)
Black	8 (2%)	10 (2%)	8 (2%)
Asian	18 (4%)	23 (5%)	21 (5%)
Other	6 (1%)	2 (1%)	1 (<1%)
<b>Weight (kg)</b>			
Mean (SD)	92.4 (22.7)	92.5 (23.9)	91.8 (25.0)
Median	89.0	88.9	87.5
Range	48 – 190.5	47 – 200	45.8 – 186
< 100 kg	288 (67%)	290 (67%)	289 (67%)
≥ 100 kg	145 (33%)	142 (33%)	142 (33%)
<b>Country</b>			
US	159 (37%)	156 (36%)	146 (34%)
Non-US	274 (63%)	276 (64%)	285 (66%)
<b>sPGA</b>			
3 - Moderate	231 (53%)	197 (46%)	204 (47%)
4 - Severe	179 (41%)	205 (47%)	193 (45%)
5 - Very Severe	23 (5%)	30 (7%)	34 (8%)
<b>PASI</b>			
Mean (SD)	20 (8)	20 (7)	20 (9)
Median	17.5	17.8	17.2
Range	12 – 60	12 – 61.2	12 – 69.2
<b>Percent BSA</b>			
Mean (SD)	28 (18)	27 (16)	27 (18)
Median	22.0	21.0	20.0
Range	10 – 95	10 – 92	10 – 95

Source: Statistical Review Pg.16

**Table 10: Additional Baseline Demographic Characteristics, ITT Population (RHAZ)**

	PBO (N=431)	IXE80Q4W (N=432)	IXE80Q2W (N=433)	Total IXE (N=865)	Total (N=1296)
<b>BMI (kg/m<sup>2</sup>)</b>					
Number of Patients, Nx	431	432	432	864	1295
Mean	30.43	30.69	30.82	30.75	30.65
SD	7.608	7.500	7.117	7.307	7.407
Minimum	16.1	17.4	17.6	17.4	16.1
Median	29.04	29.56	29.81	29.70	29.45
Maximum	66.0	76.4	64.6	76.4	76.4
<b>BMI Category, n(%)</b>					
Number of Patients, Nx	431	432	432	864	1295
Underweight (<18.5 kg/m <sup>2</sup> )	9 ( 2.1%)	4 ( 0.9%)	5 ( 1.2%)	9 ( 1.0%)	18 ( 1.4%)
Normal (>=18.5 - <25 kg/m <sup>2</sup> )	95 ( 22.0%)	87 ( 20.1%)	83 ( 19.2%)	170 ( 19.7%)	265 ( 20.5%)
Overweight (>=25 - <30 kg/m <sup>2</sup> )	138 ( 32.0%)	141 ( 32.6%)	135 ( 31.3%)	276 ( 31.9%)	414 ( 32.0%)
Obese (>=30 - <40 kg/m <sup>2</sup> )	136 ( 31.6%)	159 ( 36.8%)	160 ( 37.0%)	319 ( 36.9%)	455 ( 35.1%)
Extreme obese (>=40 kg/m <sup>2</sup> )	53 ( 12.3%)	41 ( 9.5%)	49 ( 11.3%)	90 ( 10.4%)	143 ( 11.0%)
<b>Previous systemic therapy, n(%)</b>					
Number of Patients, Nx	431	432	433	865	1296
Never used	132 ( 30.6%)	132 ( 30.6%)	108 ( 24.9%)	240 ( 27.7%)	372 ( 28.7%)
Non-biologic only	118 ( 27.4%)	132 ( 30.6%)	152 ( 35.1%)	284 ( 32.8%)	402 ( 31.0%)
Biologic only	57 ( 13.2%)	62 ( 14.4%)	49 ( 11.3%)	111 ( 12.8%)	168 ( 13.0%)
Biologic and non-biologic	124 ( 28.8%)	106 ( 24.5%)	124 ( 28.6%)	230 ( 26.6%)	354 ( 27.3%)
<b>Previous biologic therapy, n(%)</b>					
Number of Patients, Nx	431	432	433	865	1296
Never used	250 ( 58.0%)	264 ( 61.1%)	260 ( 60.0%)	524 ( 60.6%)	774 ( 59.7%)
Ever used	181 ( 42.0%)	168 ( 38.9%)	173 ( 40.0%)	341 ( 39.4%)	522 ( 40.3%)
<b>Previous biologic therapy, n(%)</b>					
Number of Patients, Nx	431	432	433	865	1296
Never used	250 ( 58.0%)	264 ( 61.1%)	260 ( 60.0%)	524 ( 60.6%)	774 ( 59.7%)
Used 1 therapy	99 ( 23.0%)	91 ( 21.1%)	95 ( 21.9%)	186 ( 21.5%)	285 ( 22.0%)
Used 2 therapies	40 ( 9.3%)	47 ( 10.9%)	36 ( 8.3%)	83 ( 9.6%)	123 ( 9.5%)
Used >= 3 therapies	42 ( 9.7%)	30 ( 6.9%)	42 ( 9.7%)	72 ( 8.3%)	114 ( 8.8%)
<b>Previous phototherapy therapy, n(%)</b>					
Number of Patients, Nx	431	432	433	865	1296
Never used	246 ( 57.1%)	227 ( 52.5%)	232 ( 53.6%)	459 ( 53.1%)	705 ( 54.4%)
Ever used	185 ( 42.9%)	205 ( 47.5%)	201 ( 46.4%)	406 ( 46.9%)	591 ( 45.6%)
<b>Previous non-biologic systemic therapy, n(%)</b>					
Number of Patients, Nx	431	432	433	865	1296
Never used	189 ( 43.9%)	194 ( 44.9%)	157 ( 36.3%)	351 ( 40.6%)	540 ( 41.7%)
Used 1 therapy	110 ( 25.5%)	110 ( 25.5%)	140 ( 32.3%)	250 ( 28.9%)	360 ( 27.8%)
Used 2 therapies	65 ( 15.1%)	59 ( 13.7%)	53 ( 12.2%)	112 ( 12.9%)	177 ( 13.7%)
Used >= 3 therapies	67 ( 15.5%)	69 ( 16.0%)	83 ( 19.2%)	152 ( 17.6%)	219 ( 16.9%)
<b>Baseline QIDS-SR16 Total Score</b>					
Number of Patients, Nx	430	431	431	862	1292
Mean	4.7	5.0	4.5	4.8	4.8
SD	4.34	4.34	4.09	4.22	4.26
Minimum	0	0	0	0	0
Median	3.0	4.0	3.0	3.0	3.0
Maximum	24	21	22	22	24

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Baseline Itch NRS Score					
Number of Patients, Nx	431	432	433	865	1296
Mean	7.0	7.0	7.2	7.1	7.1
SD	2.58	2.50	2.39	2.45	2.49
Minimum	0	0	0	0	0
Median	8.0	8.0	8.0	8.0	8.0
Maximum	10	10	10	10	10

Baseline DLQI Score					
Number of Patients, Nx	431	431	432	863	1294
Mean	12.8	13.2	13.4	13.3	13.1
SD	7.11	7.02	7.02	7.02	7.05
Minimum	0	0	0	0	0
Median	12.0	12.0	13.0	13.0	12.0
Maximum	30	30	30	30	30

Notes: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; SD = standard deviation; N = number of Patients in the analysis population; Nx = number of patients with non-missing values; Percentage is calculated by  $n/Nx \times 100\%$ .  
For weight, BMI, waist circumference, tobacco use, alcohol consumption and caffeine/xanthine ingestion, baseline is defined as the safety baseline for each period.  
Previous non-biologic systemic therapy includes the following: methotrexate, cyclosporine, retinoids, and PUVA.  
[1] p-value is based on Fisher's exact test for categorical data (Monte Carlo estimates of exact p-values are used for overall comparison) and a one-way analysis of variance (ANOVA) for continuous data with treatment group as independent factor.  
[2] Duration of Psoriasis Symptoms is calculated as: (date of informed consent - date of onset of psoriasis symptoms)/365.25.  
\* - p-value  $\leq 0.05$ .

Source: Applicant's Clinical Study Report RHAZ Pg 1161 -1180

The demographic characteristics were balanced across the treatment arms for RHAZ with a mean age of 45-46 and a majority of male subjects (66-70%). The subjects were predominantly white (92-93%), not Hispanic or Latino (80-81%) and  $\approx 1/3$  were from the US. The mean weight was 91-92 kg and the mean BMI was 30 kg/m<sup>2</sup>. With regard to baseline severity, the majority (70-76%) had previously used systemic therapies, had a mean baseline sPGA of 3.6, a mean PASI of 20, and a mean BSA of 27-28. The mean duration of psoriasis was 19 years, with a mean age of onset of 25-27 years. The mean Itch NRS was 7 out of a possible 10.

*Reviewer Comment: These demographic characteristics are consistent with what is known about the psoriasis population in the US who are treated with systemic agents.*

**Table 11: Patient Demographic Characteristics at Baseline Intent-to-Treat Population (RHBA)**

	TALTZ 80 mg		Etanercept (N=358)	Placebo (N=168)
	Q2W (N=351)	Q4W (N=347)		
<b>Age</b>				
Mean (SD)	45 (13)	45 (14)	45.3 (13)	45 (12)
Median	44	45	46	46
Range	18 – 84	18 – 82	18 – 79	20 – 76
<b>Gender</b>				
Male	221 (63%)	244 (70%)	236 (66%)	120 (71%)
Female	130 (37%)	103 (30%)	122 (34%)	48 (29%)

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<b>Race<sup>(1)</sup></b>				
White	330 (94%)	315 (92%)	331 (94%)	149 (89%)
Black	5 (1%)	11 (3%)	13 (4%)	10 (6%)
Asian	12 (3%)	11 (3%)	8 (2%)	6 (3%)
Other	3 (1%)	6 (2%)	2 (<1%)	3 (2%)
<b>Weight</b>				
Mean (SD)	89.2 (21.6)	92.5 (22.5)	92.9 (22.4)	91.8 (21.9)
Median	87.1	90.9	90.0	88.8
Range	41 – 162.3	46.8 – 216.2	48.6 – 173.2	50 – 165
< 100 kg	256 (73%)	227 (66%)	232 (65%)	111 (67%)
≥ 100 kg	95 (27%)	119 (34%)	125 (35%)	55 (33%)
<b>Country</b>				
US	104 (30%)	105 (30%)	111 (31%)	49 (29%)
Non-US	247 (70%)	242 (70%)	247 (69%)	119 (71%)
<b>sPGA</b>				
3 - Moderate	178 (51%)	166 (48%)	186 (52%)	86 (51%)
4 - Severe	151 (43%)	164 (47%)	156 (43%)	70 (42%)
5 - Very Severe	22 (6%)	17 (5%)	16 (5%)	12 (7%)
<b>PASI</b>				
Mean (SD)	19 (7)	20 (7)	19 (7)	21 (8)
Median	17.3	17.8	17.2	17.7
Range	12 – 57.5	12 – 46.8	12 – 61.2	12 – 54
<b>Percent BSA</b>				
Mean (SD)	25 (16)	27 (17)	25 (16)	27 (18)
Median	20	20	20	20
Range	10 – 95	10 – 85	10 – 90	10 – 92

Source: Reviewer's Analysis

(1) One subject on TALTZ 80 mg Q2W, four subjects on TALTZ 80 mg Q4W and four subjects on etanercept had missing race information.

Source: Statistical Review Pg.17

**Table 12: Additional Baseline Demographic Characteristics, ITT Population (RHBA)**

	PBO (N=168)	ETN (N=358)	IXE80Q4W (N=347)	IXE80Q2W (N=351)	Total IXE (N=698)	Total (N=1224)
<b>BMI (kg/m<sup>2</sup>)</b>						
Number of Patients, Nx	165	357	343	351	694	1216
Mean	30.85	31.25	30.62	30.08	30.35	30.68
SD	7.141	7.252	6.589	7.020	6.811	6.994
Minimum	18.3	17.0	17.2	15.2	15.2	15.2
Median	30.16	29.91	29.67	28.72	29.26	29.56
Maximum	60.6	58.6	53.8	60.2	60.2	60.6
<b>BMI Category, n(%)</b>						
Number of Patients, Nx	165	357	343	351	694	1216
Underweight (<18.5 kg/m <sup>2</sup> )	1 ( 0.6%)	1 ( 0.3%)	2 ( 0.6%)	2 ( 0.6%)	4 ( 0.6%)	6 ( 0.5%)
Normal (≥18.5 - <25 kg/m <sup>2</sup> )	31 ( 18.8%)	70 ( 19.6%)	62 ( 18.1%)	75 ( 21.4%)	137 ( 19.7%)	238 ( 19.6%)
Overweight (≥25 - <30 kg/m <sup>2</sup> )	48 ( 29.1%)	109 ( 30.5%)	117 ( 34.1%)	128 ( 36.5%)	245 ( 35.3%)	402 ( 33.1%)
Obese (≥30 - <40 kg/m <sup>2</sup> )	70 ( 42.4%)	130 ( 36.4%)	128 ( 37.3%)	116 ( 33.0%)	244 ( 35.2%)	444 ( 36.5%)
Extreme obese (≥40 kg/m <sup>2</sup> )	15 ( 9.1%)	47 ( 13.2%)	34 ( 9.9%)	30 ( 8.5%)	64 ( 9.2%)	126 ( 10.4%)

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	PBO (N=168)	ETN (N=358)	IXE80Q4W (N=347)	IXE80Q2W (N=351)	Total IXE (N=698)	Total (N=1224)
<b>Previous systemic therapy, n(%)</b>						
Number of Patients, Nx	168	358	347	351	698	1224
Never used	64 (38.1%)	133 (37.2%)	115 (33.1%)	126 (35.9%)	241 (34.5%)	438 (35.8%)
Non-biologic only	61 (36.3%)	149 (41.6%)	147 (42.4%)	141 (40.2%)	288 (41.3%)	498 (40.7%)
Biologic only	19 (11.3%)	33 (9.2%)	28 (8.1%)	29 (8.3%)	57 (8.2%)	109 (8.9%)
Biologic and non-biologic	24 (14.3%)	43 (12.0%)	57 (16.4%)	55 (15.7%)	112 (16.0%)	179 (14.6%)
<b>Previous non-biologic systemic therapy, n(%)</b>						
Number of Patients, Nx	168	358	347	351	698	1224
Never used	83 (49.4%)	166 (46.4%)	143 (41.2%)	155 (44.2%)	298 (42.7%)	547 (44.7%)
Ever used	85 (50.6%)	192 (53.6%)	204 (58.8%)	196 (55.8%)	400 (57.3%)	677 (55.3%)
<b>Baseline QIDS-SR16 Total Score</b>						
Number of Patients, Nx	167	358	347	351	698	1223
Mean	4.7	4.5	4.4	4.6	4.5	4.5
SD	4.14	4.07	4.04	3.84	3.94	4.00
Minimum	0	0	0	0	0	0
Median	3.0	3.0	3.0	3.0	3.0	3.0
Maximum	20	23	20	21	21	23
<b>Baseline Itch NRS Score</b>						
Number of Patients, Nx	166	357	345	351	696	1219
Mean	6.4	6.6	6.5	6.7	6.6	6.6
SD	2.67	2.58	2.50	2.51	2.50	2.55
Minimum	0	0	0	0	0	0
Median	7.0	7.0	7.0	7.0	7.0	7.0
Maximum	10	10	10	10	10	10
<b>Baseline DLQI Score</b>						
Number of Patients, Nx	165	358	345	350	695	1218
Mean	12.8	12.7	11.6	12.4	12.0	12.3
SD	7.24	7.03	6.65	6.86	6.76	6.91
Minimum	0	1	0	0	0	0
Median	12.0	11.0	11.0	12.0	11.0	11.0
Maximum	30	30	29	30	30	30

Notes: PBO = Placebo; ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; Nx = number of patients with non-missing values; SD = standard deviation; Percentage is calculated by n/Nx\*100%.  
For weight, BMI, waist circumference, tobacco use, alcohol consumption and caffeine/xanthine ingestion baseline is defined as the safety baseline for each period.  
Previous non-biologic systemic therapy includes the following: methotrexate, cyclosporine, retinoids, and PUVA.  
[1] p-value is based on Fisher's exact test for categorical data (Monte Carlo estimates of exact p-values are used for overall comparison) and a one-way analysis of variance (ANOVA) for continuous data with treatment group as independent factor.  
[2] Duration of Psoriasis Symptoms is calculated as: (date of informed consent - date of onset of psoriasis symptoms)/365.25.  
\* - p-value <= 0.05.

Source: Applicant's Clinical Study Report RHBA Pg 1540-1576

*Reviewer Comment: The baseline demographic characteristics for trial RHBA were very similar to those for trial RHAZ. One difference noted is that a smaller percentage of subjects in trial RHBA had previously used systemic therapies (62-67% vs 70-76% for trial RHAZ). This is likely attributable to the exclusion criterion for RHBA specifying that no previous use of etanercept was permitted. According to the applicant, this was to avoid bias since etanercept was a comparator treatment. Overall, these demographic characteristics are consistent with what is known about the psoriasis population in the US who are treated with systemic agents.*

**Table 13: Patient Demographic Characteristics at Baseline Intent-to-Treat Population (RHBC)**

	TALTZ 80 mg		Etanercept (N=382)	Placebo (N=193)
	Q2W (N=385)	Q4W (N=386)		
<b>Age</b>				
Mean (SD)	46 (13)	46 (13)	46 (14)	46 (21)
Median	44.5	46	46	47
Range	19 – 79	18 – 79	17 – 88	20 – 75
<b>Gender</b>				
Male	254 (66%)	258 (67%)	269 (70%)	137 (71%)
Female	131 (34%)	128 (33%)	113 (30%)	56 (29%)
<b>Race</b>				
White	361 (94%)	360 (93%)	351 (92%)	176 (91%)
Black	5 (1%)	9 (2%)	10 (3%)	8 (4%)
Asian	12 (3%)	11 (3%)	11 (3%)	7 (4%)
Other	7 (2%)	6 (2%)	10 (3%)	2 (1%)
<b>Weight</b>				
Mean (SD)	90.4 (23.4)	91.2 (23.9)	92.2 (24.3)	91.0 (21.5)
Median	87.0	88.0	88.1	86.2
Range	52 – 176.5	46.4 – 200	43 – 177	55.5 – 176
< 100 kg	275 (72%)	274 (72%)	256 (67%)	138 (72%)
≥ 100 kg	109 (28%)	107 (28%)	126 (33%)	54 (28%)
<b>Country</b>				
US	141 (37%)	147 (38%)	146 (38%)	69 (36%)
Non-US	244 (63%)	239 (62%)	236 (62%)	124 (64%)
<b>sPGA</b>				
3 - Moderate	207 (54%)	206 (54%)	190 (50%)	92 (48%)
4 - Severe	157 (41%)	159 (41%)	174 (45%)	91 (47%)
5 - Very Severe	21 (5%)	18 (5%)	18 (5%)	10 (5%)
<b>PASI</b>				
Mean (SD)	21 (8)	21 (8)	21 (8)	21 (8)
Median	18.0	18.8	18.0	18.5
Range	12 – 63	12 – 60	12 – 57	12 – 49.1
<b>Percent BSA</b>				
Mean (SD)	28 (17)	28 (16)	28 (17)	28.6 (17)
Median	22	24	23	23
Range	10 – 90	10 – 94	10 – 95	10 – 90

Source: Statistical Review Pg. 18

**Table 14: Additional Baseline Demographic Characteristics, ITT Population (RHBC)**

	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (N=771)	Total (N=1346)
<b>BMI (kg/m<sup>2</sup>)</b>						
Number of Patients, Nx	192	382	380	384	764	1338
Mean	30.24	30.73	30.67	30.21	30.44	30.49
SD	6.339	7.586	7.310	7.139	7.223	7.207
Minimum	19.8	16.9	17.5	18.5	17.5	16.9
Median	28.95	29.29	29.39	29.05	29.13	29.13
Maximum	55.5	57.2	61.3	56.8	61.3	61.3
<b>Previous systemic therapy, n(%)</b>						
Number of Patients, Nx	193	382	386	385	771	1346
Never used	88 ( 45.6%)	160 ( 41.9%)	162 ( 42.0%)	170 ( 44.2%)	332 ( 43.1%)	580 ( 43.1%)
Non-biologic only	72 ( 37.3%)	162 ( 42.4%)	166 ( 43.0%)	157 ( 40.8%)	323 ( 41.9%)	557 ( 41.4%)
Biologic only	16 ( 8.3%)	26 ( 6.8%)	23 ( 6.0%)	25 ( 6.5%)	48 ( 6.2%)	90 ( 6.7%)
Biologic and non-biologic	17 ( 8.8%)	34 ( 8.9%)	35 ( 9.1%)	33 ( 8.6%)	68 ( 8.8%)	119 ( 8.8%)
	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (N=771)	Total (N=1346)
<b>Duration of Psoriasis Symptoms in Years [2]</b>						
Number of Patients, Nx	193	382	383	385	768	1343
Mean	18.24	18.12	18.45	17.80	18.12	18.14
SD	12.515	11.787	12.471	12.191	12.328	12.195
Minimum	0.5	0.7	0.4	0.5	0.4	0.4
Median	15.14	16.44	16.69	15.43	15.84	16.04
Maximum	51.3	50.3	63.4	63.0	63.4	63.4
<b>Age of psoriasis onset (in years)</b>						
Number of Patients, Nx	193	382	383	385	768	1343
Mean	28.6	28.1	27.5	28.2	27.9	28.0
SD	14.34	14.50	14.00	14.45	14.22	14.31
Minimum	0	0	0	0	0	0
Median	25.5	25.0	25.0	26.9	25.9	25.6
Maximum	68	66	68	64	68	68
<b>Baseline QIDS-SR16 Total Score</b>						
Number of Patients, Nx	193	382	383	385	768	1343
Mean	5.1	4.4	4.5	4.4	4.5	4.5
SD	4.38	3.87	4.20	3.98	4.09	4.08
Minimum	0	0	0	0	0	0
Median	4.0	3.0	3.0	3.0	3.0	3.0
Maximum	19	23	21	19	21	23
<b>Baseline Itch NRS Score</b>						
Number of Patients, Nx	192	382	382	384	766	1340
Mean	6.5	6.2	6.3	6.4	6.4	6.3
SD	2.63	2.63	2.60	2.59	2.60	2.61
Minimum	0	0	0	0	0	0
Median	7.0	7.0	7.0	7.0	7.0	7.0
Maximum	10	10	10	10	10	10
<b>Baseline DLQI Score</b>						
Number of Patients, Nx	193	382	382	383	765	1340
Mean	12.7	11.5	11.9	12.4	12.1	12.0
SD	7.00	6.84	6.97	6.93	6.95	6.93
Minimum	0	0	0	0	0	0
Median	11.0	10.0	11.0	11.0	11.0	11.0
Maximum	29	30	30	30	30	30

Source: Applicant's Clinical Study Report RHBC Pg 572-610

*Reviewer Comment: The baseline demographic characteristics for trial RHBC were very similar to those for trial RHAZ and RHBA. As was noted for trial RHBA, trial RHBC had a smaller percentage of subjects that had previously used systemic therapies (54-58% vs 70-76% for trial*

Clinical Review  
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Taltz (ixekizumab)

*RHAZ). This is likely attributable to the exclusion criterion for RHBC specifying that no previous use of etanercept was permitted. According to the applicant, this was to avoid bias since etanercept was a comparator treatment. Overall, these demographic characteristics are consistent with what is known about the psoriasis population in the US who are treated with systemic agents.*

**Table 15: Patient Demographics and Baseline Characteristics (Pivotal Studies) (RHAZ, RHBA, and RHBC) ITT Population**

	RHAZ (N=1296)	RHBA (N=1224)	RHBC (N=1346)	Total (N=3866)
Age (Years)				
Mean (SD)	45.7 (12.93)	45.0 (13.04)	45.8 (13.07)	45.5 (13.02)
Gender, n (%)				
Male	883 (68.1)	821 (67.1)	918 (68.2)	2622 (67.8)
Female	413 (31.9)	403 (32.9)	428 (31.8)	1244 (32.2)
Race, n (%)				
American Indian or Alaska Native	3 (0.2)	6 (0.5)	10 (0.7)	19 (0.5)
Asian	62 (4.8)	37 (3.0)	41 (3.0)	140 (3.6)
Black or African American	26 (2.0)	39 (3.2)	32 (2.4)	97 (2.5)
Native Hawaiian or Other Pacific Islander	1 (0.1)	3 (0.2)	6 (0.4)	10 (0.3)
White	1199 (92.5)	1125 (92.6)	1248 (92.7)	3572 (92.6)
Multiple	5 (0.4)	5 (0.4)	9 (0.7)	19 (0.5)
Geographic Region, n (%)				
Asia	33 (2.5)	0	0	33 (0.9)
North America	673 (51.9)	657 (53.7)	655 (48.7)	1985 (51.3)
Europe <sup>a</sup>	548 (42.3)	516 (42.2)	589 (43.8)	1653 (42.8)
Central America/South America	0	0	102 (7.6)	102 (2.6)
Australia	42 (3.2)	51 (4.2)	0	93 (2.4)
Weight Category, n (%)				
<100 kg	867 (66.9)	826 (67.7)	943 (70.4)	2636 (68.4)
≥100 kg	429 (33.1)	394 (32.3)	396 (29.6)	1219 (31.6)
Previous Systemic Therapy, n (%)				
Never Used	372 (28.7)	438 (35.8)	580 (43.1)	1390 (36.0)
Nonbiologic Only	402 (31.0)	498 (40.7)	557 (41.4)	1457 (37.7)
Biologic Only	168 (13.0)	109 (8.9)	90 (6.7)	367 (9.5)
Biologic and Nonbiologic	354 (27.3)	179 (14.6)	119 (8.8)	652 (16.9)

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	RHAZ (N=1296)	RHBA (N=1224)	RHBC (N=1346)	Total (N=3866)
Previous Nonbiologic Systemic Therapy, n (%)				
Used 1 Therapy	360 (27.8)	335 (27.4)	368 (27.3)	1063 (27.5)
Used 2 Therapies	177 (13.7)	179 (14.6)	168 (12.5)	524 (13.6)
Used ≥3 Therapies	219 (16.9)	163 (13.3)	140 (10.4)	522 (13.5)
Previous Nonbiologic Systemic Therapy: Inadequate Response, Intolerance, or Contraindication				
Used <3 Therapies	1145 (88.3)	1137 (92.9)	1254 (93.4)	3536 (91.6)
Used ≥3 Therapies	151 (11.7)	87 (7.1)	88 (6.6)	326 (8.4)
Previous Biologic Therapy, n (%)				
Used 1 Therapy	285 (22.0)	198 (16.2)	153 (11.4)	636 (16.5)
Used 2 Therapies	123 (9.5)	58 (4.7)	41 (3.0)	222 (5.7)
Used ≥3 Therapies	114 (8.8)	32 (2.6)	15 (1.1)	161 (4.2)
Previous Biologic Agent, n (%)				
Tumor Necrosis Factor (TNF)-α Inhibitor (infliximab, etanercept, adalimumab, golimumab)	342 (26.4)	139 (11.4)	95 (7.1)	576 (14.9)
Interleukin (IL) 12/23 Inhibitor (ustekinumab)	161 (12.4)	102 (8.3)	74 (5.5)	337 (8.7)
Other (efalizumab, alefacept, or other)	217 (16.7)	112 (9.2)	86 (6.4)	415 (10.7)
Previous Phototherapy Therapy, n (%)				
Never Used	705 (54.4)	654 (53.4)	824 (61.2)	2183 (56.5)
Ever Used	591 (45.6)	570 (46.6)	522 (38.8)	1683 (43.5)
Duration of Psoriasis Symptoms in Years				
Mean (SD)	19.6 (11.85)	18.7 (12.46)	18.1 (12.20)	18.8 (12.18)
Baseline static Physician Global Assessment (sPGA), n (%)				
Number of Patients with sPGA = 3	632 (48.8)	616 (50.3)	695 (51.7)	1943 (50.3)
Number of Patients with sPGA = 4,5	664 (51.2)	608 (49.7)	648 (48.3)	1920 (49.7)
Baseline Psoriasis Area and Severity Index (PASI) Score				
Mean (SD)	20.2 (7.99)	19.6 (7.22)	20.9 (8.19)	20.2 (7.84)

	RHAZ (N=1296)	RHBA (N=1224)	RHBC (N=1346)	Total (N=3866)
Baseline Itch Numeric Rating Scale (NRS) Score				
Mean (SD)	7.1 (2.49)	6.6 (2.55)	6.3 (2.61)	6.7 (2.57)
Baseline Itch NRS Score, n(%)				
<4	152 (11.7)	187 (15.3)	243 (18.1)	582 (15.1)
≥4	1144 (88.3)	1037 (84.7)	1103 (81.9)	3284 (84.9)
Baseline Dermatology Life Quality Index (DLQI) Score				
Mean (SD)	13.1 (7.05)	12.3 (6.91)	12.0 (6.93)	12.5 (6.98)
Baseline Nail Psoriasis Severity Index (NAPSI) Total Score				
Mean (SD)	25.0 (19.24)	26.9 (20.19)	25.8 (19.99)	25.8 (19.80)

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

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

SOURCE: t\_demostd\_itt\_a.rtf, t\_prepothstd\_itt\_a.rtf, t\_smco\_nri\_itt\_i.rtf

Source: Applicant's Summary of Clinical Efficacy Pg. 30-32.

Reviewer Comment: Patient demographics were similar in the three pivotal trials.

**Subject Disposition**

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**Table 16: Patient Disposition from Trials RHAZ, RHBA, and RHBC Combined, by Arm**

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Etanercept		Ixekizumab 80 mg Q2W		Ixekizumab 80 mg Q4W		Placebo			
			Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%		
			Protocol Milestone	Randomization 1	Randomized	740	100.0	1169	100.0	1165	100.0	792
	Randomization 2	Randomized	333	45.0	757	64.8	736	63.2	565	71.3		
	Study	Informed Consent Obtained	740	100.0	1169	100.0	1165	100.0	792	100.0		
Disposition Event	Subject Summary - Treatment Discontinuation	Adverse Event	10	1.4	25	2.1	24	2.1	9	1.1		
		Subject Decision	11	1.5	11	0.9	16	1.4	12	1.5		
		Protocol Violation	7	0.9	9	0.8	19	1.6	6	0.8		
		Lack Of Efficacy	4	0.5	1	0.1	4	0.3	10	1.3		
		Lost To Follow Up	7	0.9	2	0.2	4	0.3	5	0.6		
		Investigator Decision	2	0.3	4	0.3	2	0.2	2	0.3		
		Sponsor Decision	0	0.0	1	0.1	1	0.1	1	0.1		
		Other Event	Supplemental	Informed Consent Obtained	43	5.8	82	7.0	79	6.8	59	7.4

Source: Created by reviewer using [Too](#) and SDTM datasets on 6/1/2015: DS (DSDECOD, DSCAT and DSSCAT, EPOCH=INDUCTION) EX and DM (ACTARM=TRTA)

The second table from the applicant’s ISE presents the disposition by trial but does not include the placebo arm for comparison. It includes information on the disposition for the maintenance period of the trial as well.

**Table 17: Patient Completion and Disposition from Study Trials RHAZ, RHBA, and RHBC (ITT Population)**

	RHAZ (N=1296) n (%)	RHBA (N=1224) n (%)	RHBC (N=1346) n (%)	Total (N=3866) n (%)
<b>Number of Patients</b>				
Randomized at Week 0	1296 (100)	1224 (100)	1346 (100)	3866 (100)
Completed Induction Dosing Period (Week 12)	1230 (94.9)	1161 (94.9)	1275 (94.7)	3666 (94.8)
Completed Maintenance Dosing Period (Week 60)	1089 (84.0)	544 (44.4)	NA	1633 (42.2)
Ongoing in Maintenance Dosing Period	0	346 (28.3)	NA	
Completed Study	0	0	0	0
Ongoing	1057 (81.6)	1036 (84.6)	1229 (91.3)	3322 (85.9)
Discontinued Study	239 (18.4)	188 (15.4)	117 (8.7)	544 (14.1)
<b>Reason for Treatment Discontinuation (Induction Dosing Period)</b>				
Adverse Event	26 (2.0)	15 (1.2)	23 (1.7)	64 (1.7)
Subject Decision	17 (1.3)	18 (1.5)	13 (1.0)	48 (1.2)
Protocol Violation	9 (0.7)	13 (1.1)	19 (1.4)	41 (1.1)
Lost to Follow-Up	3 (0.2)	8 (0.7)	7 (0.5)	18 (0.5)
Lack of Efficacy	8 (0.6)	7 (0.6)	3 (0.2)	18 (0.5)
Investigator Decision	0	2 (0.2)	6 (0.4)	8 (0.2)
Sponsor Decision	3 (0.2)	0	0	3 (0.1)
Clinical Relapse	0	0	0	0
Parent/Caregiver Decision	0	0	0	0

Reason for Treatment Discontinuation (Maintenance Dosing Period)	RHAZ (N=1296) n (%)		RHBA (N=1224) n (%)		RHBC (N=1346) n (%)	Total (N=3866) n (%)
	Maintenance Primary Population <sup>a</sup> (N=682)	Maintenance Secondary Population <sup>b</sup> (N=547)	Maintenance Primary Population <sup>a</sup> (N=544)	Maintenance Secondary Population <sup>b</sup> (N=614)		
Adverse Event	13 (1.9)	23 (4.2)	13 (2.4)	21 (3.4)		
Lack of Efficacy	1 (0.1)	34 (6.2)	1 (0.2)	19 (3.1)		
Subject Decision	11 (1.6)	11 (2.0)	5 (0.9)	15 (2.4)		
Lost to Follow-Up	6 (0.9)	4 (0.7)	6 (1.1)	5 (0.8)		
Protocol Violation	1 (0.1)	2 (0.4)	1 (0.2)	7 (1.1)		
Investigator Decision	1 (0.1)	2 (0.4)	1 (0.2)	2 (0.3)		
Death	2 (0.3)	0	0	0		
Clinical Relapse	1 (0.1)	0	0	0		
Sponsor Decision	0	0	0	1 (0.2)		

Abbreviation: ITT = intent-to-treat; NA = not applicable; Q2W = every 2 weeks; sPGA = static Physician Global Assessment.

<sup>a</sup> Maintenance Primary Population includes all patients treated with ixekizumab during the Induction Dosing Period who achieved sPGA (0,1) at Week 12 and who received at least 1 dose of study treatment during the Maintenance Dosing Period.

<sup>b</sup> Maintenance Secondary Population includes all patients treated with ixekizumab during the Induction Dosing Period who did not achieve sPGA (0,1) at Week 12, as well as all patients treated with placebo or etanercept during the Induction Dosing Period who received at least 1 dose of study treatment during the Maintenance Dosing Period.

Note: Two additional patients in RHBA (80 mg Q2W) discontinued study treatment due to an adverse event after completing the Induction Dosing Period (Week 12) and were not re-randomized in the Maintenance Dosing Period.

Source: Applicant's ISE pg.34-35

*Reviewer Comment:*

*Between 94-95% of subjects completed the induction period of the pivotal trials. Discontinuations were balanced across the arms with 5.5%, 4.5%, 6% and 5.7% across the etanercept, Ixe 80 MG Q2W, Ixe 80 mg Q4W and the placebo arms respectively. Both Ixe arms had a higher rate of discontinuations due to adverse events (2.1% for both Ixe arms vs 1.1% for placebo and 1.4% for etanercept). A smaller number of subjects discontinued due to lost to follow-up for the Ixe arms (.2 and .3%) vs placebo (.6%) and etanercept (.9%). As expected a larger number of subjects discontinued due to lack of efficacy in the placebo group (1.3%).*

**7.1.1. Primary Endpoints**

The primary efficacy endpoints for the pivotal trials RHAZ, RHBA and RHBC were

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

The results for the pivotal trial are presented in the table below

**Table 18: Results for the Co-Primary Efficacy Endpoints at Week 12 (ITT, NRI)**

Endpoints	Trial RHAZ			Trial RHBA			Trial RHBC		
	TALTZ 80 mg		Placebo N=431	TALTZ 80 mg		Placebo N=168	TALTZ 80 mg		Placebo N=193
	Q2W N=433	Q4W N=432		Q2W N=351	Q4W N=347		Q2W N=385	Q4W N=386	
<b>Co-Primary:</b>									
sPGA of 0 or 1	82%	76%	3%	83%	73%	2%	81%	75%	7%
PASI-75	89%	83%	4%	90%	78%	2%	87%	84%	7%

Source: From Statistical Review pg.3 (modified)

*Reviewer Comment: For all three pivotal trials, both Ixe arms were statistically superior to placebo with a  $p < 0.001$  at week 12. The findings were robust with the majority of subjects (73-90%) achieving a sPGA of 0 to 1 and a PASI 75. The findings were consistent across the three pivotal trials. The applicant also performed sensitivity analyses using alternative methods of imputation. The statistical reviewer performed a “worst case scenario” sensitivity analysis (i.e., missing data for Ixe is imputed as failures and missing data for placebo is imputed as successes). In each alternative analysis both dose regimens of Ixe were still statistically superior ( $p$ -values  $< 0.001$ ) to placebo for both co-primary endpoints in all three trials.*

### 7.1.2. Secondary and Other Endpoints

Key secondary efficacy endpoints included

1. Proportion of Patients with sPGA of 0 at Week 12
2. Proportion of Patients with PASI 90 at Week 12
3. Proportion of Patients with PASI 100 at Week 12
4.  $\geq 4$  point reduction in Itch NRS

The results for the pivotal trials are presented in the table below

Clinical Review  
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Taltz (ixekizumab)

**Table 19: Results for the Secondary Efficacy Endpoint at Week 12 (ITT, NRI)**

Endpoints	Trial RHAZ			Trial RHBA			Trial RHBC		
	TALTZ 80 mg		Placebo N=431	TALTZ 80 mg		Placebo N=168	TALTZ 80 mg		Placebo N=193
	Q2W N=433	Q4W N=432		Q4W N=351	Q2W N=347		Q4W N=385	Q2W N=386	
<b>Secondary:</b>									
sPGA of 0	37%	34%	0%	42%	32%	1%	40%	36%	0%
PASI-90	71%	65%	1%	71%	60%	1%	68%	65%	3%
PASI-100	35%	34%	0%	40%	31%	1%	38%	35%	0%
≥ 4-point reduction in Itch NRS from baseline	336/391 (86%)	305/379 (80%)	58/374 (16%)	258/391 (85%)	225/393 (77%)	19/135 (14%)	264/320 (83%)	250/313 (80%)	33/158 (21%)

Source: From Statistical Review pg.3 (modified)

*Reviewer Comment: More than a third of subjects (32-42%) achieved a PASI 100 and/or a sPGA of zero on Ixe at 12 weeks. The majority of subjects (76-86%) achieved a reduction in itch NRS of ≥ 4 points. These findings support the primary efficacy endpoints and combined with them, provide compelling evidence for the efficacy of Ixe.*

### 7.1.3. Subpopulations

Results for the pivotal trials by geographic location (US vs. Non-US sites) are presented in the table below.

#### Results by location

**Table 20: Results for the Co-Primary Efficacy Endpoints at Week 12 by Country (US vs. Non-US) [ITT, NRI]**

Study (N <sub>Q2W</sub> , N <sub>Q4W</sub> , N <sub>E</sub> , N <sub>P</sub> )	sPGA of 0 or 1				PASI-75			
	TALTZ 80 mg		Etanercept	Placebo	TALTZ 80 mg		Etanercept	Placebo
	Q2W	Q4W			Q2W	Q4W		
<b>RHAZ</b>	N=433	N=432	N=431	N=431	N=433	N=432	N=431	N=431
Overall	81.8%	76.4%	-	3.2%	89.1%	82.6%	-	3.9%
US (159, 156, 146)	77.4%	69.2%	-	4.8%	88.7%	75.6%	-	3.4%
Non-US (274, 276, 285)	84.3%	80.4%	-	2.5%	89.4%	86.6%	-	4.2%
<b>RHBA</b>	N=351	N=347	N=358	N=168	N=351	N=347	N=358	N=168
Overall	83.2%	72.9%	36.0%	2.4%	89.7%	77.5%	41.6%	2.4%
US (104, 105, 111, 49)	70.2%	61.0%	21.6%	0%	85.6%	67.6%	32.4%	0%
Non-US (247, 242, 247, 119)	88.7%	78.1%	42.5%	3.4%	91.5%	81.8%	45.7%	3.4%
<b>RHBC</b>	N=385	N=386	N=382	N=193	N=385	N=386	N=382	N=193
Overall	80.5%	75.4%	41.6%	6.7%	87.3%	84.2%	53.4%	7.3%
US (141, 147, 146, 69)	74.5%	65.3%	31.5%	5.8%	87.9%	80.3%	46.6%	8.7%
Non-US (244, 239, 236*, 124)	84.0%	81.6%	47.9%	7.3%	86.9%	86.6%	57.6%	6.5%

\*Subjects in Argentina, Chile and Mexico (total of 30 subjects) received US sourced etanercept.

Source: Statistical Reviewer's Table (from midcycle review)

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*Reviewer Comment: The proportion of responders was consistently lower (though still robust) at the US sites than at the Non-US sites. This was the case for all arms: Ixe, etanercept and placebo except for the placebo arm for sPGA of 0 or 1 for RHAZ, Ixe Q2W arm for PASI 75 for RHBC and the placebo arm for PASI 75 for RHBC.*

As all subjects randomized to etanercept at US study sites received US-licensed Enbrel and the applicant conducted two pivotal trials with US-licensed Enbrel, there is sufficient data to adequately assess superiority of TALTZ to US-licensed Enbrel. The results above show both the overall population and the US only subgroup.

*Reviewer Comment:*

*In both trials RHBA and RHBC, both dose regimens of TALTZ were statistically superior (p-values < 0.001) to etanercept in both the overall population and the US only subgroup for the co-primary efficacy endpoints.*

### Results by Demographic subgroups

The results for the pivotal trials for the Induction period for Pool #1 are presented by demographic subgroup below

**Table 21: sPGA (0, 1) and PASI 75 Percentage of Patients Meeting Response Criteria at Week 12 (NRI), Pool #1, Selected Subgroups, ITT Population – RHAZ, RHBA and RHBC, Induction Period**

Subgroup	Endpoint	p-value (Interaction) <sup>a</sup>	Placebo N=792 n (%)	80 mg Q4W N=1165 n (%)	80 mg Q2W N=1169 n (%)	All Ixekizumab N=2334 n (%)
<b>Age</b>						
<40 years	Patients in Subgroup		237 (29.9)	388 (33.3)	419 (35.8)	807 (34.6)
≥40 years			554 (69.9)	773 (66.4)	748 (64.0)	1521 (65.2)
<40 years	sPGA (0,1)	0.116	6 (2.5)	311 (80.2) <sup>b</sup>	355 (84.7) <sup>b</sup>	666 (82.5)
≥40 years	PASI 75		25 (4.5)	563 (72.8) <sup>b</sup>	601 (80.3) <sup>b,c</sup>	1164 (76.5)
<40 years			9 (3.8)	333 (85.8) <sup>b</sup>	370 (88.3) <sup>b</sup>	703 (87.1)
≥40 years			26 (4.7)	618 (79.9) <sup>b</sup>	667 (89.2) <sup>b,c</sup>	1285 (84.5)
<65 years	Patients in Subgroup		731 (92.3)	1079 (92.6)	1083 (92.6)	2162 (92.6)
≥65 to <75 years			49 (6.2)	70 (6.0)	76 (6.5)	146 (6.3)
≥75 years	sPGA (0,1)		11 (1.4)	12 (1.0)	8 (0.7)	20 (0.9)
<65 years			28 (3.8)	822 (76.2) <sup>b</sup>	886 (81.8) <sup>b,c</sup>	1708 (79.0)
≥65 to <75 years	PASI 75		2 (4.1)	46 (65.7) <sup>b</sup>	63 (82.9) <sup>b,c</sup>	109 (74.7)
≥75 years			1 (9.1)	6 (50.0) <sup>d</sup>	7 (87.5) <sup>d</sup>	13 (65.0)
<65 years		0.125	32 (4.4)	893 (82.8) <sup>b</sup>	958 (88.5) <sup>b,c</sup>	1851 (85.6)
≥65 to <75 years			2 (4.1)	50 (71.4) <sup>b</sup>	71 (93.4) <sup>b,c</sup>	121 (82.9)
≥75 years			1 (9.1)	8 (66.7) <sup>d</sup>	8 (100.0) <sup>b</sup>	16 (80.0)

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Subgroup	Endpoint	p-value (Interaction) <sup>a</sup>	Placebo N=792 n (%)	80 mg Q4W N=1165 n (%)	80 mg Q2W N=1169 n (%)	All Ixekizumab N=2334 n (%)
<b>Weight</b>						
<100 kg	Patients in Subgroup		538 (67.9)	791 (67.9)	819 (70.1)	1610 (69.0)
≥100 kg			251 (31.7)	368 (31.6)	349 (29.9)	717 (30.7)
<100 kg	sPGA (0,1)	0.793	26 (4.8)	625 (79.0) <sup>b</sup>	692 (84.5) <sup>b,c</sup>	1317 (81.8)
≥100 kg			5 (2.0)	248 (67.4) <sup>b</sup>	264 (75.6) <sup>b,c</sup>	512 (71.4)
<100 kg	PASI 75	0.448	27 (5.0)	677 (85.6) <sup>b</sup>	738 (90.1) <sup>b,c</sup>	1415 (87.9)
≥100 kg			8 (3.2)	273 (74.2) <sup>b</sup>	299 (85.7) <sup>b,c</sup>	572 (79.8)
<b>Sex</b>						
Male	Patients in Subgroup		560 (70.7)	791 (67.9)	766 (65.5)	1557 (66.7)
Female			232 (29.3)	374 (32.1)	403 (34.5)	777 (33.3)
Male	sPGA (0,1)	0.338	20 (3.6)	587 (74.2) <sup>b</sup>	632 (82.5) <sup>b,c</sup>	1219 (78.3)
Female			11 (4.7)	287 (76.7) <sup>b</sup>	324 (80.4) <sup>b</sup>	611 (78.6)
Male	PASI 75	0.767	23 (4.1)	641 (81.0) <sup>b</sup>	680 (88.8) <sup>b,c</sup>	1321 (84.8)
Female			12 (5.2)	310 (82.9) <sup>b</sup>	357 (88.6) <sup>b,c</sup>	667 (85.8)
<b>Race</b>						
American Indian or Alaska Native	Patients in Subgroup		4 (0.5)	6 (0.5)	5 (0.4)	11 (0.5)
Asian			34 (4.3)	45 (3.9)	42 (3.6)	87 (3.7)
Black or African American	sPGA (0,1)	0.989	26 (3.3)	30 (2.6)	18 (1.5)	48 (2.1)
Native Hawaiian or Other Pacific Islander			1 (0.1)	3 (0.3)	4 (0.3)	7 (0.3)
White	PASI 75	0.987	726 (91.7)	1072 (92.0)	1092 (93.4)	2164 (92.7)
Multiple			1 (0.1)	5 (0.4)	7 (0.6)	12 (0.5)
American Indian or Alaska Native	sPGA (0,1)	0.989	0	4 (66.7)	3 (60.0)	7 (63.6)
Asian			1 (2.9)	31 (68.9) <sup>b</sup>	32 (76.2) <sup>b</sup>	63 (72.4)
Black or African American	PASI 75	0.987	0	20 (66.7) <sup>b</sup>	14 (77.8) <sup>b</sup>	34 (70.8)
Native Hawaiian or Other Pacific Islander			0	2 (66.7)	1 (25.0)	3 (42.9)
White	PASI 75	0.987	30 (4.1)	812 (75.7) <sup>b</sup>	900 (82.4) <sup>b,c</sup>	1712 (79.1)
Multiple			0	3 (60.0)	6 (85.7)	9 (75.0)
American Indian or Alaska Native	sPGA (0,1)	0.987	0	5 (83.3) <sup>d</sup>	5 (100.0) <sup>d</sup>	10 (90.9)
Asian			2 (5.9)	36 (80.0) <sup>b</sup>	34 (81.0) <sup>b</sup>	70 (80.5)
Black or African American	PASI 75	0.987	2 (7.7)	24 (80.0) <sup>b</sup>	17 (94.4) <sup>b</sup>	41 (85.4)
Native Hawaiian or Other Pacific Islander			0	2 (66.7)	3 (75.0)	5 (71.4)
White	PASI 75	0.987	31 (4.3)	878 (81.9) <sup>b</sup>	971 (88.9) <sup>b,c</sup>	1849 (85.4)
Multiple			0	4 (80.0)	7 (100.0)	11 (91.7)
<b>Baseline Disease Severity</b>						
sPGA (3)	Patients in Subgroup		382 (48.2)	569 (48.8)	616 (52.7)	1185 (50.8)
sPGA (4,5)			410 (51.8)	593 (50.9)	553 (47.3)	1146 (49.1)
sPGA (3)	sPGA (0,1)	0.213	21 (5.5)	449 (78.9) <sup>b</sup>	511 (83.0) <sup>b</sup>	960 (81.0)
sPGA (4,5)			10 (2.4)	425 (71.7) <sup>b</sup>	445 (80.5) <sup>b,c</sup>	870 (75.9)
sPGA (3)	PASI 75	0.282	22 (5.8)	467 (82.1) <sup>b</sup>	547 (88.8) <sup>b,c</sup>	1014 (85.6)
sPGA (4,5)			13 (3.2)	484 (81.6) <sup>b</sup>	490 (88.6) <sup>b,c</sup>	974 (85.0)
PASI <20	Patients in Subgroup		490 (61.9)	701 (60.2)	755 (64.6)	1456 (62.4)
PASI ≥20			302 (38.1)	464 (39.8)	414 (35.4)	878 (37.6)
PASI <20	sPGA (0,1)	0.565	22 (4.5)	528 (75.3) <sup>b</sup>	616 (81.6) <sup>b,c</sup>	1144 (78.6)
PASI ≥20			9 (3.0)	346 (74.6) <sup>b</sup>	340 (82.1) <sup>b,c</sup>	686 (78.1)
PASI <20	PASI 75	0.227	25 (5.1)	562 (80.2) <sup>b</sup>	664 (87.9) <sup>b,c</sup>	1226 (84.2)
PASI ≥20			10 (3.3)	389 (83.8) <sup>b</sup>	373 (90.1) <sup>b,c</sup>	762 (86.8)

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Abbreviations: ITT = intent-to-treat; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment.

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

b  $p < .001$  versus PBO

c  $p < .001$  versus 80 mg Q4W

d  $p < .05$  versus PBO

e  $p < .05$  versus 80 mg Q4W

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

Source: Applicant's ISE pg. 99- 107 (modified)

*Reviewer Comment: With the exception of the comparison between the >40 years and <40 years groups (which approached significance) there was no statistically significant difference in response rate across sub-groups.*

See Statistical Review for subgroup analyses by individual trials (Tables 32-34).

### Effect of Body Weight on Efficacy

The clinical pharmacology reviewer had the following comments:

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 ( $\geq 100$  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 recommend 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  $\geq 100$  kg). Overall, the proposed dosing regimen regardless of body weight is acceptable.

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**Table 22: Week 12 sPGA (0, 1) and PASI 75 Response Rates in the Induction Period Based on the Combined Data from RHAZ, RHBA and RHBC Stratified by Body Weight and Treatment Groups.**

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

Source: Clinical Pharmacology Review pg. 5

*Reviewer Comment: I agree with the clinical pharmacology reviewer that the proposed dosing regimen regardless of body weight is acceptable.*

#### 7.1.4. Dose and Dose-Response

The response rates for both co-primary efficacy endpoints were slightly higher for the Q2W dose regimen compared to the Q4W dose regimen in the induction period of all three pivotal trials as seen in the table below.

**Table 23: Results for the Co-Primary Efficacy Endpoints at Week 12 (ITT, NR)**

	TALTZ 80 mg		Placebo
	Q2W	Q4W	
<b>Trial RHAZ</b>	N=433	N=432	N=431
sPGA of 0 or 1	354 (82%)	330 (76%)	14 (3%)
PASI-75	386 (89%)	357 (83%)	17 (4%)
<b>Trial RHBA</b>	N=351	N=347	N=168
sPGA of 0 or 1	292 (83%)	253 (73%)	4 (2%)
PASI-75	315 (90%)	269 (78%)	4 (2%)
<b>Trial RHBC</b>	N=385	N=386	N=193
sPGA of 0 or 1	310 (81%)	291 (75%)	13 (7%)
PASI-75	336 (87%)	325 (84%)	14 (7%)

Source: Statistical Review pg. 19

*Reviewer Comment: The difference between doses varied from a low of 6% to a high of 12%. Since there was no consistent dose-response seen with regard to adverse events (with a few exceptions such as injection site reactions, nausea, otitis externa, tinea and candidiasis), I agree with the applicant that the higher dose should be proposed for marketing. See Section 8.5.2 Analysis of Submission Specific Safety Issues; subsection Infections for further discussion of increased risk of specific infections with Ixe.*

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According to the clinical pharmacology reviewer:

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 80 mg q2w dosing regimen achieved significantly higher response rates than the 80 mg q4w dosing regimen from Week 8 to Week 12. 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.

See above under Section 7.1.3 **Subpopulations** for discussion of the effect on efficacy of body weight.

See below under Section 7.1.5 **Onset, Duration, and Durability of Efficacy Effects** for further discussion of dose-response during the maintenance period.

#### 7.1.5. **Onset, Duration, and Durability of Efficacy Effects**

To evaluate the maintenance and durability of response, subjects originally randomized to Ixe and who were responders at Week 12 (i.e., sPGA score of 0 or 1) in RHAZ and RHBA were re-randomized to an additional 48 weeks of either a maintenance dose of Ixe or placebo. Non-responders (sPGA >1) at Week 12 and subjects who relapsed (sPGA ≥3) during the maintenance period were placed on Ixe 80 mg Q4W.

For responders at Week 12, the percentage of subjects who maintained this response at Week 60 (48 weeks following re-randomization) in the integrated trials (RHAZ and RHBA) was higher for subjects treated with Ixe 80 mg Q4W (75%) compared to those treated with placebo (7%). For responders at Week 12 re-randomized to treatment withdrawal (i.e., placebo), the median time to relapse (sPGA ≥3) was 164 days in the integrated trials. Among these subjects, 66% regained a response of at least 0 or 1 on the sPGA within 12 weeks of restarting treatment with Ixe 80 mg Q4W.

For maintenance, the applicant’s secondary efficacy endpoint (i.e., proportion of subjects maintaining a sPGA score of 0 or 1 at Week 60) was in the multiplicity testing strategy, and the results for each individual trial are presented in the table below.

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**Table 24: Maintenance of Response (sPGA 0 or 1) at Week 60**

<b>Treatment Arm (Induction → Maintenance)</b>	<b>Study RHAZ</b>	<b>Study RHBA</b>
Q2W → Q4W	89/119 (75%)	47/62 (76%)
Q2W → Q12W	48/117 (41%)	20/67 (30%)
Q2W → Placebo	9/117 (8%)	6/86 (7%)
Q4W → Q4W	78/110 (71%)	34/57 (60%)
Q4W → Q12W	37/110 (34%)	21/61 (34%)
Q4W → Placebo	8/109 (7%)	3/72 (4%)

Source: Statistical Review pg. 23

*Reviewer Comment: The Q4W maintenance arm was significantly more effective at maintaining response than the Q12W arm. The Q12W arm did result in a statistically significant proportion of subjects maintaining response versus the placebo. The sponsor is proposing Q4W for maintenance dosing. I agree with this choice.*

**Table 25: Relapse (sPGA ≥ 3) During Maintenance Period**

<b>Treatment Arm (Induction → Maintenance)</b>	<b>Study RHAZ</b>	<b>Study RHBA</b>
<u>Q2W → Placebo</u>		
Number of Subjects	96/117 (82%)	76/86 (88%)
Median Time to Relapse (days)	151	167
<u>Q4W → Placebo</u>		
Number of Subjects	89/109 (82%)	63/72 (88%)
Median Time to Relapse (days)	148	142

Source: Statistical Review pg. 23

*Reviewer Comment: The majority of subjects relapsed within 5-6 months when switched from Ixe to placebo. The time to relapse was slightly longer in the subjects who received the higher dose in the induction period.*

See the Statistical Review for an in depth discussion and pictorial display (Figures 4-8) of the efficacy of Ixe over time in both the induction and the maintenance dosing periods.

The statistical reviewer concluded that

There were no major statistical issues affecting overall conclusions. The treatment effects were large and consistent across trials and endpoints. The amount of missing data was relatively small (≤ 6%) at Week 12... Treatment effects were generally consistent across subgroups... Efficacy findings from three

pivotal Phase 3 trials (Trials RHAZ, RHBA, and RHBC) established the efficacy of both dose regimens of TALTZ 80 mg for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

There were no significant differences in efficacy in important subpopulations that would be expected to have implications for the generalizability of benefit to the broader population that might receive the drug.

### 7.2.2. Other Relevant Benefits

All relevant benefits are discussed in the preceding sections and/or in the integrated summary below.

## 7.3. Integrated Assessment of Effectiveness

The evidence submitted by the applicant to support the approval of Ixekizumab for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy has met the statutory evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use. The applicant submitted three adequate and well-controlled (placebo and active) clinical trials (RHAZ, RHBA and RHBC) which provided the data that provided substantial evidence of effectiveness. See Sections 6.1.1, 6.2.1 and 6.3.1 for discussion of study design for the pivotal trials.

There were 2776 subjects exposed to the study drug in the psoriasis development program at or near the proposed dose for marketing (proposed dose = loading dose of 160 mg at baseline followed by 80 mg once every 2 weeks for 12 weeks of induction then every 4 weeks for maintenance) for at least 12 weeks. Of these, 2190 were exposed for 12 months.

RHAZ, RHBA and RHBC evaluated two dose regimens of Ixe during a 12-week induction period (Weeks 0-12). Ixe subjects received a loading dose of 160 mg at baseline (Week 0) followed by 80 mg once every 2 weeks (Q2W) or once every 4 weeks (Q4W). Trials RHAZ and RHBA evaluated maintenance of response for an additional 48 weeks at doses of 80 mg at either Q4W or Q12W intervals (Weeks 12-60). The population consisted of subjects 18 years and older with moderate to severe plaque psoriasis defined as a PASI score  $\geq 12$ , Static Physician's Global Assessment (sPGA) score of at least 3 (moderate) and body surface area (BSA) involvement  $\geq 10\%$ .

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The co-primary efficacy endpoints were the proportion of subjects achieving a sPGA score of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline at Week 12 and the proportion of subjects achieving a  $\geq 75\%$  improvement in PASI (PASI-75) from baseline at Week 12. Secondary efficacy endpoints at Week 12 included the proportion of subjects with sPGA score of 0 (clear), PASI-90, PASI-100, and a  $\geq 4$ -point improvement of itch severity as measured by an itch Numeric Rating Scale (NRS). For all three trials, both dose regimens of Ixe were statistically superior ( $p$ -values  $< 0.001$ ) to placebo for all the previously noted primary and secondary efficacy endpoints. For the induction dose proposed for marketing the proportion of responders for a sPGA of 0 or 1 were 82%, 83% and 81% respectively for trials RHAZ, RHBA and RHBC. For the induction dose proposed for marketing the proportion of PASI 75 responders were 89%, 90% and 87% respectively for trials RHAZ, RHBA and RHBC. For the induction dose proposed for marketing the proportion of PASI 90 responders were 71%, 71% and 68% respectively for trials RHAZ, RHBA and RHBC. For the induction dose proposed for marketing the proportion of PASI 100 responders were 35%, 40% and 38% respectively for trials RHAZ, RHBA and RHBC. See Section 7.1 **Assessment of Efficacy Across Trials** for further details.

The data provided by the pivotal trials is persuasive and is highly clinically meaningful. The design of the trials was in accord with FDA's advice during development (with a few exceptions noted in this review). The endpoints were appropriate, clinically relevant and similar to endpoints for previously approved products for this indication. The treatment effect was large and consistent across trials and within subgroups. The duration of the effect was adequate.

The only limitation noted for the Ixekizumab development program was in study design and was the exclusion of subjects with a history of suicide attempts or a current score of  $\geq 3$  on item #12 of the QIDS which indicated active suicidal ideation or a past suicide attempt. This may limit the generalizability of the results with regard to safety in this population in the post-marketing setting. See Section 8.5.1 **Analysis of Submission Specific Safety Issues** subsection **Depression and Suicidality** for further discussion of this topic.

From an efficacy standpoint, Ixekizumab has been shown to be highly efficacious and will be a welcome addition to the current armamentarium of products for moderate to severe plaque psoriasis. I recommend that the primary and key secondary efficacy endpoints results for the dose proposed for marketing for induction be presented in a table including all 3 pivotal trials versus placebo. In addition, I recommend a statement in the text of Section 14 CLINICAL STUDIES be included that provides the results for the US sites only for an integrated analysis for etanercept versus Ixekizumab. A text statement in Section 14 CLINICAL STUDIES to describe the results for the maintenance period of trials RHAZ and RHBA is also recommended. See Section 10 **Labeling Recommendations** and the approved label for details.

## 8 Review of Safety

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### 8.1. Safety Review Approach

This review will focus primarily on evaluation of safety from the induction and maintenance dosing periods for the 3 pivotal trials RHAZ, RHBA and RHBC. As the trials were similar in design pooled analysis sets were used for the majority of the evaluations. Key portions of the 4 month safety update report were also reviewed. In trials RHBA and RHBC an active comparator arm was included. US-sourced etanercept was used in the trials conducted in the US. For the most part, EU-sourced etanercept was used in the trials conducted outside the US. Only data pertaining to the US-sourced etanercept will be included in this review. The only evaluation performed for Rheumatoid arthritis subjects were analyses of deaths and serious adverse events of special interest.

There was a brief period of clinical hold for IND 100834 when a death in the nonclinical studies was noted. See Section 3.2 for discussion of this event.

A potential safety concern identified for another biologic agent that targets IL-17A, brodalumab was an increase in suicidality. Because of concern about a class effect, an in depth evaluation of this adverse event of special interest was performed for Ixe. The sponsor identified hypersensitivity as an adverse event of special interest (AESI) and an in depth evaluation of this adverse event was also performed. Other AESI included infections, with emphasis on any potential opportunistic infections (a detailed evaluation of subjects who converted from neg to positive on TB status is included), malignancies and inflammatory bowel disease (IBD). See Section 8.5 **Analysis of Submission-Specific Safety Issues** for further discussion of these topics.

### 8.2. Review of the Safety Database

The applicant proposed five integrated analysis datasets for safety which were agreed upon during a guidance meeting for which written responses were provided on 1/28/2014. These 5 pooled groups included

1. Primary Psoriasis Placebo-Controlled Integrated Analysis Set: RHAZ, RHBA, RHBC (N=3119, for the safety population) 3 pivotal studies, 0-12 weeks
2. Psoriasis Placebo- and Active-Controlled Integrated Analysis Set: RHBA, RHBC (N=2562, for the safety population) 2 active comparator pivotal studies, 0-12 weeks
3. Maintenance Dosing Period: RHAZ, RHBA (N=1226) 2 pivotal studies 12-60 weeks
4. All Psoriasis Ixe Exposures Integrated Analysis Set: RHAZ, RHBA, RHBC, RHAT, RHBL, RHAJ, RHAG (N=4204)
5. All Rheumatoid Arthritis (RA) Ixe Exposures Analysis Set: RHAF, RHAK, RHAL, RHAM (N=532)

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The table below presents more information on these pooled groups:

**Table 7: Integrated Analysis Sets for Safety**

**Table 2.5.5.1. Exposure to Ixekizumab by Integrated Analysis Set for Pooled Studies**

Analysis Set	Primary Ps Placebo-Controlled				Ps Placebo- and Active-Controlled					Ps Maintenance				All Ps IXE Exposures	All RA IXE Exposures
Studies Included	RHAZ, RHBA, RHBC				RHBA, RHBC					RHAZ, RHBA				RHAZ, RHBA, RHBC, RHAT, RHBL, RHAI, RHAG	RHAF, RHAK, RHAL, RHAM
Population	Ps Safety				Ps Safety					Maintenance Dosing Period Primary				All Ps Ixekizumab Exposure Safety	All RA Ixekizumab Exposure Safety
Treatment Group	PBO	IXE 80 Q4W	IXE 80 Q2W	Total IXE	PBO	ETN	IXE 80 Q4W	IXE 80 Q2W	Total IXE	PBO	IXE 80 Q12W	IXE 80 Q4W	Total IXE	IXE (All Doses Pooled)	IXE (All Doses Pooled)
N	791	1161	1167	2328	360	739	729	734	1463	402	408	416	824	4204	532
Days, n															
≥84	643	1019	1027	2046	318	648	655	656	1311						
≥90										316	349	392	741	3972	497
≥183										146	275	364	639	3536	401
≥365										2	0	1	1	2190	348
≥548														1070	16
≥730														378	0
Patient-years <sup>a</sup>	180.0	265.9	268.6	534.5	83.2	169.2	167.6	168.9	336.5	184.1	269.5	326.7	596.2	4729.7	533.5

Abbreviations: ETN = etanercept; IXE = ixekizumab; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; IXE80Q12W = ixekizumab 80 mg every 12 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; Ps = psoriasis; RA = rheumatoid arthritis.

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

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

Source: Applicant’s Clinical Overview pg. 42

My review focuses primarily on the Primary Psoriasis Placebo-Controlled Pool (Pool #1) and on the Maintenance Pool (Pool #3) with occasional references to the All Psoriasis Ix Exposures Integrated Analysis Set (Pool #4) as these included the majority of the psoriasis subjects treated with Ixe over time at the dose proposed for marketing.

### 8.2.1. Overall Exposure

The safety of Ixe was evaluated in 3 pivotal phase 3 trials: RHAZ, RHBA and RHBC and in 4 supporting psoriasis trials: RHAG, RHAJ, RHAT and RHBL. RHAG, a phase 1 dose escalation trial in psoriasis subjects is not included in the following table because of the short treatment duration (4 weeks). The subjects who were treated with relevant doses for the other 3 supporting trials in subjects with psoriasis: RHAJ (population PK/PD trial), RHAT (Japanese trial), and RHBL [open-label trial to compare the pre-filled syringe (PFS) and the auto-injector (AI)] are included in the safety database table presented below. Only one of the Rheumatoid arthritis trials, RHAK (phase 2 dose-ranging trial) is of sufficient size and duration that I included it in the safety database.

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**Table 26: Safety database for Ixekizumab (Ixe)**

Safety Database for Ixe					
Individuals exposed to the study drug in the psoriasis development program at or near the proposed dose for marketing for at least 12 weeks					
N=2776					
Clinical Trial Groups	Ixe 80 mg q 2 Weeks	Ixe 80 mg q 4 Weeks	Etanercept	Placebo	Totals
Controlled trials for psoriasis: pivotal phase 3					
RHAZ <sup>i</sup>	433	432		431	1296
RHBA <sup>i</sup>	351	347	358	168	1224
RHBC <sup>i</sup>	385	386	382	193	1346
Total for pivotal Phase 3 trials	1169	1165	740	792	3866
Controlled trials for psoriasis: non-pivotal, Phase 2					
RHAJ	25 <sup>ii</sup>	28 <sup>iii</sup>		27	80
Non-controlled trials for psoriasis					
RHAT <sup>i,iv</sup>	91				91
RHBL <sup>i,v</sup>	204				204
Controlled trials conducted for Rheumatoid Arthritis					
RHAK	57 <sup>vi</sup>	37 <sup>vii</sup>		54	148
Totals	1546				

<sup>i</sup> Subjects each received a loading dose of 160 mg of Ixe

<sup>ii</sup> These subjects received 75 mg at weeks 0, 2, 4, 8, 12 and 16

<sup>iii</sup> These subjects received 150 mg at weeks 0, 2, 4, 8, 12 and 16

<sup>iv</sup> Japanese subjects received 80 mg at weeks 2, 4, 8, 10 then 80 mg q 4 weeks

<sup>v</sup> Randomized 1:1 to either Prefilled Syringe (PFS) or Autoinjector (AI)-both 80 mg q 2 weeks

<sup>vi</sup> These subjects received 80 mg at weeks 0, 1, 2, 4, 6, 8, and 10.

<sup>vii</sup> These subjects received 180 mg at weeks 0, 1, 2, 4, 6, 8, and 10

Source: Clinical Reviewer's Table

**Table 27: Duration of Exposure to Ixe**

>= 84 days or longer	>=6 months	>=12 months	>=18 months	>=24 months
N=3972	N=3536	N=2190	N=1070	378

Source: Applicant's Clinical Overview pg. 42

The numbers of individuals exposed to Ixe in the Applicant's development program exceed those recommended in ICH guidelines and are adequate for agency evaluation of safety in subjects with psoriasis. There were 4204 psoriasis subjects exposed to at least one dose of Ixe of whom 2190 were exposed for at least one year.

### 8.2.2. Relevant characteristics of the safety population:

**Table 28: Demographics for Pool#1: Primary Psoriasis Placebo-Controlled Population**

Demographic Baseline Characteristics		Etanercept N=739	Ixekizumab 80 mg Q2W N=1167	Ixekizumab 80 mg Q4W N=1161	Placebo N=791	Overall N=3858					
Age	Mean (SE)	45.5 (13.3)	45.1 (12.9)	45.4 (13.1)	46.2 (12.8)	45.5 (13.0)					
	Min	17	17	18	18	17					
	Q1	35	35	36	37	36					
	Median	46	45	46	47	46					
	Q3	56	54	55	55	55					
	Max	88	84	88	79	88					
	Count	%	Count	%	Count	%					
Age Group	Age under 65 years	685	92.7	1083	92.8	1079	92.9	731	92.4	3578	92.7
	Age 65 and over	54	7.3	84	7.2	82	7.1	60	7.6	280	7.3
Sex	F	235	31.8	401	34.4	374	32.2	232	29.3	1242	32.2
	M	504	68.2	766	65.6	787	67.8	559	70.7	2616	67.8
Race	American Indian Or Alaska Native	4	0.5	5	0.4	6	0.5	4	0.5	19	0.5
	Asian	19	2.6	41	3.5	45	3.9	34	4.3	139	3.6
	Black Or African American	23	3.1	18	1.5	30	2.6	26	3.3	97	2.5
	Multiple	6	0.8	7	0.6	5	0.4	1	0.1	19	0.5
	Native Hawaiian Or Other Pacific Islander	2	0.3	4	0.3	3	0.3	1	0.1	10	0.3
	White	681	92.2	1091	93.5	1068	92.0	725	91.7	3565	92.4
	Missing	4	0.5	1	0.1	4	0.3	0	0.0	9	0.2
Ethnicity	Hispanic Or Latino	78	10.6	93	8.0	90	7.8	50	6.3	311	8.1
	Not Hispanic Or Latino	541	73.2	881	75.5	887	76.4	613	77.5	2922	75.7
	Unknown	120	16.2	193	16.5	184	15.8	128	16.2	625	16.2

Source: Created by reviewer using SDTM datasets on 6/4/2015: DS (DSDECOD, DSCAT and DSSCAT, EPOCH=INDUCTION) and DM (ACTARM=TRTA)

The baseline characteristics for pool #1, the primary psoriasis placebo-controlled population revealed that mean age was ≈ 45 years, the majority of the subjects were white (91-93%) and the majority were male (65-70%). Age, sex and ethnicity overall were consistent with the general population of patients with psoriasis in the US.

### 8.2.3. Adequacy of the safety database:

The safety database was adequate to evaluate the safety of Ixe in the intended population of moderate to severe psoriasis patients.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall the quality of the data appears to be adequate. Data quality and fitness were evaluated in conjunction with the Jump Start team and no significant deficiencies that affected the pivotal trials were discovered.

### 8.3.2. Categorization of Adverse Events

The coding of adverse events in the BLA appeared adequate and allowed for accurate estimation of adverse event risks. Adverse events (AEs) were summarized in frequencies (unadjusted incidence) and in exposure-adjusted incidence rates (per 100 patient-years) for

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both the Induction and the Maintenance Periods. The coding dictionary used in the pivotal phase three trials RHAZ, RHBA and RHBC was MedDRA version 16.1.

### 8.3.3. Routine Clinical Tests

Laboratory assessments were presented as mean changes from baseline to last observation; change from the minimum value during the baseline period to the minimum value during the treatment period; change from the maximum value during the baseline period to the maximum value during the treatment period; and incidence of treatment-emergent (or follow-up emergent) abnormal, high, or low laboratory values.

Data were summarized by treatment group and treatment period.

Hepatic test abnormalities were included in the special safety topics and therefore additional analysis for these included TEAE, SAE, AE resulting in discontinuation of study drug, exposure-adjusted incidence rates for TEAE and SAE (Induction and maintenance periods only), follow-up emergent AE, follow-up emergent SAE, elevations in hepatic laboratory tests and eDISH plot (Evaluation of Drug-Induced Serious Hepatotoxicity).

Cytopenias were included in the special safety topics and therefore additional analysis for these included TEAE, SAE, AE resulting in discontinuation of study drug, exposure-adjusted incidence rates for TEAE and SAE (Induction and maintenance periods only), and follow-up emergent AE and follow-up emergent SAE.

## 8.4. Safety Results

### 8.4.1. Deaths

There were 10 deaths reported in the clinical development program for Ixe that were included in the initial submission of the BLA. One of these was in a subject with psoriasis who had not been randomized to treatment (RHBC 157-03303). Of the remaining 9 deaths in the initial submission, 5 were in psoriasis subjects on Ixe, 3 in rheumatoid arthritis (RA) subjects on Ixe and 1 in a subject on etanercept in trial RHBC (not discussed). There were no deaths in placebo subjects. An additional 3 deaths in subjects exposed to Ixe were reported in the 4 month safety update.

The following are summaries of the narratives provided by the applicant regarding the 11 deaths on Ixe treatment followed by my assessment of the likelihood that the death was related to the treatment.

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### **Psoriasis Subjects on Ixe**

1. RHAZ-256-4908 –Unknown cause

This subject was a 52 year old white male from Poland who participated in the pivotal trial RHAZ and was assigned to the Ixe Q4W arm for both induction and maintenance periods. He started Rx on 2-27-13 and died on [REDACTED] (b) (6) days after beginning Ixe) while on treatment (most recent dose on 6-19-13). The subject had a PMH significant for hypertension (HTN) and cigarette smoking (ongoing, 33pk-yers). Meds included valsartan, hydrochlorothiazide (HCTZ) and ticlopidine. The patient spoke with the investigator on 7-10-13 (the day he was due for a regularly scheduled visit) to report general discomfort and stomach ache and was advised to contact his primary care physician. The subject's death was reported by his son but cause of death was unknown. No autopsy was performed. The site was unable to contact the family (only contact info was subject's cell phone). This subject had one other AE during the trial which was a mild episode of headache on 2-27-13. According to the applicant, "It was not possible to obtain documentation of the patient's death from his general practitioner and no additional information concerning the gastrointestinal (GI) condition of the patient could be obtained due to personal data protection law". For this reason the applicant was unable to assess relatedness to the investigational product.

*Reviewer Comment: I agree with the applicant that it is not possible to assess causality given the lack of information regarding the subject's death.*

2. RHAZ-307-5326 – Sudden cardiac death

This subject was a 70 year old white female from Romania who participated in the pivotal trial RHAZ and was assigned to the Ixe 80 mg Q2W arm for induction and the 80mg Q4W arm for the maintenance period. Her PMH included: HTN, coronary disease, old MI and diabetes mellitus (DM). Concomitant medication included: atorvastatin, clopidogrel, acetylsalicylic acid (ASA), insulin lispro, insulin glargine, zofenopril and carvedilol. She started Rx on 2-18-13. She experienced 2 mild AEs : erythema at the injection site on 3-4-13 and UTI on 4-10-13. She died on [REDACTED] (b) (6) days after beginning Ixe) while on treatment. The presenting symptoms as reported by the patient's relative were typical for angina; chest pain and left arm pain. She experienced myocardial infarction and died at home. Corrective treatment and laboratory findings were not provided. The autopsy report findings were: direct cause (immediate) was acute cardiorespiratory failure. According to the applicant, "the events of myocardial infarction and death were independently adjudicated by external consultants who concluded that the patient's death was due to sudden cardiac death but did not confirm that the patient had experienced an ischemic myocardial infarction". The event was considered related by the investigator.

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*Reviewer Comment: It is not possible to rule out a contribution to the above event by the investigational product. However, the subject had a history of a previous MI and multiple risk factors which would predispose her to sudden cardiac death. Without more information it is not possible to make a definitive attribution.*

3. RHBA-259-06030 – Presumed cardiovascular death

This subject was a 39 year old white male from Poland who participated in the pivotal trial RHBA and was assigned to the Ixe Q4W arm for induction and the 80mg Q12W arm for the maintenance period. He started Rx on 5-13-13 and died on [REDACTED] (b) (6) after beginning Ixe) while on treatment during the long term extension period of the trial. The subject had a PMH significant for dyslipidemia. Concomitant meds included levothyroxine sodium and fluconazole (possibly not taken as per the patient's wife report). Subject experienced a moderate AE of elevated LFTs (> 3x ULN) from 12-27-13 thru 2-14-14 and again from 4-14-14 thru 7-10-14. It is notable that his baseline LFTs were slightly above the ULN. The patient's wife stated that he abused alcohol and noted daily alcohol consumption from 7-28-14 until 8-7-14. He then experienced vomiting and stomach pains on 8-8-14 (these symptoms had been present earlier on alcoholic intoxication). On 8-9-14, at 09:00, the patient looked unwell and complained of headache and stomach pains. Shortly afterwards the patient was found unconscious by his daughter. The emergency services were called, resuscitation was without success. According to the applicant, it was suspected that after few days of vomiting and alcohol intoxication, the patient might had electrolytic disturbances which could lead to the cardiac arrest. Autopsy was not performed. The investigator offered the opinion that the cause of death was most probably electrolyte disturbance due to alcohol intoxication and did not judge it to be related to the investigational product. The event of cardiac death was independently adjudicated by external reviewers who concluded that the death was presumed cardiovascular.

*Reviewer Comment: It is not possible to rule out a contribution to the above event by the investigational product. The subject had a history of dyslipidemia which is a risk factor for cardiac disease. I agree with the investigator that excessive alcohol intake with subsequent GI issues might predispose to an electrolyte abnormality that might have contributed to the event. Without more information it is not possible to make a definitive attribution.*

4. RHBC-115-02061 – Cerebrovascular accident (CVA)

This subject was a 66 year old white female from the US who participated in the pivotal trial RHBC and was assigned to the Ixe Q2W arm for induction and took 80mg Q4W arm for the term extension period (LTE) period. Her PMH included cerebrovascular accident (CVA), gastric ulcer, anemia, gastroesophageal reflux disease (GERD), HTN, hyperlipidemia, deep vein thrombosis (DVT) and tobacco user. Concomitant Medications included lansoprazole, iron,

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multivitamin, ascorbic acid, warfarin sodium. She started Rx on 8-1-13 and died on (b) (6) (b) (6) after beginning Ixe) while on treatment during the long term extension period of the trial. She had one mild AE on 8-4-13 of UTI. On (b) (6) the patient went to the emergency room with left sided weakness, slurred speech and confusion with an inability to arouse the patient and not much response to stimuli. The subject experienced the adverse events of agitation, anxiety, atrial fibrillation (Afib), cardiomyopathy, carotid artery stenosis, convulsions, DM, rhabdomyolysis, supraventricular tachycardia, urinary tract infection UTI) and a SAE of severe CVA. A magnetic resonance image (MRI) showed acute anterior circulation infarcts with hemorrhagic transformation/ petechial deoxyhemoglobin hemorrhage. Shower of emboli suspected. On (b) (6) the CVA resulted in the death of the patient. An autopsy was not performed. The investigator did not consider the CVA related to the investigational product. The event of CVA was independently adjudicated by external consultants who confirmed that the cause of death was due to cardiovascular cerebrovascular event (intracranial hemorrhage or non-hemorrhagic stroke); the stroke was adjudicated as an ischemic stroke; and the events of Afib and supraventricular tachycardia were confirmed as serious arrhythmias.

*Reviewer Comment: I agree with the investigator that in this subject with a history of CVA and multiple risk factors for CVA (Afib, cardiomyopathy, arrhythmias etc.) it is unlikely that the death was related to the investigational product.*

#### 5. RHBL-116-4003 – Cardio-respiratory arrest

This subject was a 55 year old Hispanic male from Puerto Rico who participated in trial RHBL (delivery device trial) and was assigned to the autoinjector (AI) Ixe Q2W arm for induction and took 80mg Q4W arm for the LTE period via prefilled syringe (PFS). His PMH included coronary artery disease (CAD), hypertension (since 2006), type 2 DM (since 2006), and dyslipidemia (since 2012), back pain, obesity and stent placement. Concomitant Medications included insulin human, insulin glargine, ASA, captopril, ciprofloxacin, clopidogrel, glipizide, omeprazole, ranitidine, and simvastatin. He started Rx on 6-24-13 and died on (b) (6) after beginning Ixe) while on treatment during the long term extension period of the trial. He had a mild AE of skin infection on 6-28-13 and a moderate AE of arthropod bite on (b) (6) According to his wife, the patient felt unwell and had chest pains. An ambulance was called and the paramedics found the patient unresponsive with a pulse of 36 bpm. The patient died in the ambulance on the way to the hospital. An autopsy was not performed. There were no lab results. In the opinion of the investigator, the cardio-respiratory arrest was not related to Ixe, and not related to protocol procedures. The event of death was adjudicated independently by external consultants and concluded the death met the criteria of a presumed cardiovascular event.

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*Reviewer Comment: I agree with the investigator that given the subjects risk factors for a cardiac event (prior stent placement, dyslipidemia, diabetes mellitus, hypertension and obesity) it is unlikely that the death was related to the investigational product.*

Additional deaths in psoriasis subjects from the 4 month safety update

6. RHBA-102-01056: Coronary artery disease (CAD)

This subject was a 63 year old obese white female who participated in the pivotal trial RHBA and was assigned to the placebo arm for induction. Relevant medical history included hypertension since 2000 that was treated with amlodipine and furosemide and a FH CAD (father ↓ at age 48 of MI). She started treatment with Ixe 80mg Q4W on 9/19/12 and died on [REDACTED] (b) (6) after beginning Ixe). On 6/28/12 she was noted to have Right bundle branch (RBB) block. She died in her sleep [REDACTED] (b) (6) and no autopsy was performed. The death was independently adjudicated by external consultants who concluded that the event was cardiovascular - sudden cardiac death. In the opinion of the investigator, the event was not related to Ixe.

*Reviewer Comment: I agree with the investigator that given the subjects risk factors for a cardiac event (hypertension, FH CAD and obesity) it is unlikely that the death was related to the investigational product.*

7. RHBC-156-3253: Accidental death

This subject was a 47 yo morbidly obese white male with psoriasis who started treatment with Ixe 80mg Q4W on 6/18/13 and died [REDACTED] (b) (6) after beginning Ixe). He was working in a forest and was crushed by a falling tree. In the opinion of the investigator, the event was not related to Ixe.

*Reviewer Comment: I agree with the investigator that this accidental death is extremely unlikely to be related to the IP.*

8. RHBC-165-3415: ? MI

This subject was a 52 yo obese white male with psoriasis who started treatment with Ixe 80mg Q4W on 11/12/13 and died [REDACTED] (b) (6) after beginning Ixe). It was reported by a colleague that the subject died presumably due to a heart attack but no additional information was able to be obtained. In the opinion of the investigator, the event was not related to Ixe.

*Reviewer Comment: It is not possible to rule out a contribution to the above event by the investigational product. Without more information it is not possible to make a definitive attribution.*

### **Rheumatoid Arthritis Subjects on Ixe**

#### 9. RHAK - 125-2205 - granulomatous meningitis

This subject was a 68 year old white male with RA from the US who participated in trial RHAK (phase 2 dose-ranging trial for use of Ixe in RA) and was assigned to Ixe 180 mg arm for induction followed by 160 mg Q4W during the open label extension (OLE) period. His PMH included RA, HTN, hypercholesterolemia, and chronic obstructive pulmonary disease (COPD) after a 40 pack-year smoking history. Concomitant meds included atorvastatin calcium, ASA, metoprolol, methotrexate, folic acid, budesonide in combination with formoterol fumarate, tiotropium bromide, and dextropropoxyphene napsilate in combination with paracetamol. He started Rx on 2-4-10 and stopped Rx on 6-21-10 due to lack of efficacy. On 7-3-10, the patient had an inner ear infection with vertigo. The following day, the patient had developed some hearing loss. In 9-2010, the hearing loss was worsening. On 11-18-10, the otolaryngologist noted that the hearing loss was steadily progressive. The otolaryngologist felt that the hearing loss was due to autoimmune hearing loss, thus the patient received prednisone 60mg/day for around a month. On 12-7-10, he received one dose of abatacept. On 12-30-10, anticardiolipin Ab, IgM was positive (27 U/mL) and russell's viper venom time (dRVVT) was 47.5, which was consistent with the presence of a lupus anticoagulant. The patient received two doses of infliximab on 1-3-11 and 1-7-11. It was thought the hearing loss might be auto-immune; therefore he was treated with high doses of steroids with no improvement in hearing. (b) (6) approximately (b) (6) after last receiving blinded study drug and approximately (b) (6) (b) (6) after last receiving open label Ixe, the patient was hospitalized due to progressive vomiting. That same day, the patient was diagnosed with erosive esophagitis and duodenitis. The cause of esophagitis was reported as reflux induced. His WBC was around 100 upon admission with an absolute neutrophil count (ANC) of zero. Computed tomography (CT) of the brain revealed thickening of the dura in the brainstem and a mass at the base of the brain. Meningeal biopsy of the dura showed granulomatous inflammation within dense connective tissue. Stains for infectious organisms were negative. The patient was also diagnosed with pseudomembranous colitis and left lower lobe infiltrates. On (b) (6) the patient underwent a brain biopsy which showed granulomatous meningitis; some evidence of early necrotizing granulomas; no evidence of tuberculosis (TB). Granulomatous meningitis was assumed to be autoimmune; infection and malignancy were intensely evaluated and ruled out. On (b) (6) the patient developed atrial fibrillation with rapid ventricular response rate and hypotension secondary to sepsis. It was also noted that he had gram-negative rods in his urine. Antibiotics resulted in resolution of the UTI. On (b) (6) the patient was transferred to a long-term acute care facility. On (b) (6) the patient experienced aspiration hypoxia which led to cardiac and respiratory arrest, and the patient expired. Per the investigator, it was not completely clear which event was the immediate cause of death; sepsis, urosepsis, respiratory distress, etc, but

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the overarching etiology was the granulomatous meningitis. The investigator considered the event of granulomatous meningitis was possibly related to Ixe.

*Reviewer Comment: It is not possible to rule out a contribution to the above event by the investigational product. The onset of the first symptoms of the event (hearing loss) was shortly after the subject had received approximately 4 months of treatment with Ixe. Autoimmune processes have been associated with biologic therapies. However, multiple confounding factors such as multiple other immunosuppressive medications and intermittent bouts of infection preclude making any definitive attribution with regard to the cause of death.*

#### 10. RHAK – 145-3200 – lung adenocarcinoma

This subject was a 64 year old white female with RA from the US who participated in trial RHAK (phase 2 dose-ranging trial for use of Ixe in RA) and was assigned to Ixe 80 mg arm for induction followed by 160 mg Q4W during the open label extension (OLE) period. Her PMH included RA, chronic anemia, COPD, and osteoporosis. The patient smoked 0.5 to 1 packs per day for many years. Concomitant meds included folate, hydrocodone with acetaminophen, alendronate, celecoxib since 2008, methotrexate 17.5mg weekly since March 2009, and prednisone 5mg daily since 8-13-09. A screening chest x-ray on 9-29-09 revealed the appearance of COPD without evidence of active pulmonary inflammation; slight blunting of the left costovertebral angle was suspicious for small pulmonary fluid collection and right angle was not well visualized. She started Rx with Ixe on 10-21-09 and received her last dose of Ixe on 4-6-10. On 4-7-10, the patient complained of chills and weakness lasting approximately one month. The patient's hemoglobin (HGB) was 7.7 (previous Hgb on 2-9-10 was 12.4). The patient was diagnosed with anemia. The patient received 2 units of packed red blood cells. Hematology and gastrointestinal consults were recommended. The patient continued to feel weak, developed diffuse abdominal pain especially in the epigastric region, loss of appetite, and a weight loss of five to ten pounds. In mid-April 2010, the patient identified a lump in the abdomen. The patient had developed a persistent productive cough with yellowish phlegm. On (b) (6) the patient presented to the emergency room with the complaints. A 5cm in diameter smooth rounded palpable mass just above the umbilicus in the mid abdomen was noted. A CT scan of the abdomen and pelvis revealed numerous cannonball metastatic lesions throughout both lobes of the liver. ON (b) (6) a CT scan of the chest revealed a bilobed soft tissue lesion identified in the anterior portion of the left upper lobe of the lung. A biopsy of the liver lesions revealed poorly differentiated stage IV adenocarcinoma metastases; the presumed primary site was the lung. On (b) (6) she was discharged to hospice care. She died (b) (6) of metastatic adenocarcinoma of the lung. In the opinion of the study investigator, the metastatic adenocarcinoma with primary lung cancer was not related to study drug or study protocol. After speaking with the consulting oncologist, the study investigator believed this was a classic presentation of late stage metastatic lung cancer in a patient with a long history of tobacco use.

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*Reviewer Comment: It is not possible to rule out a contribution to the above event by the investigational product. However, multiple confounding factors such as multiple other immunosuppressive medications (methotrexate since 3/09 and prednisone 5 mg since 8/09) and a history of smoking preclude making a definitive statement as to the contribution of the investigational product to either the development or the progression of her malignancy.*

#### 11. RHAK -704-9382 – Unknown cause

This subject was a 67 year old American Indian/Alaskan Native female with RA from Peru who participated in trial RHAK (phase 2 dose-ranging trial for use of Ixe in RA) and was assigned to Ixe 10 mg arm for induction followed by 160 mg Q4W during the open label extension (OLE) period. Her PMH included hypothyroidism. Concomitant meds included prednisone, levothyroxine, diazepam, folic acid, esomeprazole, vitamins, methotrexate 15 mg QW and etoricoxib. She started Rx on 5-25-10 and received her last dose of Ixe on 4-27-11. She died on (b) (6). She experienced a mild AE of HTN on 2-23-11 and diltiazem was initiated. On 4-27-11 she had mildly elevated LFTs, moderately decreased platelets (52 billion/L (normal reference range: 130-394 billion/L) and moderately elevated phosphate. She had a possible diagnosis of auto immune hepatitis and a hepatic biopsy was planned. On 5-20-11, methotrexate was discontinued because the hepatic enzymes were still elevated. On 7-24-11 an abdominal ultrasound revealed increased size of the liver. On (b) (6) since she last received Ixe she was hospitalized. Per the investigator, the current diagnosis was UTI (b) (6) and hepatopathy. The initial symptoms included nausea, vomiting, weakness, lower limb edema, epistaxis, and fever. On (b) (6) it was reported that patient died (b) (6) and the cause of death was unknown. The circumstances surrounding the patient's death were unknown. The cause of death per death certificate is not available. Family refused to release any further information. Autopsy was not performed. The investigator did not feel the fatal event was related to the investigational agent due to the time elapsed between the hospitalization and the last dose of Ixe.

*Reviewer Comment: I agree with the investigator that it seems unlikely that the investigational product was related to the hospitalization and death of the subject given that it was over 5 months since the last dose.*

#### 8.4.2. **Serious Adverse Event**

The table below displays the SAEs for the induction period by System-Organ Class (SOC) for Pool #1. There were a total of 46 SAEs in the combined Ixe arms with a higher percentage in the Q4W arm versus the Q2W arm.

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**Table 29: SAEs - Induction Period, Primary Psoriasis Placebo-Controlled Integrated Analysis Set (RHAZ, RHBA, and RHBC)**

Preferred Term	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)
<b>Patients with ≥1 SAE</b>	12 (1.5)	26 (2.2)	20 (1.7)	46 (2.0)
Cellulitis	1 (0.1)	2 (0.2)	1 (0.1)	3 (0.1)
Appendicitis	0	0	2 (0.2)	2 (0.1)
Depression	0	0	2 (0.2)	2 (0.1)
Chronic obstructive pulmonary disease	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Crohn's disease	0	1 (0.1)	1 (0.1)	2 (0.1)
Suicide attempt	0	1 (0.1)	1 (0.1)	2 (0.1)
Erysipelas	0	2 (0.2)	0	2 (0.1)
Prostatitis <sup>a</sup>	0	1 (0.1)	0	1 (0.1)
Bipolar disorder	1 (0.1)	0	1 (0.1)	1 (0.0)
Fall	1 (0.1)	0	1 (0.1)	1 (0.0)
Abscess oral	0	0	1 (0.1)	1 (0.0)
Anxiety	0	0	1 (0.1)	1 (0.0)
Arthritis	0	0	1 (0.1)	1 (0.0)
Biliary colic	0	0	1 (0.1)	1 (0.0)
Cholecystitis	0	0	1 (0.1)	1 (0.0)
Dehydration	0	0	1 (0.1)	1 (0.0)
Diabetes mellitus	0	0	1 (0.1)	1 (0.0)
Drug hypersensitivity	0	0	1 (0.1)	1 (0.0)

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BLA 125521  
Taltz (ixekizumab)

Preferred Term	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)
Duodenitis	0	0	1 (0.1)	1 (0.0)
Gastritis	0	0	1 (0.1)	1 (0.0)
Hepatic function abnormal	0	0	1 (0.1)	1 (0.0)
Hypersensitivity vasculitis	0	0	1 (0.1)	1 (0.0)
Lumbar radiculopathy	0	0	1 (0.1)	1 (0.0)
Oesophagitis	0	0	1 (0.1)	1 (0.0)
Peritonitis	0	0	1 (0.1)	1 (0.0)
Renal impairment	0	0	1 (0.1)	1 (0.0)
Skin lesion	0	0	1 (0.1)	1 (0.0)
Subdural haematoma	0	0	1 (0.1)	1 (0.0)
Urticaria	0	0	1 (0.1)	1 (0.0)
Acute myocardial infarction	1 (0.1)	1 (0.1)	0	1 (0.0)
Inguinal hernia	1 (0.1)	1 (0.1)	0	1 (0.0)
Angioedema	0	1 (0.1)	0	1 (0.0)
Atrial fibrillation	0	1 (0.1)	0	1 (0.0)
Atrioventricular block first degree	0	1 (0.1)	0	1 (0.0)
Bronchopneumonia	0	1 (0.1)	0	1 (0.0)
Cerebral artery embolism	0	1 (0.1)	0	1 (0.0)
Colitis ischaemic	0	1 (0.1)	0	1 (0.0)
Epilepsy	0	1 (0.1)	0	1 (0.0)
Invasive ductal breast carcinoma	0	1 (0.1)	0	1 (0.0)
Pancreatitis acute	0	1 (0.1)	0	1 (0.0)
Pustular psoriasis	0	1 (0.1)	0	1 (0.0)
Pyelonephritis acute	0	1 (0.1)	0	1 (0.0)
Renal failure acute	0	1 (0.1)	0	1 (0.0)
Retinal detachment	0	1 (0.1)	0	1 (0.0)
Thoracic vertebral fracture	0	1 (0.1)	0	1 (0.0)
Tonsillitis	0	1 (0.1)	0	1 (0.0)
Transient ischaemic attack	0	1 (0.1)	0	1 (0.0)
Type 2 diabetes mellitus	0	1 (0.1)	0	1 (0.0)
Urinary tract infection	0	1 (0.1)	0	1 (0.0)
Urosepsis	0	1 (0.1)	0	1 (0.0)
Acute respiratory failure	1 (0.1)	0	0	0 <sup>b</sup>
Cholelithiasis	1 (0.1)	0	0	0
Drug eruption	1 (0.1)	0	0	0
Erythrodermic psoriasis	1 (0.1)	0	0	0 <sup>b</sup>
Hypopharyngeal cancer	1 (0.1)	0	0	0
Infectious mononucleosis	1 (0.1)	0	0	0
Palmoplantar keratoderma	1 (0.1)	0	0	0 <sup>b</sup>
Psoriasis	1 (0.1)	0	0	0 <sup>b</sup>
Skin bacterial infection	1 (0.1)	0	0	0 <sup>b</sup>
Tibia fracture	1 (0.1)	0	0	0 <sup>b</sup>

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Abbreviations: IXE80Q2W = ixekizumab 80 mg Q2W; IXE = ixekizumab; IXE80Q4W = ixekizumab 80 mg Q4W;  
MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n =  
number of patients with at least 1 serious adverse event in the specified category; SAE = serious adverse event.

<sup>a</sup> Denominator adjusted because gender-specific event for males: N = 559 (placebo), N = 787 (ixekizumab 80 mg  
Q4W), N = 766 (ixekizumab 80 mg Q2W).

<sup>b</sup> p < .05 compared to placebo.

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Source: Applicant' ISS pg 72

*Reviewer Comment: The number of subjects experiencing SAEs in the induction period in pool #1 was low (46). There was no dose-response displayed. The only SAEs that occurred in more than one subject in the Ixe arms were cellulitis (3 subjects), appendicitis (2 subjects) and depression (2 subjects). An increased incidence of infections is an acknowledged adverse event for Ixe and is well described in the label. There was no significant difference between placebo and the Ixe groups in the overall percentage of subjects reporting SAEs in the induction period.*

The table below displays the SAEs for the maintenance period by System-Organ Class (SOC) for Pool #3. There were a total of 48 SAEs in the combined Ixe arms with a higher incidence rate in the Q12W arm versus the Q4W arm.

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**Table 30: SAEs - Person-Time-Adjusted Incidence Rate, Maintenance Period, Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)**

	Placebo N=402 n (IR)	80 mg Q12W N=408 n (IR)	80 mg Q4W N=416 n (IR)	Total IXE N=824 n (IR)
Patients with $\geq 1$ SAE	15 (8.1)	23 (8.5)	25 (7.7)	48 (8.1)
Total Patient-Years	184.1	269.5	326.7	596.2
Preferred term				
Fall	2 (1.1)	0	2 (0.6)	2 (0.3)
Cholecystitis	0	0	2 (0.6)	2 (0.3)
Coronary artery disease	0	1 (0.4)	1 (0.3)	2 (0.3)
Inguinal hernia	0	1 (0.4)	1 (0.3)	2 (0.3)
Osteoarthritis	0	1 (0.4)	1 (0.3)	2 (0.3)
Intervertebral disc protrusion	0	2 (0.7)	0	2 (0.3)
Prostate cancer <sup>a</sup>	0	1 (0.6)	0	1 (0.2)
Pilonidal cyst	1 (0.5)	0	1 (0.3)	1 (0.1)
Subcutaneous abscess	1 (0.5)	0	1 (0.3)	1 (0.1)
Abscess	0	0	1 (0.3)	1 (0.1)
Acute myocardial infarction	0	0	1 (0.3)	1 (0.1)
Alcohol poisoning	0	0	1 (0.3)	1 (0.1)
Asthma	0	0	1 (0.3)	1 (0.1)
Bile duct obstruction	0	0	1 (0.3)	1 (0.1)
Bursitis	0	0	1 (0.3)	1 (0.1)
Cholelithiasis	0	0	1 (0.3)	1 (0.1)
Chronic tonsillitis	0	0	1 (0.3)	1 (0.1)
Congenital ectopic pancreas	0	0	1 (0.3)	1 (0.1)
Death	0	0	1 (0.3)	1 (0.1)
Dyspnoea	0	0	1 (0.3)	1 (0.1)
Infected skin ulcer	0	0	1 (0.3)	1 (0.1)
Intervertebral disc disorder	0	0	1 (0.3)	1 (0.1)
Joint dislocation	0	0	1 (0.3)	1 (0.1)

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	Placebo N=402 n (IR)	80 mg Q12W N=408 n (IR)	80 mg Q4W N=416 n (IR)	Total IXE N=824 n (IR)
Joint injury	0	0	1 (0.3)	1 (0.1)
Myocardial infarction	0	0	1 (0.3)	1 (0.1)
Non-cardiac chest pain	0	0	1 (0.3)	1 (0.1)
Pancreatitis relapsing	0	0	1 (0.3)	1 (0.1)
Postoperative wound infection	0	0	1 (0.3)	1 (0.1)
Pyogenic granuloma	0	0	1 (0.3)	1 (0.1)
Road traffic accident	0	0	1 (0.3)	1 (0.1)
Rotator cuff syndrome	0	0	1 (0.3)	1 (0.1)
Sepsis	0	0	1 (0.3)	1 (0.1)
Syncope	0	0	1 (0.3)	1 (0.1)
Tendon rupture	0	0	1 (0.3)	1 (0.1)
Upper limb fracture	0	0	1 (0.3)	1 (0.1)
Wrist fracture	0	0	1 (0.3)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.5)	1 (0.4)	0	1 (0.1)
Aortic stenosis	0	1 (0.4)	0	1 (0.1)
Appendicitis	0	1 (0.4)	0	1 (0.1)
Cholestasis	0	1 (0.4)	0	1 (0.1)
Colitis ulcerative	0	1 (0.4)	0	1 (0.1)
Coronary artery occlusion	0	1 (0.4)	0	1 (0.1)
Coronary artery stenosis	0	1 (0.4)	0	1 (0.1)
Deep vein thrombosis	0	1 (0.4)	0	1 (0.1)
Encephalopathy	0	1 (0.4)	0	1 (0.1)
Infectious mononucleosis	0	1 (0.4)	0	1 (0.1)
Multiple sclerosis	0	1 (0.4)	0	1 (0.1)
Nephrolithiasis	0	1 (0.4)	0	1 (0.1)
Pericardial effusion	0	1 (0.4)	0	1 (0.1)
Pneumonia pseudomonal	0	1 (0.4)	0	1 (0.1)
Pulmonary embolism	0	1 (0.4)	0	1 (0.1)
Pustular psoriasis	0	1 (0.4)	0	1 (0.1)
Small intestine adenocarcinoma	0	1 (0.4)	0	1 (0.1)
Suicide attempt	0	1 (0.4)	0	1 (0.1)
Type 2 diabetes mellitus	0	1 (0.4)	0	1 (0.1)
Uterine leiomyoma <sup>b</sup>	1 (0.5)	0	0	0
Crohn's disease	2 (1.1)	0	0	0
Arthralgia	1 (0.5)	0	0	0
Bradycardia	1 (0.5)	0	0	0
Carotid artery stenosis	1 (0.5)	0	0	0
Clostridium difficile infection	1 (0.5)	0	0	0
Fibula fracture	1 (0.5)	0	0	0
Hepatic mass	1 (0.5)	0	0	0
Humerus fracture	1 (0.5)	0	0	0

	Placebo N=402 n (IR)	80 mg Q12W N=408 n (IR)	80 mg Q4W N=416 n (IR)	Total IXE N=824 n (IR)
Ischaemic stroke	1 (0.5)	0	0	0
Papillary thyroid cancer	1 (0.5)	0	0	0
Parkinson's disease	1 (0.5)	0	0	0
Pleurisy	1 (0.5)	0	0	0
Pneumonia	1 (0.5)	0	0	0
Upper gastrointestinal haemorrhage	1 (0.5)	0	0	0

Abbreviations: IR = Incidence Rate; IXE = ixekizumab; IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q12W = ixekizumab 80 mg Q12W; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients with at least 1 serious adverse event in the specified category; OR = odds ratio; SAE = serious adverse event.

a Denominator adjusted because gender-specific event for male patients: PY=122.3 (Placebo), PY=180.6 (Ixekizumab 80 mg Q12W), 225.9 (Ixekizumab 80 mg Q4W).

b Denominator adjusted because gender-specific event for female patients: PY=61.8 (Placebo), PY=88.9 (Ixekizumab 80 mg Q12W), PY = 100.8 (Ixekizumab 80 mg Q4W).

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Source: Applicant' ISS pg 77

*Reviewer Comment: The number of subjects experiencing SAEs in the maintenance period in pool #3 was low (46). There was no dose-response displayed. There was no significant difference between placebo and the Ixe groups in the overall incidence rate of subjects reporting SAEs in the maintenance period.*

The majority of the narrative summaries for SAEs that occurred in subjects exposed to Ixe in the development program (up to the date of 9/15/14) were reviewed. There were a total of 303 subjects in the "All psoriasis Ixe Exposure Integrated Analysis Set" (APIEIAS) who experienced at least 1 SAE. There were a total of 53 subjects in the "All RA Ixe Exposure Integrated Analysis Set" (ARAIEIAS) who experienced at least 1 SAE. Some specific representative SAEs of interest are described (in more detail) below and in Attachment A at the end of this document and are grouped by SOC. I have also included adverse events of special interest (AESIs) that I felt were not related when the adverse event was from a category that merited special evaluation such as suicide attempt or hypersensitivity. An additional 328 subjects were included in the 4 month safety update, only certain of the SAEs of "special interest" were reviewed from this additional submission.

### **Depression/Suicidality: Ideation/Attempt**

*Reviewer Comment: If not mentioned in the narrative below the score for item #12 (thoughts of suicide) =0.*

1. RHAJ-105-1507: Suicide attempt

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69 yo white male with psoriasis with no previous relevant medical or family history of depression was treated with Ixe from 9/20/10 through 7/24/12. Between 11/10 and 4/11 the subject had QIDS scores of 3-4 (no depression) and item #12 was 0 (no thoughts of suicide). A friend died in (b) (6) and on (b) (6) months of exposure) he was diagnosed with severe depression and began bupropion. On (b) (6) he attempted suicide by trying to slash his throat with a knife and was hospitalized for treatment of his depression. He was “overwhelmed due to multiple stressors which included financial problems, recent retirement (unable to cope with that), poor coping skills, and being afraid of uncertain future with financial difficulties”. He was stabilized with medications and was discharged on (b) (6). The IP was continued throughout the event and the investigator considered the event was not related to the IP.

*Reviewer Comment: I agree with the investigator since the patient recovered from the depression while continuing on the IP and had other stressors that likely caused the depression.*

## 2. RHAZ-151-03001: Suicide attempt

49 yo white female with psoriasis and a h/o depression, anxiety and a previous suicide attempt 8 years ago on concomitant medications venlafaxine, ranitidine, fluticasone propionate, salmeterol xinafoate, medroxyprogesterone acetate, estrogens conjugated, estrogens conjugated and clomipramine hydrochloride was treated with Ixe from 8/27/12 through 1/14/14. On 5/28/12 her baseline QIDS=12 (moderate depression). On 8/22/12 her QIDS=22 (very severe depression) while on placebo (induction). On 11/12/12, 2/6/13 and 5/28/13 her QIDS=20 (severe depression) while on maintenance with Ixe after 3, 6 and 9 months of treatment. On 7/29/13 her QIDS=21 (very severe depression) after 11 months of Ixe. Question #12 was zero (no thoughts of suicide) each time it was tested (same dates as QIDS was performed).

On (b) (6) months of exposure) she was hospitalized for what was identified as a “non-life threatening” suicide attempt and depression. According to the narrative

The husband of the patient had an affair with his niece and the patient cut herself and took a minor drug overdose hoping he would stay with her, which he did not. The non-life threatening attempted suicide was considered recovered that same day. About eight years ago, the patient did the same thing, she attempted suicide by cutting herself with a knife that was not sharp, in an attempt to prove a point to her husband, not to follow through with suicide.

She was discharged on (b) (6) on mirtazapine. She was treated with Ixe on 12/9/13 (prior to informing the investigator about the suicide attempt). Once made aware of the suicide attempt the subject was discontinued from the trial on 1/14/14. On 1/14/14 her QIDS=8 (mild

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depression). In the opinion of the investigator, the events of non-life threatening attempted suicide and depression were considered not related to blinded study drug or protocol procedures. The investigator further stated that the non-life threatening attempted suicide was due to her husband having an affair with his niece and the depression was related to marital disharmony.

*Reviewer Comment: I agree with the investigator that the depression and suicide attempt were related to her marital situation and it is not likely that the investigational product was contributory.*

3. RHBA-151-03006: Suicide attempt X 2

40 yo white male with psoriasis and a h/o mild depression since 2012, on escitalopram was treated with lxe from 11/23/12 through 7/25/13. His baseline QIDS=0 (no depression). On 2/14/13 (~ 3 months of exposure) his QIDS=12 (moderate depression) and the answer to question #12=1 (I feel that life is empty or wonder if it's worth living). On 5/15/13 his QIDS=9 (mild depression) and the answer to question #12=1 (I feel that life is empty or wonder if it's worth living). On (b) (6) months of exposure) he was hospitalized for two suicide attempts within a three week time frame (this information has not been verified, only as reported by the patient). No additional information is available as the subject has declined to sign a release. He was discontinued from the trial. In the opinion of the investigator the events were not related to the IP.

*Reviewer Comment: I disagree with the investigator. A lack of detailed information does not exclude the possibility that the IP contributed to the event. His baseline QIDS was normal and subsequently after lxe exposure was abnormal and indicated depression. There may have been other factors but we cannot assume a lack of causality without knowing them.*

4. RHBA-216-04612: Suicide attempt

55 yo white female with psoriasis and a h/o depression (2004) and alcohol abuse was treated with lxe from 6/20/13 through 8/23/13. Her baseline QIDS=2 (no depression) on 5/13/13. On (b) (6) on lxe) she experienced depression and attempted suicide by trying to inject air into her veins with the trial syringes. It was reported that a close friend had died and her life partner (they were not married) had quitted their relationship the day before her suicide attempt. She underwent outpatient psychiatric evaluation and it was determined that she did not need hospitalization. On 8/23/13 her QIDS=13 (moderate depression) and item #12=2 (I think of suicide or death several times a week for several minutes). The IP was discontinued. In the opinion of the investigator the events were not related to the IP.

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*Reviewer Comment: I disagree with the investigator. Though there may have been additional contributing factors I do not believe it is possible to exclude the possibility that the IP contributed to the event.*

5. RHBA-405-06292: wrist laceration (? Suicide attempt)

46 yo obese white male with psoriasis was treated with Ixe from 9/30/13 through 12/23/13 and again from 2/17/14 through 7/18/14. On 9/30/13, his baseline QIDS = 3 (no depression). On 12/23/13 (after 3 months of Ixe) his QIDS total score was 4 (no depression) and he was re-randomized to placebo. On 6/9/14 (after 4 months back on Ixe), his QIDS=3 (no depression). On (b) (6), the patient harmed himself under the influence of alcohol by lacerating the right wrist. The wound was superficial, he was not hospitalized and the investigator reported this as a "mild event". The principal investigator judged this suicidal behavior as impulsive with lack of intent and assessed the event occurrence was probably in relation to the ingestion of alcohol. Though the investigator decided to continue the patient in the study as the patient did not meet the discontinuation criteria of reporting a score of 3 on QIDS item 12; the sponsor decided to discontinue the patient as the patient was considered at risk.

*Reviewer Comment: I disagree with the investigator. Though the laceration may have been superficial I would still consider this a suicide attempt and therefore a serious adverse event. There does not appear to be any correlation between the treatment with Ixe and the QIDS score but this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the event.*

6. RHBA-456-06687: Suicide Attempt

29 yo obese white male with psoriasis and a h/o smoking and untreated depression since 2009 as well as three previous suicide attempts in last 3 years (not disclosed to investigator) was treated with Ixe from 12/7/13 through 3/1/14. On 12/7/13: his baseline QIDS=8 (mild depression) and the answer to question #12=1 (I feel that life is empty or wonder if it's worth living). On (b) (6) of exposure to Ixe) he attempted suicide by taking an over dose of ibuprofen (24 tabs total) and codeine (12 tabs total) at midnight (he alerted friends to the planned attempt at 11PM one hour prior to attempt). He was seen in the ER and evaluated by a psychiatrist to whom he admitted "had had been depressed for the last several weeks and that his suicide attempt was precipitated by losing his job after arriving at work two hours late due to road blocks and losing his girlfriend (after getting back with her earlier in the year) as well as having financial issues". This was when he admitted having had three previous attempts on his life in the three previous years. He was sent home with a family member on mirtazapine with plans to admit him to a community psych facility once a bed was available. He continued injecting the IP and was hospitalized from (b) (6) for treatment of his depression. The investigator learned of the attempt on 3/5/14 and held the IP. On 3/5/14 his

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QIDS=2 (no depression) but he was discontinued from the trial. On 3/15/14 his QIDS=7 (mild depression) at follow-up visit. In the opinion of the investigator the events were not related to the IP.

*Reviewer Comment: I disagree with the investigator. There does not appear to be any correlation between the treatment with Ixe and the QIDS score but this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the event.*

#### 7. RHBC 152-3058: Suicide attempt

34 yo white female with psoriasis with a h/o depression (2010) was treated with Ixe from 8/1/13 through 4/15/14. On 5/9/13, her baseline QIDS=9 (mild depression). On 8/1/13 her QIDS=11 (moderate depression) and item 12 (thoughts of suicide or death) score was 1 (I felt that life was empty or wondered if it was worth living). On 1/16/14, her QIDS=8 (mild depression) and item 12 (thoughts of suicide or death) score was 1 (I felt that life was empty or wondered if it was worth living).

On 4/15/14, her QIDS = 3 (no depression) and item 12 (thoughts of suicide or death) score was 0 (I didn't think of suicide or death). She discontinued the IP on that day due to need to be treated with a live virus vaccine. On [REDACTED] (b) (6) off Ixe after [REDACTED] (b) (6) of treatment) she attempted suicide via an overdose of alcohol and carbon monoxide exposure. She reported numerous family stressors for the last 3 months as well as worsening psoriasis as triggers. She was hospitalized on [REDACTED] (b) (6) for the depression and left lower lobe pneumonia, was treated and was discharged on [REDACTED] (b) (6). In the opinion of the investigator the events were not related to the IP.

*Reviewer Comment: I disagree with the investigator. There does not appear to be any correlation between the treatment with Ixe and the QIDS score but this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the event.*

#### Additional cases presented in the 4 month safety update

#### 8. RHAZ 452-6568: Suicide Attempt

45 yo white male with psoriasis and a h/o depression, alcohol abuse and bipolar disorder (since 2011) was treated with Ixe from 12/13/12 through 11/25/14. On 9/19/12 (prior to receiving Ixe) his QIDS=4 (no depression) and Item 12 =0 (I do not think of suicide or death). His QIDS was 3 and 4 (no depression) between trial initiation and 5/1/14. On [REDACTED] (b) (6) months of Ixe exposure) he attempted suicide by taking an overdose of 24 valium tablets. He stated he was

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having “domestic problems”. He was hospitalized for one day. On 11/25/14 his QIDS=12 (moderate depression) and item 12=2 (I think of suicide or death several times a week for several minutes). In the opinion of the investigator the events were not related to the IP.

*Reviewer Comment: I disagree with the investigator. There does not appear to be any correlation between the treatment with Ixe and the QIDS score but this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the event.*

#### 9. RHBA 486-6765: Suicide Attempt

47 yo white female with psoriasis and a h/o moderate depression since 2010 on bupropion, flupentixol-melitracen (Deanxit), duloxetine, escitalopram oxalate, mirtazapine, quetiapine, sulpiride, trazodone, and venlafaxine was treated with Ixe from 1/23/13 through 4/17/13 and again from 9/30/13 through 2/18/15. On screening on 1/9/13 her QIDS=19 (severe depression) and item 12 score was 1 (Felt that life was empty or wondered if it was worth living). On 1/23/13 her baseline QIDS=15 (moderate depression) and item 12= 0. On 9/3/14 (off Ixe x 5 months) her QIDS = 8 (mild depression) and item 12 = 0 (I do not think of suicide or death). On (b) (6) back on Ixe) she attempted suicide by taking pills (antidepressants-no other details known) and was hospitalized the next day. On (b) (6) her QIDS=27 (severe depression) and item 12=3 (thoughts of suicide or death several times a day in some detail, or made specific plans for suicide or actually tried to take my life). In the opinion of the investigator the events were not related to the IP.

*Reviewer Comment: I disagree with the investigator. There does not appear to be any correlation between the treatment with Ixe and the QIDS score but this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the event.*

#### 10. RHBC-140-2855: Suicidal ideation, anxiety, bipolar disorder, depression, re-categorized as suicide attempt when additional information became available during C-CASA review

26 yo African American male with psoriasis and a h/o asthma and drug abuse (marijuana and 3, 4-methylenedioxyamphetamine=ecstasy) was treated with Ixe from 7/31/13 through 12/4/14. At screening on 7/2/13 his QIDS=13 (moderate depression). On 9/13/13 (≈2 months exposure to Ixe) he reported having a family dispute and becoming anxious and depressed. He was hospitalized for treatment of depression on (b) (6). He was diagnosed with bipolar disorder and treated with valproate semisodium, hydroxyzine embonate, and quetiapine fumarate. He discontinued these meds at an unknown date since he couldn't afford them. On 9/24/14, (≈2.5 months exposure to Ixe) his QIDS =3' (no depression). On 10/24/13(≈3 months exposure to Ixe) his QIDS=2 (no depression).

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Sometime in 10/14 (b) (6) prior to the (b) (6) event) he was fired due to drug use on the job. He had also recently been arrested for burglary but denied recollection of the crime. On (b) (6) months on Ixe), he decided to end his life by locking himself in a motel room and trying to overdose on MDMA. On (b) (6) months on Ixe), he was hospitalized due to moderate depression and severe suicidal ideation. Other symptoms included hallucinations, auditory hallucinations and homicidal ideations. Urine drug screen was positive for marijuana metabolites, and negative for all other drugs. He was treated with medication and was discharged on (b) (6). On 12/4/14, his QIDS=15 (moderate depression). On 4/9/14, his QIDS = 0 (no depression). In the opinion of the investigator the events were possibly related to the IP.

*Reviewer's comment: This is a complicated case. The onset of the bipolar disorder does correlate with the initiation of the IP. There does not appear to be any correlation between the treatment with Ixe and the QIDS score but this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the events of depression and suicidal ideation.*

11. RHAZ-146-02910: Alcohol (methanol) poisoning (? Suicide attempt)

48 yo white male with psoriasis was treated with Ixe from 11/1/12 through 5/17/13. On (b) (6) months of exposure) he was hospitalized for treatment of methanol poisoning after presenting to the ER with severe stomach pains and vomiting. The patient refused to sign a release form so no details are available. He was discharged on (b) (6). In the opinion of the investigator, the event was not related to the IP.

*Reviewer Comment: With so little information available it is not possible to rule out a contribution from the IP to this event. It is not even possible to be sure that this does not represent a suicide attempt.*

12. On etanercept-RHBA-105-01204: Suicidal ideation (mild)

57 yo white male with psoriasis experienced suicidal ideation **while on treatment with etanercept** during the induction phase of RHBA. On 9/12/12, the patient's baseline QIDS total score was 2 (no depression) and item 12 (thoughts of death or suicide) score was 0 (I do not think of suicide or death). He started etanercept on 9/12/12 and discontinued it on 10/6/12 (his decision). On 12/30/12, 86 days after the last dose of etanercept, the patient reported adverse events including mild suicidal ideation, moderate anxiety, and mild depression.

*Reviewer Comment: I decided to keep this summary here (despite the subject not receiving Ixe) as an illustration of the suicidality that can be seen in psoriasis subjects with this degree of disease. It is possible that the etanercept was a contributing factor to the event. There has been*

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*a recent OSE review of neuropsychiatric events associated with the use of TNF inhibitors (dated Sept 17, 2015) which stated*

*Psychiatric events ranged from subtle symptoms such as anxiety to hallucination, mania, paranoia, and frank psychosis. There were also cases of depression and suicidality associated with TNF- $\alpha$  blocker use... The time from TNF- $\alpha$  blocker administration to the onset of symptoms was generally within one month of initiating a TNF- $\alpha$  blocker. In several cases, neuropsychiatric symptoms developed within the first 24 hours after the first administration... The resolution of symptoms after drug discontinuation and reoccurrence of symptoms upon drug reintroduction are compelling. The cases that reported reoccurrence of symptoms with subsequent doses (without drug discontinuation) are even more compelling.*

*Of note, the current US package insert for certolizumab is labeled for suicide attempt, bipolar disorder, and anxiety in the Adverse Drug Reaction – Clinical Trial section. Product labeling for TNF- $\alpha$  blockers in Europe and Canada also contain a variety of neuropsychiatric events, including delirium, confusion, mental impairment, abnormal thinking, personality disorder, depression, and suicide attempt in the clinical study and post-marketing experience sections.*

*The final recommendation was to update the Warnings and Precautions Sections of TNF inhibitors to include a warning for an increased risk of neuropsychiatric events (including depression and suicidality) and to update the Adverse Reactions – Postmarketing Experience section to include Psychiatric Disorders – depression, suicidal ideation, suicide attempt, and completed suicide .*

#### Cases of serious depression (requiring hospitalization)

RHAZ-205-04187: Depression requiring hospitalization

63 yo white female with psoriasis and a h/o depression (on concomitant med mirtazapine) and Parkinson's disease with muscular weakness was treated with Ixe from 3/26/13 through 6/18/13 and again from 11/7/13 through 5/20/14. At baseline her QIDS score=2 (no depression). On 6/13/13 after receiving 2.5 months of Ixe her QIDS score=4 (no depression). She was then switched to placebo. On 9/1/13 she reported "severe psychological stress" related to worsening of her Parkinson's disease. She restarted Ixe after her psoriasis relapsed on 11/7/13. On (b) (6) (back on Ixe x (b) (6)) was hospitalized to optimize her Parkinson's treatment regimen. She reported recently separating from her long term life partner. Beck's depression inventory performed during that hospitalization was reportedly normal. Pramipexole dihydrochloride was added to her Parkinson's regimen and duloxetine was added for depression. She was discharged on (b) (6) and c/o mood swings and fatigue which her doctor thought might be related to the pramipexole.

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On 12/13/13 (back on lxe x 5 weeks) her QIDS score=12 (moderate depression). On (b) (6) she was hospitalized again for worsening of Parkinson's disease and the pramipexole was discontinued. On 3/20/14 (≈4 months of lxe exposure), her QIDS score= 19 (severe depression) and item 12 (thoughts of suicide or death) score was 1 (I feel that life is empty or wonder if it's worth living). On (b) (6), the patient was hospitalized again for the worsening of Parkinson's disease and depression. On 5/20/14 (≈6 months of lxe exposure), her QIDS score = 24 (very severe depression) and item 12 (thoughts of suicide or death) score was 1 (I feel that life is empty or wonder if it's worth living). In the opinion of the investigator the depression and mood swings were not related to the IP.

*Reviewer Comment: This is a very complicated case with multiple confounders including her underlying Parkinson's disease, personal relationship issues and other medications. I agree with the investigator that the ups and downs of her moods seem more correlated to these other factors than with her treatment with the IP. I do not believe it is possible to exclude the possibility that the IP contributed to the events of depression.*

RHAZ-208-04287: Depressed mood and pain

48 yo white female with a h/o psoriatic arthritis, HTN, DM, ↑lipids, migraine and abuse during childhood was treated with lxe from 9/24/12 through 12/18/12 and from 4/4/13 through 7/29/14. Her baseline QIDS score= 4 (no depression) in 9/12. Her QIDS=10 (mild depression) in 12/12 after 4 months of lxe. In 3/13, her QIDS=13 (moderate depression) with the answer to question #12=1 (I feel that life is empty or wonder if it's worth living) off lxe (on placebo x 3 mos). In 11/13 her QIDS=2 (no depression) after 6 months back on lxe. On (b) (6) months of continuous lxe exposure) she experienced depressed mood with diffuse pain and sadness “due to remembering abuse during childhood” and was hospitalized. She was treated with medication and was discharged the following day. In 5/14, her QIDS=5 (no depression) after one year of continuous lxe exposure. In the opinion of the investigator the depression was not related to the IP.

*Reviewer Comment: I disagree with the investigator, though there appears to be little correlation between the subjects' mood and her score on the QIDS, this may not be a sensitive enough measure and I do not believe it is possible to exclude the possibility that the IP contributed to the events of depression.*

See Section 8.5.1 **Analysis of Submission Specific Safety Issues** for further discussion of suicidality and lxe

### **Infections**

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RHBA-254-06155: TB test conversion (QuantiFERON-TB Gold)

56 yo white Polish female with psoriasis and a h/o neg QuantiFERON-TB Gold on 5/13/13 and a h/o BCG vaccine was treated with etanercept from 5/13/13 to 8/13/13, with placebo from 8/13/13 to 3/14/14 and then with Ixe from 3/14/14 to 5/14/14. On (b) (6) months of exposure to Ixe) she had routine Tb testing (called for yearly under the protocol) and was found to have converted to + on her QuantiFERON-TB Gold Test. She was hospitalized for extended pulmonary diagnosis and to start tuberculosis treatment on (b) (6). Pulmonary consult obtained indicated that her mother was suspected of having TB. The investigator considered the event possibly related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution of the IP to this event. There were 26 cases in the original BLA submission of subjects who converted from negative to positive on a TB test. A variety of tests were used including QuantiFERON Gold (14 subjects), T-spot (1 subject) and PPD (3 subjects). In an additional 8 subjects the "test" used was not specified. An informal survey across DDDP Medical Officers revealed that conversion of TB status is a common finding in clinical trials for moderate to severe psoriasis with systemic immunomodulatory agents. With regards to approved products, there were 68 reported cases in the ustekinumab development program. With regard to products whose NDA submission is currently being reviewed, 70 cases were reported in the tofacitinib development program (with one case of active TB). See Section 8.5.2 **Analysis of Submission Specific Safety Issues**; subsection **Infections** heading Tuberculosis for further discussion of this issue.*

RHAK-602-8090: Appendicitis

53 yo black female with RA on the concomitant meds MTX and methylprednisolone was treated with Ixe from 6/30/10 through 7/14/10. She developed R iliac pain on (b) (6) days of exposure) was treated with Ixe on (b) (6) and later that day was admitted to the hospital where on (b) (6) laparotomy revealed appendicitis. In the opinion of the investigator, the event of appendicitis was possibly related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution of the IP to the infection that precipitated the event.*

RHAK-608-8330: Appendicitis

41 yo Hispanic female with RA on the concomitant meds MTX and ibuprofen was treated with Ixe from 5/19/10 through 6/2/10. On 5/19/10 and 5/27/10 she received Ixe. On (b) (6) days of exposure) she was hospitalized for appendicitis and appendectomy was performed. She was discharged on (b) (6) She was treated with one additional dose of Ixe on 6/4/10 but was

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then discontinued from the study at the sponsor's request. In the opinion of the investigator the event was related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution of the IP to the infection that precipitated the event.*

RHAZ-133-2625: Appendicitis

37 yo white female with psoriasis was treated with Ixe from 4/18/13 through 6/18/14. On (b) (6) months of exposure) she was hospitalized for appendicitis with complaints of abdominal pain. She underwent an appendectomy and was discharged on (b) (6). The IP was held during the event but restarted on 1/7/14. In the opinion of the investigator, the event was not related to the IP.

*Reviewer Comment: Reviewer Comment: I do not agree with the investigator, it is not possible to rule out a contribution of the IP to this event.*

RHAZ-504-07055: Appendicitis

39 yo white male with psoriasis was treated with Ixe from 11/14/12 through 2/1/13. On (b) (6) weeks of exposure) he was hospitalized for appendicitis. He underwent appendectomy on (b) (6). He was discharged on (b) (6). In the opinion of the investigator, the event was not related to the IP.

*Reviewer Comment: Reviewer Comment: I do not agree with the investigator, it is not possible to rule out a contribution of the IP to this event.*

RHBA-154-03815: Appendicitis

31 yo white female with psoriasis was treated with Ixe from 3/22/13 through 4/17/14. On (b) (6) months of exposure) she was hospitalized for appendicitis. She underwent an appendectomy but the pathology specimen did not reveal any inflammation of the appendix. In the opinion of the investigator, the event was not related to the IP.

*Reviewer Comment: Though this event was listed under appendicitis, given the lack of pathology I would agree that whatever caused this event we do not have enough information to attribute this to the IP.*

RHBC-115-2057: Appendicitis

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29 yo white male with psoriasis was treated with Ixe from 4/25/13 through 5/9/13. On (b) (6) days of exposure) he was hospitalized and underwent a laparoscopic appendectomy. He was discharged on (b) (6). He was discontinued from the trial based on the event. In the opinion of the investigator, the event was related to the IP.

*Reviewer Comment: Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution of the IP to this event.*

RHBC-655-9411: Appendicitis

60 yo obese Hispanic male with psoriasis was treated with Ixe from 12/30/13 through 6/24/14. On (b) (6) months of exposure) he was hospitalized and underwent an appendectomy. He was discharged on (b) (6). In the opinion of the investigator, the event was not related to the IP.

*Reviewer Comment: I do not agree with the investigator, it is not possible to rule out a contribution of the IP to this event.*

*Reviewer Comment Regarding Infections*

*It is notable that there were 7 cases of appendicitis in the Ixe arms (one of these, subject # RHBA-154-03815 may not have actually been appendicitis) and no cases in placebo. The RA subjects in trial RHAK were both on MTX (and one was also on prednisolone) so these subjects were clearly immunosuppressed aside from the Ixe therapy. The proposed labeling does include potential increased risk of infection under warnings and precautions. See Section 8.5.2 **Analysis of Submission Specific Safety Issues**; subsection **Infections** heading Appendicitis for further discussion of this topic.*

**Hypersensitivity**

RHAK-456-6492: Serum-sickness like reaction

39 yo Asian female with RA was treated with Ixe on 5/11/10 and one week later on 5/18/10 experienced urticaria which resolved with antihistamine. The subject received additional doses of Ixe on 5/20/10 and 5/27/10. On 5/28/10 and 6/4/10 the subject c/o an injection site reaction (ISR) with itching and redness at the site and antihistamines were increased. On (b) (6) she was hospitalized for extensive urticaria and facial and extremity angioedema. BP and pulse were WNL. She was treated with systemic steroids and additional antihistamines. On (b) (6) she developed abdominal pain and ultrasound revealed mild abdominal ascites and pleural effusions. The investigator considered the events related to the IP.

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*Reviewer Comment: I agree with the investigator that the IP caused the serum-sickness like event.*

RHAZ-208-04318: Urticaria requiring hospitalization

39 yo obese white male with psoriasis and a h/o urticaria (20 years ago) was treated with Ixe from 3/27/13 through 8/14/13. On 4/8/13 (~2 weeks of exposure-one dose) he developed "severe urticaria". He also had "cold symptoms" from 4/6/13 through 4/9/13 but denies any medications taken for them. He was hospitalized on (b) (6) when he developed swelling of the lips and hands in addition to hives but denied SOB/airway symptoms and vital signs were WNL. He was treated with antihistamines and was discharged on (b) (6). On 4/23/13 his anti-drug antibodies (ADA) were positive (for the first time) with a titer of 1:640 (no neutralizing Abs). The IP was resumed on 4/23/13 without incident. On 14-Aug-2013 (visit nine), positive antibodies (titer 1:40,960) with neutralizing antibodies present were obtained. He was discontinued from the study for lack of response. The investigator considered the event possibly related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution of the IP to the event. It is interesting that the IP was restarted without incident but the timing of the development of the ADA is certainly suspicious.*

RHAZ-257-04928: Drug Hypersensitivity

36 yo white female with psoriasis was treated with Ixe from 9/14/12 through 9/28/12 (2 doses given). On 9/29/12 (one day after dose 2) she developed itching of the face, trunk and upper limbs with an erythematous rash. She had no SOB or other "systemic symptoms". She was discontinued from the trial. The investigator considered the event related to the IP.

*Reviewer Comment: I agree with the investigator that the IP caused the event. Hypersensitivity reactions are an expected AE for foreign proteins such as biologic therapies.*

RHBA-161-03522: Anaphylactic reaction

55 yo Asian female with psoriasis with a h/o allergic reactions to medications was treated with a single dose of Ixe on 7/25/13. On 8/5/13 (11 days after her loading dose of Ixe) she experienced generalized urticaria of moderate severity. On (b) (6) she presented to the ER with a 2 day h/o SOB, difficulty breathing, shakiness; and an uncomfortably itchy, red, raised rash that started in the right hip leg area and extended to her entire body (chest, back, arms and legs). She stated the rash developed more over the previous 24 hours and the start of chills and rigors that day. She denied cough, facial or tongue swelling, diarrhea, recent travel, and change in her diet. No changes in

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medications or taking herbs. On exam her chest was clear, vital signs were normal and she had no edema. She was treated with diphenhydramine hydrochloride, paracetamol, pseudoephedrine hydrochloride (Benadryl) and intravenous fluid. She remained in the emergency department for observation on the night of (b) (6) but was not admitted to the hospital. The final diagnosis was drug reaction.

On (b) (6) she was hospitalized for “anaphylaxis”. Her throat exam was reportedly normal on exam at admission. Air entry was equal bilaterally and she was clear to the bases on chest exam. She was started on prednisone and an antihistamine. Her blood work remained normal and her SOB and pruritus resolved over four days. On (b) (6) she was discharged. Per the discharge summary the diagnosis was “diffuse erythematous rash possibly secondary to experimental drug therapy”.

On 8/26/14 positive antibody test (titer 1:80) without neutralizing antibodies was noted. On 10/8/14 she was discontinued from the trial, positive antibody result (titer 1:1280) with positive neutralizing antibodies was present. In the opinion of the investigator, anaphylaxis was possibly related to the IP.

*Reviewer Comment: I agree with the investigator that the IP caused the event. I agree with both the investigator and the discharging physician that this event represented a severe drug reaction but did not represent anaphylaxis. Though she c/o SOB throughout she had a normal PE with no evidence of airway obstruction, edema or wheezing/asthma on chest exam. The time course of her presentation from initial development of urticaria on 8/5/13 to hospitalization on (b) (6) argues against the diagnosis of anaphylaxis which by definition is a rapidly progressive process.*

RHBA-162-03554: Angioedema

61 yo white male with psoriasis and a h/o “drug intolerance” to ibuprofen on concomitant meds paracetamol and diphenhydramine was treated on 10/3/12 (with Ixe) and again received an injection (this time placebo) on 10/15/12. On the same day as his second dose (which was placebo since he was assigned to the Q 4 Week arm) within “seconds following injection” he began “feeling strange” and “sweating”. He lay down for an hour but “felt unwell the whole day”. The next morning on 10/16/12 his right eye became red and itchy, he c/o frontal headache with congestion but no fever, signs of upper respiratory infection (URI), SOB, rash or thickening of throat. He presented to the study site on 10/18/12 still “feeling unwell” and the IP was discontinued and he was discharged from the trial. On 10/21/12 the event was considered resolved. In the opinion of the investigator, the event was possibly related to the IP.

*Reviewer Comment: I agree that this event was possibly related to the IP but do not feel the event represents a case of angioedema. The only swelling was unilateral swelling of the right*

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*eye which was treated with topical tobramycin ointment suggesting the appearance was consistent with a localized inflammatory process. Angioedema would be bilateral and in most cases would involve other areas (such as the lips if it was predominantly facial). The subjects other symptoms were vague and he was never hospitalized and was treated with antihistamines and the topical tobramycin. Though the event occurred “seconds” after administration of the second dose of the blinded study drug the product administered was placebo on 10/15/13 which adds another confusing aspect to the event.*

RHBA-162-03585: Hypersensitivity reaction

46 yo white male with psoriasis and a h/o allergy to PCN was treated with Ixe from 12/16/13 through 9/2/14. He had injection site reactions (ISRs) on 6/3/14, 6/27/14 and 7/28/14 all of which resolved. He began receiving cetirizine for ISRs beginning on 6/27/14. He received a prophylactic dose of cetirizine on 8/24/14 and 8/25/14. On 8/25/14, the patient had an injection site reaction consisting of redness, swelling and pruritus. On 8/27/14 (~ 9 months of exposure) he developed bilateral eye swelling under lower lids. He had no trouble breathing or swallowing. He was assessed by the investigator and given an epinephrine pen and was monitored. He was sent home with cetirizine and prednisone daily for five days. On 8/27/14 he recovered from systemic allergic reaction. He was discontinued from the trial based on the event. In the opinion of the investigator, the event was possibly related to the IP.

*Reviewer Comment: I agree that this event was related to the IP.*

RHBA-205-04192: Angioedema with tongue and lip swelling

54 yo white male with a h/o HTN, smoking, ↑lipids, obesity, depression, DM, steatosis hepatitis (3/13) and psoriatic arthritis on concomitant medications ASA, ramipril, pantoprazole sodium sesquihydrate, allopurinol, atorvastatin, metformin hydrochloride/sitagliptin phosphate monohydrate, insulin detemir, insulin aspart and paroxetine was treated with Ixe from 7/22/13 through 9/11/14. On 7/4/14 he received a dose of Ixe. On 7/6/14 (~ 11 months of exposure) he experienced palmar redness and itching of the upper extremities and was treated on 7/9/14 by an outside dermatologist with oral corticosteroids (unknown dose). On (b) (6) he experienced worsening of swelling in the area of the head and throat and was hospitalized. His numerous medications were discontinued and the IP was held. ENT examination showed swelling of his larynx and hypopharynx as well as his tongue. The lower lip also had edematous swelling. On (b) (6) he recovered from the event and was discharged. The discontinued concomitant medications were not rechallenged and causal allergic relationship was not tested, but drug allergic relationship was probable and was assumed. Ixe was resumed on 8/15/14 without incident. In the opinion of the investigator, the event was not related to the IP.

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*Reviewer Comment: I agree with the investigator, resumption of the IP without incident makes it highly unlikely that it was the cause of the described event. It is likely that one of the discontinued concomitant meds was the culprit.*

RHBA-216-04603: Urticaria

26 yo white male with psoriasis was treated with Ixe on 6/25/13. On 7/5/13 (10 days after his first and only dose of Ixe) he experienced urticaria which began near the injection site. On 7/6/13 he c/o joint pain and the urticaria generalized. On (b) (6) he was hospitalized with dizziness, itching and chills as well as diffuse urticaria. ADAs were positive for the first time with a titer of 1:1280 (neutralizing abs neg). Vital signs were WNL. On (b) (6) he developed fever. He responded to steroids and antihistamines and was discharged on (b) (6). The IP was discontinued. Subsequent ADA titers were + with neutralizing abs at a titer of 1: 640. In the opinion of the investigator, the event was related to the IP.

*Reviewer Comment: I agree that this event was related to the IP.*

*Reviewer Comment Regarding Hypersensitivity*

*The cases described above represent a variety of types and degrees of severity of hypersensitivity reactions. This is an expected adverse event for a foreign biologic protein. The majority of even these severe cases were not life-threatening and the subjects recovered without sequelae. I do not believe any of the cases actually represent anaphylaxis. The issue of hypersensitivity reactions is well described in the proposed labeling. See Section 8.5.4 **Analysis of Submission Specific Safety Issues**; subsection **Allergic Reactions/Hypersensitivities including injection sites reactions** for further discussion of this issue.*

See Attachment A at the end of this document for Narratives 1: Representative cases of SAEs - Cerebro-cardiovascular Events.

See Attachment A at the end of this document for Narratives 2: Representative cases of SAEs – Malignancies.

**Inflammatory Bowel disease (IBD)**

RHAZ-202-04056: Ulcerative Colitis (UC) flare

27 yo white male with psoriasis and a h/o gastrointestinal disorder (18 kg weight loss in month before starting Ixe, on prednisolone at enrollment) since 2008 and food allergy was treated with Ixe from 4/10/13 through 6/21/13. On 4/23/13 (≈2 weeks of exposure) he experienced a first episode on treatment of what was later diagnosed as UC. On (b) (6) after (b) (6) on Ixe

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and (b) (6) after stopping the treatment with Ixe, the patient was hospitalized due to the acute attack of UC. He was hospitalized again on (b) (6) due to the acute attack of UC. In the opinion of the investigator, the event was not related to the IP.

*Reviewer Comment: I disagree with the investigator. Thought the subject may have had UC before treatment with Ixe the multiple severe flares suggest that the IP may have exacerbated the disorder.*

RHAZ-251-04682: Crohn's disease exacerbation

45 yo obese white male with psoriasis and a h/o smoking (quit 9/13), "stomach aches" worsening since 2009 was treated with Ixe from 10/2/12 through 1/2/13 and again from 5/22/13 through 8/4/14. From 12/20 through 12/27/12 (on Ixe x 2 months) the subject c/o mild abdominal pain which resolved without therapy. He was switched to placebo on 1/2/13. On (b) (6) (on placebo (b) (6)) he was hospitalized due to stomach pain and diarrhea which on (b) (6) was diagnosed as Crohn's disease. He restarted treated with Ixe upon relapse of psoriasis on 5/22/13. He had another episode of abdominal pain and diarrhea starting 10/12/13 and was hospitalized again on (b) (6) for Crohn's flare. In the opinion of the investigator, the events were not related to the IP.

*Reviewer Comment: I disagree with the investigator. Thought the subject may have had stomach pains before treatment with Ixe the multiple severe flares requiring hospitalization suggest that the IP may have exacerbated the disorder.*

RHAZ-405-06243: Crohn's disease

45 yo white male with psoriasis and a h/o smoking, back pain and anemia (mild normocytic) on enrollment was treated with Ixe from 9/11/12 through 11/20/12. In early November he noted onset of intermittent diarrhea. On 11/15/12 (≈2 months of exposure) he c/o vomiting and nausea (his partner and daughter had a similar illness at that time) so the symptoms were felt to be related to a virus. On 11/29/12, he c/o weight loss and persistent nausea. On (b) (6) he was hospitalized for what was later diagnosed as Crohn's disease. He was treated with prednisolone and was discharged on (b) (6). In the opinion of the investigator, the events were possibly related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution to the above event by the investigational product.*

RHBA-215-04570: UC

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42 yo white female with psoriasis and a h/o HTN, ↑lipids was treated with Ixe from 6/24/13 through 10/14/13. On 10/16/13 (≈4 months of exposure) she began to experience diarrhea and was treated with metronidazole. On [REDACTED] (b) (6) she was hospitalized for what later was diagnosed as UC. In the opinion of the investigator, the events were related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution to the above event by the investigational product.*

RHBA-254-06143: UC

42 yo white female with psoriasis and a h/o being a staph carrier was treated with Ixe from 4/3/13 through 6/18/14. On 1/2/14 (≈9 months of exposure) she experienced diarrhea and was treated with antibiotics. In 4/13 she underwent colonoscopy which revealed nonspecific findings. She was suspected to have Crohn's disease and was treated with oral steroids and azathioprine. On [REDACTED] (b) (6) months of exposure) she patient was hospitalized due to worsening of her GI symptoms associated with abdominal pain and fever. Repeat colonoscopy was suggestive of UC. During treatment the subject experienced delirium felt to be secondary to systemic steroids. The IP was discontinued. In the opinion of the investigator, the UC was related to the IP.

*Reviewer Comment: I agree with the investigator, it is likely that the IP contributed to this event.*

*Reviewer Comment Regarding Inflammatory Bowel Disease*

*It appears possible given the cases presented above that the use of Ixe may exacerbate or result in new onset of IBD. This issue has been seen with another IL-17A antagonist secukinumab. The proposed labeling for Ixe adequately addresses this issue. See Section 8.5.8 **Analysis of Submission Specific Safety Issues**; subsection **Autoimmune Disease: Crohn's disease and Ulcerative Colitis (UC)** for further discussion of this topic.*

See Attachment A at the end of this document for Narratives 4: Representative cases of SAEs – Miscellaneous.

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

**Table 31: Disposition for Induction Period**

*Disposition Events by Arm for All Subjects*

NDA/BLA 125521  
Study: Induction  
Analysis run date: 2015-06-01 12:18:53 AM

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Etanercept		Ixekizumab 80 mg Q2W		Ixekizumab 80 mg Q4W		Placebo	
			Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Protocol Milestone	Randomization 1	Randomized	740	100.0	1169	100.0	1165	100.0	792	100.0
	Randomization 2	Randomized	333	45.0	757	64.8	736	63.2	565	71.3
	Study	Informed Consent Obtained	740	100.0	1169	100.0	1165	100.0	792	100.0
Disposition Event	Subject Summary - Treatment Discontinuation	Adverse Event	10	1.4	25	2.1	24	2.1	9	1.1
		Subject Decision	11	1.5	11	0.9	16	1.4	12	1.5
		Protocol Violation	7	0.9	9	0.8	19	1.6	6	0.8
		Lack Of Efficacy	4	0.5	1	0.1	4	0.3	10	1.3
		Lost To Follow Up	7	0.9	2	0.2	4	0.3	5	0.6
		Investigator Decision	2	0.3	4	0.3	2	0.2	2	0.3
		Sponsor Decision	0	0.0	1	0.1	1	0.1	1	0.1
Other Event	Supplemental	Informed Consent Obtained	43	5.8	82	7.0	79	6.8	59	7.4

Source: : Created by reviewer using SDTM datasets on 6/1/2015: DS (DSDECOD, DSCAT and DSSCAT, EPOCH=INDUCTION) EX and DM (ACTARM=TRTA)

*Reviewer Comment: There was a higher rate of discontinuations due to Adverse Events in the Ixe arms (2.1%) versus the placebo arm (1.1) during the induction period but it was not a statistically significant finding.*

The most common AEs leading to discontinuation in the induction period are presented in the table below

**Table 32: AEs Leading to Discontinuations, Induction Period, Pool#1**

**Table APP.2.7.4.41. Adverse Events Leading to Discontinuation of Study Drug (Including Death), MedDRA Preferred Term by Decreasing Frequency Induction Dosing Period Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)**

Preferred term	PBO (N=791) n (%)	IXE80Q4W (N=1161) n (%)	IXE80Q2W (N=1167) n (%)	Total IXE (N=2328) n (%)	Total (N=3119) n (%)
Patients with >=1 AE Leading to Discontinuation of Study Drug (Including Death)	9 ( 1.1%)	24 ( 2.1%)	25 ( 2.1%)	49 ( 2.1%)	58 ( 1.9%)
Injection site reaction	0	0	4 ( 0.3%)	4 ( 0.2%)	4 ( 0.1%)
Appendicitis	0	0	2 ( 0.2%)	2 ( 0.1%)	2 ( 0.1%)
Aspartate aminotransferase increased	0	0	2 ( 0.2%)	2 ( 0.1%)	2 ( 0.1%)
Psoriasis	2 ( 0.3%)	1 ( 0.1%)	1 ( 0.1%)	2 ( 0.1%)	4 ( 0.1%)
Cellulitis	0	1 ( 0.1%)	1 ( 0.1%)	2 ( 0.1%)	2 ( 0.1%)
Crohn's disease	0	1 ( 0.1%)	1 ( 0.1%)	2 ( 0.1%)	2 ( 0.1%)
Diarrhoea	0	1 ( 0.1%)	1 ( 0.1%)	2 ( 0.1%)	2 ( 0.1%)
Ascites	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Colitis ulcerative	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Drug hypersensitivity	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Injection site erythema	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Malaise	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Nausea	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Oedema peripheral	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Osteomyelitis	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Sarcoidosis	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Stearorrhoea	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Subdural haematoma	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Suicide attempt	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)
Urticaria	0	0	1 ( 0.1%)	1 ( 0.0%)	1 ( 0.0%)

Notes: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients with at least one adverse event in the specified category; AE = adverse event. See complete footnote on last page of the output.

Dataset: home/lillyce/prd/ly2439821/integrations/ps\_submission/data/adam/adslp, adaep  
Program: home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/t\_aedispt\_safety\_i\_ppc.sas  
Output: home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/tf1\_output/t\_aedispt\_safety\_i\_ppc.rtf

Source: Applicant's Summary-clin-safety-app pg. 1149/8171

*Reviewer Comment: Injection site reaction was the most common AE leading to discontinuation which occurred in 4 subjects in the Ixe Q2W arm. This is an expected adverse event during the induction phase of a trial with a foreign biologic protein and is included in labeling. Appendicitis and increased AST occurred in 2 subjects each in the Ixe Q2W arm. The appendicitis is unexpected and could reflect some immunosuppressive effects of the IP. I investigated further and found a total of 7 cases of appendicitis in the Ixe arms across the trials (5 in psoriasis, 2 in RA subjects who were also on MTX). See Section 8.4.2 **Serious Adverse Events** under subsection **Infections** for summaries of the narratives on these cases and Section 8.5 **Analysis of Submission-Specific Safety Issues** for further discussion.*

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**Table 33: Disposition for Maintenance Period**

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Ixekizumab 80 mg Q12W		Ixekizumab 80 mg Q4W		Placebo	
			Subject Count	%	Subject Count	%	Subject Count	%
Protocol Milestone	Randomization 1	Randomized	410	100.0	416	100.0	403	100.0
	Randomization 2	Randomized	410	100.0	416	100.0	403	100.0
	Study	Informed Consent Obtained	410	100.0	416	100.0	403	100.0
Disposition Event	Subject Summary - Treatment Discontinuation	Adverse Event	19	4.6	11	2.6	12	3.0
		Subject Decision	6	1.5	6	1.4	10	2.5
		Lost To Follow Up	4	1.0	2	0.5	13	3.2
		Lack Of Efficacy	5	1.2	1	0.2	7	1.7
		Investigator Decision	2	0.5	3	0.7	2	0.5
		Protocol Violation	0	0.0	0	0.0	4	1.0
		Clinical Relapse	0	0.0	1	0.2	1	0.2
		Death	0	0.0	2	0.5	0	0.0
		Sponsor Decision	0	0.0	0	0.0	1	0.2
Other Event	Supplemental	Informed Consent Obtained	31	7.6	25	6.0	28	6.9

Source: : Created by reviewer using SDTM datasets on 6/4/2015: DS (DSDECOD, DSCAT and DSSCAT, EPOCH=MAINTENANCE) EX and DM (ACTARM=TRTA)

*Reviewer Comment: A similar percentage of subjects discontinued due to adverse events in the Ixe Q4W arm (2.6%) versus the placebo (3.0%). The rate was slightly higher for the Ixe Q12W arm (4.6%).*

The most common AEs leading to discontinuation in the maintenance period are presented in the table below

**Table 34: AEs Leading to Discontinuations, Maintenance Period**

Table APP.2.7.4.43. Adverse Events Leading to Discontinuation of Study Drug (Including Death), MedDRA Preferred Term by Decreasing Frequency Maintenance Dosing Period Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)

Preferred term	PBO (N=402) n (%)	IXE80Q12W (N=408) n (%)	IXE80Q4W (N=416) n (%)	Total IXE (N=824) n (%)	Total (N=1226) n (%)
Patients with >=1 AE Leading to Discontinuation of Study Drug (Including Death)	8 ( 2.0%)	9 ( 2.2%)	12 ( 2.9%)	21 ( 2.5%)	29 ( 2.4%)
Pregnancy *b	1 ( 0.7%)	0	1 ( 0.8%)	1 ( 0.4%)	2 ( 0.5%)
Tuberculin test positive	0	0	2 ( 0.5%)	2 ( 0.2%)	2 ( 0.2%)
Mycobacterium tuberculosis complex test positive	0	2 ( 0.5%)	0	2 ( 0.2%)	2 ( 0.2%)
Acute myocardial infarction	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Alcohol poisoning	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Death	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Dermatitis allergic	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
HIV infection	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Injection site reaction	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Interferon gamma release assay positive	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Latent tuberculosis	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Myocardial infarction	0	0	1 ( 0.2%)	1 ( 0.1%)	1 ( 0.1%)
Cholestasis	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)
Colitis ulcerative	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)
Encephalopathy	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)
Multiple sclerosis	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)
Otitis media	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)
Small intestine adenocarcinoma	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)
Suicide attempt	0	1 ( 0.2%)	0	1 ( 0.1%)	1 ( 0.1%)

Notes: PBO = Placebo; IXE80Q12W = Ixekizumab 80 mg Q12W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients with at least one adverse event in the specified category; AE = adverse event. See complete footnote on last page of the output.

Dataset: home/lilly/psr/prd/ly2439821/integrations/ps\_submission/data/adam/adslp, adaep  
Program: home/lilly/psr/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/t\_aedispt\_mpp\_m\_sas  
Output: home/lilly/psr/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/tf1\_output/t\_aedispt\_mpp\_m\_rtf

Source: Applicant’s Summary-clin-safety-app pg. 1163/8171

*Reviewer Comment: Two subjects in the Ixe arms discontinued due to “tuberculin test positive”, an additional two subjects in the Ixe arms discontinued due to “mycobacterium tuberculosis complex test positive”, a single subject in the Ixe arms discontinued due to “latent tuberculosis”, and a single subject in the Ixe arms discontinued due to “interferon gamma release assay positive”. These are all tests for either reactivation or new onset tuberculosis. Upon further investigation I found a total of 26 subjects who converted from negative on some form of testing for tuberculosis to positive during treatment with Ixe ( for the initial submission material). See page 66 section 8.4.2 **Serious Adverse Events** under subheading **Infections** for further discussion of this topic.*

#### 8.4.4. Significant Adverse Events

##### Grade 4 Neutropenia

Patient RHBC 126-2274

56 yo American Indian/Alaskan Native male treated with etanercept initially from 1/9/14

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through 7/8/13 was switched to lxe for the LTE period on 5/6/14. His baseline absolute neutrophil count (ANC) was low at  $1.79 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ) on 12/12/13. He developed a Grade 4 neutropenia ( $0.49 \times 10^9/L$ ) noted on 6/27/14 while receiving lxe 80 mg Q4W ( $\approx 6$  weeks of therapy) with no reports of infectious events. On subsequent testing, the ANC recovered to Grade 2 range (Visit 12:  $1.22 \times 10^9/L$ ) where it had been for the preceding Visits 6 & 7 (while on etanercept) and Visits 8 & 9 when receiving lxe 80 mg Q4W. This subject also experienced grade 3 thrombocytopenia (while on etanercept on 4/7/14).

*Reviewer Comment: It is not possible to r/o a contribution to this event from the IP. However, this subject had a low neutrophil count before treatment with any agent and did not experience any infections during this period.*

Patient RHBC 103-1704

Patient RHBC 103-1704 had Grade 4 neutropenia 14 days after starting lxe 80 mg Q4W in the induction period with no reports of infection or concomitant medication use. Baseline ANC was  $8.69 \times 10^9/L$ . Fourteen days after starting lxe, the ANC was  $0.48 \times 10^9/L$ . Two days later ANC was  $7.78 \times 10^9/L$  (had returned to normal). Subsequent ANCs remained within normal range until Day 588 of lxe 80 mg Q4W at which time patient had Grade 3 neutropenia (ANC of  $0.66 \times 10^9/L$ ) with no reports of infection. Three days later ANC was  $6.25 \times 10^9/L$  and remains within normal range (as per applicant) as the patient continues in the LTE Period.

*Reviewer Comment: Since this subject did not have 2 values in a row in the neutropenic range this was not considered an AE and no narrative with detail was provided. An update was requested from the applicant who informed DDDP that the subject is still ongoing in the study with no AEs or further decreased ANC.*

See Attachment A at the end of this document for Narratives 4: Cases of Grade 3 Neutropenia.

### Grade 3 Thrombocytopenia

RHBC-106-1256

34 yo white male was started on lxe 80 mg Q4W on 4/9/13. His baseline CBC was WNL including platelet (plt) count. On 7/8/13 he entered the LTE with a plt count WNL. On 8/25/14 (504 days of exposure) he developed Grade 3 thrombocytopenia with a plt count of  $47 \times 10^9/L$  (LLN  $140 \times 10^9/L$ ). On 8/27/14 (his last available visit) it decreased to  $44 \times 10^9/L$  (LLN  $140 \times 10^9/L$ ). The subject was discontinued from the study due to the low plt count. There were no recent AEs or concomitant medications at the time of this event.

*Reviewer Comment: The thrombocytopenia experienced by this subject was profound. I requested follow-up from the applicant and was informed that 2 months after discontinuing the IP the plt count was still abnormal at  $77 \times 10^9/L$  (LLN  $140 \times 10^9/L$ ). The site informed the*

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*applicant that the patient was asymptomatic at the last follow-up visit but was a frequent traveler and did not wish to be followed any longer at the site. Etiology of thrombocytopenia is unknown but felt to be possibly related to the study drug by the investigator. This is a worrisome case with persistence of the thrombocytopenia 2 months after discontinuing the Ixe. It is however, the only case of thrombocytopenia that persisted after discontinuing the investigational product. Proposed labeling includes the risk of neutropenia in section 6 but does not mention thrombocytopenia. I will watch for any evidence of further cases of persistent thrombocytopenia. Discussion is ongoing at the time of this review regarding inclusion of thrombocytopenia in labeling.*

**ALT and/ or AST ≥ 10X ULN**

Units for LFTs are U/L unless otherwise specified.

RHBC-102-1628

50 yo white female with psoriasis Rxed with MTX from 2007 through 2011 with a positive h/o alcohol use but no h/o liver disease was treated with Ixe 80mgQ4W starting on 9/11/13. She had been diagnosed with latent tuberculosis during screening and was treated with isoniazid from 7/24/13 through 12/4/13. Her screening tests for viral hepatitis were all negative. Her total bilirubin remained normal throughout her participation in the trail. Her other LFT's were as follows:

<b>Date</b>	<b>Rx</b>	<b>ALT (ULN=34)</b>	<b>AST (ULN=34)</b>	<b>GGT (ULN=49)</b>	<b>Alk Phos (ULN=123)</b>
8/28/13 (screening)		WNL	WNL	WNL	WNL
9/11/13 (baseline-labs prior to Rx)	Ixe 80mgQ4W	WNL	WNL	WNL	WNL
9/22/13- AE of mild headache Rxed with ibuprofen from 9/22 through 9/30/13					
9/25/13	Ixe 80mgQ4W	73	81	WNL	WNL
10/9/13*	Ixe 80mgQ4W	102*	93	WNL	WNL
11/6/13**	Ixe 80mgQ4W	228**	192**	?	WNL
11/19/13***	Ixe 80mgQ4W	403***	373***	50	138
12/4/13	Rx d/c'd	422***	319**	69	131
12/19/13	none	105*	82		
1/2/14		59	48	WNL	WNL

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\*ALT 3X ULN reported as moderate AE, \*\*ALT + AST ≥ 5X ULN, \*\*\*ALT + AST ≥ 10X ULN  
Source: Reviewer's table

*Reviewer Comment: This subject did experience elevation of her LFTs that developed shortly after she began treatment with the IP. The confounders include her treatment with isoniazid (though it is notable that her LFTs remained WNL for 6 weeks of Rx with isoniazid alone from 7/24/13 through 9/11/13) and ibuprofen. Based on the timing I think it is likely that the lxe did contribute to this event.*

RHAZ-153-03107

54 yo morbidly obese white male with psoriasis with a positive h/o alcohol use, DM and HTN but no h/o liver disease was treated with lxe 80mgQ2W starting on 5/29/12. His LFT's were as follows:

Date	Rx	ALT (ULN=43)	AST (ULN=36)	GGT (ULN=61)	Alk Phos (ULN=131)
5/29/12 (baseline-labs prior to Rx)	lxe 80mgQ2W	66	51	78	?
7/25/12- began Rx with felodipine for HTN					
8/21/12-began maintenance	lxe 80mgQ12W	WNL	WNL	WNL	WNL
11/13/12-relapse	lxe 80mgQ4W	WNL	WNL	WNL	WNL
7/25/13-began LTE period	lxe 80mgQ4W	47	WNL	WNL	WNL
10/3/13- mild URI Rxed levofloxacin, 3/6/14-abscess of limb+ URI-Rxed with azithromycin (3/9-3/13/14), ipratropium, salbutamol, ceftriaxone, clindamycin, acetaminophen-oxycodone(3/17/14), vancomycin (3/17-3/21/14) amoxicillin-clavulanate (3/22-4/4/14) and amoxicillin (3/29-5/8/14)					
3/31/14	lxe 80mgQ4W	WNL	WNL	WNL	WNL
6/17/14***# (750 days of exposure to lxe)	lxe 80mgQ4W	575***	482***	412	242
After 841 days of exposure to lxe	lxe 80mgQ4W	104	81	335	?
After 921 days of exposure to lxe	lxe 80mgQ4W	41	33	WNL	108
9/3/15	lxe 80mgQ4W	32	WNL	WNL	WNL

\*\*\*ALT + AST ≥ 10X ULN, #on 6/17/14 tbili=22 (ULN =21), direct bili=12 (ULN=7)

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Green highlights-information obtained from applicant in IR response dated 9/15/15

Source: Reviewer's Table

*Reviewer Comment: For some reason the LFT's >10X ULN were not reported as an adverse event. I requested follow-up information from the applicant. The data highlighted in green above was obtained. It would be unusual for drug-induced liver injury to manifest itself after the subject had been on treatment for so long (more than 2 years of exposure) and then resolve while still on therapy. I think it is unlikely that the IP contributed to this event.*

RHBA-664-08922

48 yo obese white male with psoriasis with a h/o MTX use from 1/2011 through 8/2012 on isoniazid (for latent TB, initiated on 1/18/13) as a concomitant medication but no h/o liver disease was treated with lxe 80mg Q2w starting on 3/20/13. He had an elevated aPTT at his screening [aPTT=33.9 sec (ULN=31 sec)] and baseline [aPTT=40.7 sec (ULN=31 sec)] visit. Baseline hepatitis screening revealed a positive Hep A Ab (IgM -). His LFT's are below:

Date	Rx	ALT (ULN=43)	AST (ULN=36)	GGT (ULN=49)	Alk Phos (ULN=123)
3/20/13 (baseline-labs prior to Rx)	lxe 80mgQ2W	46	WNL	WNL	WNL
3/26/13	lxe 80mgQ2W	WNL	WNL	WNL	WNL
4/2/13	lxe 80mgQ2W	48	WNL	WNL	WNL
4/16/13	lxe 80mgQ2W	65	37	WNL	WNL
6/11/13-began maintenance	lxe 80mgQ4W	47	WNL	WNL	WNL
8/5/13	lxe 80mgQ4W	WNL	WNL	WNL	WNL
10/23/13 – isoniazid therapy discontinued					
2/20/14 -reported as mild AE <sup>#</sup>	lxe 80mgQ4W	285**	742***	WNL	WNL
2/25/14 <sup>^</sup>	lxe 80mgQ4W	138*	114*	WNL	WNL
3/18/14 <sup>&amp;</sup>	lxe 80mgQ4W	WNL	WNL	WNL	WNL
5/15/14 <sup>&amp;</sup>	lxe 80mgQ4W	WNL	WNL	WNL	WNL

\*ALT + AST 3X ULN, \*\*ALT ≥ 5X ULN, \*\*\*AST ≥ 10X ULN, <sup>#</sup>CK=21128 (ULN=198), <sup>^</sup>CK=2618, <sup>&</sup>CK=571

Source: Reviewer's Table

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*Reviewer Comment: This subject did experience elevation of his LFTs that was brief and occurred after ~ 11 months of lxe treatment and resolved without discontinuing therapy. There was an associated elevation of CK simultaneously. That and the fact that the AST/ALT ratio was > 2 suggest the possibility of a muscle source for the elevated transaminases. The confounders include his obesity and treatment with isoniazid. His LFTs were mildly elevated at baseline on isoniazid before lxe was initiated. However, it is notable that he had been off the isoniazid for 3 months at the time of the event. It is not possible to r/o that the lxe did contribute to this event.*

RHAZ-153-03112

36 yo obese white female with psoriasis and bipolar disorder on concomitant meds carbamazepine (since 2008) and venlafaxine (since 2002) with a h/o etoh use but no h/o liver disease was started on lxe 80mg Q4W on 6/21/12. Her Hep screening tests were negative. Her baseline GGT was elevated and fluctuated above normal throughout the induction period. Her other LFTs are below

Date	Rx	ALT (ULN=34)	AST (ULN=36)	GGT (ULN=49)	Alk Phos (ULN=123)
6/21/12 (baseline-labs prior to Rx)	lxe 80mgQ4W	WNL	WNL	70	WNL
7/18/12	lxe 80mgQ4W	47	WNL	?	WNL
8/15/12	lxe 80mgQ4W	40	WNL	?	WNL
9/12/12-began maintenance	lxe 80mgQ4W	WNL	WNL	83	WNL
8/15/13- began LTE – continued lxe 80mgQ4W					
1/30/14	lxe 80mgQ4W	137*	53	151	WNL
2/18/14	lxe 80mgQ4W	51	WNL	79	WNL
7/16/14 –not reported as an AE (756 days of exposure to lxe)	lxe 80mgQ4W	359***	44	242	WNL
7/23/14	lxe 80mgQ4W	60	WNL	137	WNL
1002 days	lxe 80mgQ4W	18	?	?	?
6/18/15	lxe	15	?	?	?

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	80mgQ4W				
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\*ALT ≥ 3X ULN, \*\*\*ALT ≥ 10X ULN

Green highlights-information obtained from applicant in IR response dated 9/15/15

Source: Reviewer's Table

*Reviewer Comment: This subject had a brief but significant elevation of ALT against a background of chronic mildly elevated GGT. It is again unclear why this was not reported as an AE. I requested follow-up information and the data highlighted in green were obtained. Given that the subject's labs normalized while still on treatment it is unlikely that the IP contributed significantly to this event.*

RHBC-655-09421

32 yo obese female with psoriasis with a h/o cholelithiasis and etoh use on estradiol valerate and norethisterone (OCP) who was started lxe 80mgQ2W on 1/20/14. Her screening hepatitis tests were negative.

Date	Rx	ALT (ULN=31)	AST (ULN=31)	GGT (ULN=43)	Alk Phos (ULN=123)
1/20/14 (baseline-labs prior to Rx)	lxe 80mgQ2W	17 (WNL)	16 (WNL)	26 (WNL)	WNL
1/30/14 – done at a local lab^	lxe 80mgQ2W	672***	555***	373	WNL
1/31/14 – diagnosed with moderate AE of biliary colic (ultrasound showed hepatic stenosis and chronic cholecystitis), Rxed with papaverine-atropine from 1/31/14 to 2/20/14					
2/3/14 – reported as moderate AE	lxe 80mgQ2W	203*	WNL	266	WNL
(b) (6) – AE upgraded to severe as subject was hospitalized, lxe stopped on 3/27/14 (last dose actually on 2/6/14) and subject withdrew from trial, had surgery (date unknown) laparoscopic cholecystectomy					
4/14/14 – phone report from subject- “good condition”					

\*ALT 3X ULN, \*\*\*AST ≥ 10X ULN, ^total bilirubin=2.20

Source: Reviewer's Table

*Reviewer Comment: This subject had transaminase elevation secondary to biliary disease. It is unlikely that the lxe contributed to this event.*

RHAZ-135-02703

40 yo morbidly obese white male with psoriasis but no h/o liver disease was started on lxe 80mg Q2W on 1/30/12. His screening hepatitis tests were negative. The investigator stated that the event of elevated transaminases was caused by “too much exercise” but also stated it was possibly related to lxe. His LFTs are below:

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Date	Rx	ALT (ULN=43)	AST (ULN=36)	GGT (ULN=43)	Alk Phos (ULN=123)
1/30/12 (baseline-labs prior to Rx)	Ixe 80mgQ2W	WNL	WNL	WNL	WNL
2/5/12 ^-reported as AE	Ixe 80mgQ2W	192*	654***	WNL	WNL
2/19/12 <sup>&amp;</sup>	Ixe 80mgQ2W	218**	377***	WNL	WNL
2/14/12 <sup>#</sup> - Ixe discontinued	Ixe 80mgQ2W	72	WNL	WNL	WNL

\*ALT 3X ULN, \*\*ALT 5X ULN, \*\*\*AST ≥ 10X ULN, ^CK=36,950 (ULN=198), &CK=10,742, #CK=367  
Source: Reviewer's Table

*Reviewer Comment: This subject did experience elevation of his LFTs that was brief. There was an associated elevation of CK simultaneously. That and the fact that the AST/ALT ratio was > 2 suggest the possibility of a muscle source for the elevated transaminases. The confounders include his obesity. I think it unlikely that Ixe contributed to this event.*

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The applicant defined a TEAE as an event that first occurred or worsened in severity after baseline and on or before the date of the last visit within the treatment period. A common AE was defined as an event occurring in ≥1% of patients. The most frequently reported adverse events that occurred in the Induction dosing period are presented below by individual trial results:

**Table 35: Overview of Adverse Events, Induction Dosing Period by Individual Study (Studies RHAZ, RHBA, and RHBC)**

	<b>RHAZ</b> N=1296	<b>RHBA</b> N=1221	<b>RHBC</b> N=1341
Deaths, n (%)	0	0	0
Serious adverse events, n (%)	23 (1.8)	23 (1.9)	25 (1.9)
Patients with ≥1 TEAE, n (%)	731 (56.4)	720 (59.0)	677 (50.5)
<b>Most frequently reported TEAEs, n (%)</b>			
Nasopharyngitis	137 (10.6)	117 (9.6)	85 (6.3)
Upper respiratory tract infection	61 (4.7)	68 (5.6)	29 (2.2)
Injection site reaction	73 (5.6)	98 (8.0)	124 (9.2)
Injection site erythema	45 (3.5)	41 (3.4)	28 (2.1)
Arthralgia	22 (1.7)	29 (2.4)	34 (2.5)
Headache	49 (3.8)	58 (4.8)	48 (3.6)
Discontinuation due to adverse event, n (%)	26 (2.0)	17 (1.4)	23 (1.7)

Note: Most frequently reported TEAEs are those occurring in ≥3% of ixekizumab-treated patients (total IXE group) in at least 1 study.

Abbreviations: IXE = ixekizumab; N = number of patients; n = number of patients in the specified category; RHBA = IIF-MC-RHBA; RHBC = IIF-MC-RHBC; RHAZ = IIF-MC-RHAZ; TEAE = treatment-emergent adverse event.

Sources: t\_aesm\_safety\_i.rtf; t\_teaptsm\_safety\_i.rtf; t\_aedispt\_safety\_i.rtf for each study.

Source: Summary of Clinical Safety Page 50

*Reviewer Comment: The most common adverse events were fairly consistent across trials and were those that would be expected such as nasopharyngitis, URI and headache (which are common occurrences in all trials) and injection site reactions (common occurrence in trials of biologic proteins).*

The majority of the analyses will be performed on the pooled analysis sets #1 (pooled psoriasis placebo-controlled induction) and #3 (pooled psoriasis maintenance) as previously noted. See Section 8.2 **Review of the Safety Database** for discussion of methods. Unadjusted incidence was used as the primary means to assess AEs from the induction period because the treatment duration was the same (12 weeks) in each study and the rates of early discontinuation were low and similar across treatments. The maintenance study periods were longer (48 weeks), and duration of exposure varied markedly across treatments. Therefore, exposure-adjusted rates were the focus of maintenance period evaluations. This was the case for both the sponsor-performed analyses and those that I performed.

**Table 36: Summary of Adverse Events, Induction Dosing Period, Pool #1, Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)**

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

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

<sup>a</sup> Statistically significant compared with placebo.

<sup>b</sup> Statistically significant compared with ixekizumab 80 mg Q4W.

Source:

[home/lillyce/prd/ly2439821/integrations/ps\\_submission/programs\\_nonsdd/tfl\\_output/t\\_aesm\\_safety\\_i\\_ppc.rtf](home/lillyce/prd/ly2439821/integrations/ps_submission/programs_nonsdd/tfl_output/t_aesm_safety_i_ppc.rtf)

Source: Applicant's Summary of Clinical Safety Page 52

*Reviewer Comment: No deaths occurred in the induction period. The incidence of TEAEs was higher for the Ixe arms (58.4% for Ixe 80mg Q2 and 58.8 % for Ixe80mg Q4) then for placebo (46.8%). However, the majority of the TEAEs were of mild (Ixe 32.8% vs placebo 25.3%) or moderate severity (Ixe 22.5% vs placebo 18%). The incidence of severe AEs was similar in the Ixe (3.3%) and placebo (3.5%) arms. The incidence of serious AEs was similar in the Ixe (2.0%) and placebo (1.5%) arms. The incidence of discontinuations due to AE was numerically slighter higher for the combined Ixe treatment arms (Ixe 2.1% vs placebo 1.1%) but the difference was not statistically significant.*

The most common TEAEs in ≥ 1% of patients in the total Ixe group are presented below by MedDRA preferred term for the induction dosing period for Pool #1.

**Table 37: TEAEs Occurring in ≥ 1% of Patients in the Total Ixe Group, MedDRA PT by Decreasing Frequency—Induction Dosing Period, Pool#1 (RHAZ, RHBA, and RHBC)**

Preferred Term	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)
Patients with ≥1 TEAE	370 (46.8%)	683 (58.8%) <sup>a</sup>	681 (58.4%) <sup>a</sup>	1364 (58.6%) <sup>a</sup>
Nasopharyngitis	69 (8.7%)	104 (9.0%)	111 (9.5%)	215 (9.2%)
Injection site reaction	9 (1.1%)	89 (7.7%) <sup>a</sup>	117 (10.0%) <sup>a,b</sup>	206 (8.8%) <sup>a</sup>
Headache	23 (2.9%)	50 (4.3%)	51 (4.4%)	101 (4.3%)
Upper respiratory tract infection	28 (3.5%)	45 (3.9%)	51 (4.4%)	96 (4.1%)
Injection site erythema	2 (0.3%)	32 (2.8%) <sup>a</sup>	52 (4.5%) <sup>a,b</sup>	84 (3.6%) <sup>a</sup>
Arthralgia	17 (2.1%)	22 (1.9%)	29 (2.5%)	51 (2.2%)
Pruritus	18 (2.3)	26 (2.2%)	20 (1.7%)	46 (2.0%)
Injection site pain	14 (1.8%)	17 (1.5%)	28 (2.4%)	45 (1.9%)
Diarrhoea	8 (1.0%)	18 (1.6%)	25 (2.1%)	43 (1.8%)
Fatigue	9 (1.1%)	20 (1.7%)	19 (1.6%)	39 (1.7%)
Nausea	5 (0.6%)	15 (1.3%)	23 (2.0%) <sup>a</sup>	38 (1.6%) <sup>a</sup>
Oropharyngeal pain	4 (0.5%)	20 (1.7%) <sup>a</sup>	16 (1.4%)	36 (1.5%) <sup>a</sup>
Blood creatine phosphokinase increased	10 (1.3%)	13 (1.1%)	19 (1.6%)	32 (1.4%)
Urinary tract infection	10 (1.3%)	19 (1.6%)	12 (1.0%)	31 (1.3%)
Cough	7 (0.9%)	14 (1.2%)	16 (1.4%)	30 (1.3%)
Back pain	9 (1.1%)	16 (1.4%)	14 (1.2%)	30 (1.3%)
Bronchitis	7 (0.9%)	15 (1.3%)	12 (1.0%)	27 (1.2%)
Psoriasis	24 (3.0%)	13 (1.1%) <sup>a</sup>	13 (1.1%) <sup>a</sup>	26 (1.1%) <sup>a</sup>
Sinusitis	6 (0.8%)	13 (1.1%)	11 (0.9%)	24 (1.0%)

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

<sup>a</sup> Statistically significant compared with placebo.

<sup>b</sup> Statistically significant comparison for ixekizumab 80 mg Q2W versus ixekizumab 80 mg Q4W.

Source:

home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/tfl\_output/t\_teae1pt\_safety\_i\_ppc.rtf

Source: Applicant's Summary of Clinical Safety Page 59

*Reviewer Comment: As is often seen in clinical trials, TEAEs such as nasopharyngitis, headache and URI are amongst the most commonly seen AEs. However the incidence did not differ significantly from that seen in placebo. Injection site reaction and injection site erythema were more commonly seen in the Ixe arms than in placebo and in fact were more frequent in the Q2 than the Q4 arm as would be expected. This is adequately addressed in labeling. The only other TEAEs seen with a statistically significantly greater frequency for Ixe than for placebo were nausea and oropharyngeal pain. These were low in incidence (1-2%). It is possible that oropharyngeal pain could represent a symptom related to low grade undiagnosed oropharyngeal candidiasis (which is seen more commonly in the Ixe arms). See Section 8.5.2*

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*Analysis of Submission-Specific Safety Issues subheading Infections for discussion of candidiasis.*

The clinical pharmacology reviewer noted:

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).

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... 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... 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.

The Applicant proposed to include the following table in Section 6.1, the **ADVERSE REACTIONS** section of labeling under the subheading **Clinical Trials Experience**

**Table 21: Adverse Reactions Reported by ≥ 1% of Patients with Plaque Psoriasis through Week 12 in the 3 Pivotal Trials**

Adverse Reactions	TALTZ		PLACEBO
	80 mg Q2W (N=1167) (n%)	(b) (4)	(N=791) (n%)
Injection site reactions	196 (16.8%)		26 (3.3%)
Upper respiratory tract infection <sup>a</sup>	163 (14.0%)		101 (12.8%)
Nausea	23 (2.0%)		5 (0.6%)
Oropharyngeal pain	16 (1.4%)		4 (0.5%)
Tinea infections	17 (1.5%)		1 (0.1%)

<sup>a</sup> Upper respiratory tract infection includes: nasopharyngitis and upper respiratory tract infection [Table 2.5.8.2](#)

Source: Applicant’s proposed labeling

*Reviewer Comment:* (b) (4)  
(b) (4) The information for etanercept (for US sites only where US sourced etanercept was used) was added.

The following table will be proposed to the applicant for inclusion in labeling. Labeling negotiations were ongoing at the time of this review.

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**Table 38: Adverse Reactions Occurring in  $\geq 1\%$  of TALTZ-treated Subjects with Plaque Psoriasis Through Week 12**

	<b>TALTZ 80 mg Q2W</b> <b>(N=1167) (n%)</b>	<b>Etanercept <sup>a</sup>(N=287)</b> <b>(n%)</b>	<b>Placebo</b> <b>(N=791) (n%)</b>
<b>Injection site reactions</b>	196 (17)	32 (11)	26 (3)
<b>Upper respiratory tract infection <sup>b</sup></b>	163 (14)	23 (8)	101 (13)
<b>Nausea</b>	23 (2)	1 (<1%)	5 (1)
<b>Tinea infections</b>	17 (2)	0	1 (<1%)

<sup>a</sup> U.S. approved etanercept

<sup>b</sup> Upper respiratory tract infection includes: nasopharyngitis and upper respiratory tract infection

Source: Reviewer's Table

The following text will be proposed as an addition to the labeling:

Active Comparator Trials



An overview of the exposure-adjusted Adverse Event rates for the maintenance period is presented below:

**Table 39: Summary of Exposure-Adjusted Adverse Events, Maintenance Dosing Period, Pool #3, Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)**

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

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

<sup>a</sup> Statistically significant compared with placebo.

Source: t\_aesmex\_mpp\_m\_m.rtf

Source: Applicant's Summary of Clinical Safety Page 55

*Reviewer Comment: Two deaths occurred in the maintenance period. See Section 8.4.1 Deaths for details. During the maintenance period the IR for TEAEs was actually higher for placebo than for the Ixe arms. As was the case for the induction period, the majority of the TEAEs were of mild or moderate severity with exposure-adjusted incidence rates in the 40's-50's per 100 patient-years range for both Ixe and placebo. The incidence rate per 100 patient-years of serious AEs was identical in the combined Ixe arm and the placebo arms (8.1). The incidence rate per 100 patient-years of discontinuations due to AE was higher for placebo arm (4.3) than for Ixe (3.5) but the difference was not statistically significant.*

The most common TEAEs in ≥ 1% of patients in the total Ixe group, exposure-adjusted are presented below by MedDRA preferred term for the maintenance dosing period for Pool #3.

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**Table 40: TEAEs Occurring in ≥1% of Patients in the Total Ixe Group, Exposure-Adjusted, MedDRA PT by Decreasing Frequency, Maintenance Dosing Period, Pool #3 (RHAZ and RHBA)**

Preferred term	Placebo N=402 n (IR)	80 mg Q12W N=408 n (IR)	80 mg Q4W N=416 n (IR)	Total IXE N=824 n (IR)
Total patient-years	184.1	269.5	326.7	596.2
Patients with ≥1 TEAE	231 (125.5)	294 (109.1)	320 (97.9)	614 (103.0)
Nasopharyngitis	46 (25.0)	66 (24.5)	82 (25.1)	148 (24.8)
Upper respiratory tract infection	31 (16.8)	38 (14.1)	38 (11.6)	76 (12.7)
Headache	11 (6.0)	24 (8.9)	19 (5.8)	43 (7.2)
Arthralgia	12 (6.5)	23 (8.5)	19 (5.8)	42 (7.0)
Injection site reaction	2 (1.1)	11 (4.1)	27 (8.3) <sup>a,b</sup>	38 (6.4) <sup>a</sup>
Sinusitis	10 (5.4)	16 (5.9)	15 (4.6)	31 (5.2)
Back pain	8 (4.3)	18 (6.7)	13 (4.0)	31 (5.2)
Influenza	6 (3.3)	14 (5.2)	13 (4.0)	27 (4.5)
Bronchitis	4 (2.2)	15 (5.6)	12 (3.7)	27 (4.5)
Urinary tract infection	7 (3.8)	8 (3.0)	15 (4.6)	23 (3.9)
Diarrhoea	12 (6.5)	9 (3.3)	11 (3.4)	20 (3.4)
Oropharyngeal pain	5 (2.7)	8 (3.0)	11 (3.4)	19 (3.2)
Pharyngitis	6 (3.3)	11 (4.1)	8 (2.4)	19 (3.2)
Hypertension	6 (3.3)	10 (3.7)	8 (2.4)	18 (3.0)
Blood creatine phosphokinase increased	4 (2.2)	8 (3.0)	8 (2.4)	16 (2.7)
Injection site erythema	2 (1.1)	7 (2.6)	8 (2.4)	15 (2.5)
Gastroenteritis	9 (4.9)	8 (3.0)	7 (2.1)	15 (2.5)
Psoriasis	9 (4.9)	10 (3.7)	5 (1.5)	15 (2.5)
Tinea pedis	1 (0.5)	5 (1.9)	9 (2.8)	14 (2.3)
Pruritus	5 (2.7)	6 (2.2)	8 (2.4)	14 (2.3)
Rhinitis	2 (1.1)	9 (3.3)	5 (1.5)	14 (2.3)
Folliculitis	2 (1.1)	5 (1.9)	8 (2.4)	13 (2.2)
Seasonal allergy	1 (0.5)	5 (1.9)	8 (2.4)	13 (2.2)
Abdominal pain upper	3 (1.6)	2 (0.7)	10 (3.1)	12 (2.0)
Pyrexia	2 (1.1)	4 (1.5)	8 (2.4)	12 (2.0)
Oral candidiasis	1 (0.5)	5 (1.9)	7 (2.1)	12 (2.0)
Cough	3 (1.6)	6 (2.2)	6 (1.8)	12 (2.0)
Toothache	2 (1.1)	6 (2.2)	6 (1.8)	12 (2.0)
Gastroenteritis viral	1 (0.5)	6 (2.2)	6 (1.8)	12 (2.0)
Fatigue	1 (0.5)	8 (3.0)	4 (1.2)	12 (2.0)
Pain in extremity	3 (1.6)	6 (2.2)	5 (1.5)	11 (1.8)

Preferred term	Placebo N=402 n (IR)	80 mg Q12W N=408 n (IR)	80 mg Q4W N=416 n (IR)	Total IXE N=824 n (IR)
Conjunctivitis	2 (1.1)	6 (2.2)	5 (1.5)	11 (1.8)
Myalgia	1 (0.5)	7 (2.6)	4 (1.2)	11 (1.8)
Gastroesophageal reflux disease	3 (1.6)	3 (1.1)	7 (2.1)	10 (1.7)
Otitis externa	0	3 (1.1)	7 (2.1)	10 (1.7)
Dermatitis contact	2 (1.1)	4 (1.5)	6 (1.8)	10 (1.7)
Tonsillitis	1 (0.5)	4 (1.5)	6 (1.8)	10 (1.7)
Contusion	0	5 (1.9)	5 (1.5)	10 (1.7)
Oral herpes	3 (1.6)	7 (2.6)	3 (0.9)	10 (1.7)
Vulvovaginal mycotic infection	0	1 (1.1)	2 (2.0)	3 (1.6)
Vomiting	8 (4.3)	5 (1.9)	4 (1.2)	9 (1.5)

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; AE = adverse event; IXE = ixekizumab; IR = ; MedDRA = Medical Dictionary for Regulatory Activities; N = ; n = patients with ≥1 event; OR = odds ratio; TEAE = treatment-emergent adverse event.

a Statistically significant compared with placebo and OR >1.

b Statistically significant comparison between ixekizumab 80 mg Q12W and ixekizumab 80 mg Q4W.

Source: t\_teasocsmex\_mpp\_m\_m.rtf

Source: Applicant's Summary of Clinical Safety Page 64

*Reviewer Comment: As was seen for the induction period, the majority of the TEAEs seen in the maintenance period did not differ significantly between the Ixe arms and the placebo once exposure-adjustment was performed. Some of the cases with a numerical difference that are notable and would be expected include injection site reaction, injection site erythema, tinea pedis, oral candidiasis and otitis externa (usually candidal in nature). See Section 8.5.2 **Analysis of Submission-Specific Safety Issues** subheading **Infections** for discussion of candidiasis. Only injection site reaction was statistically significant compared with placebo and had an OR > 1.*

#### 8.4.6. Laboratory Findings

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

#### Hematology

The Applicant has defined specific LLN for analysis of the Ixe data. These limits are generally consistent with various commonly accepted reference limits (CTCAE), with consideration of gender and age differences. The LLLN has been set for the following as: Leukocytes:

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LLN=4.0x10<sup>9</sup>/L, Neutrophils: LLN=2.0x10<sup>9</sup>/L, Lymphocytes: LLN=1.1x10<sup>9</sup>/L and Platelets: LLN=150x10<sup>9</sup>/L.

There was a significant difference in the percentage of patients meeting criteria for treatment emergent-low (TE-low) values for leukocytes, neutrophils and platelets for each of the Ixe groups compared with the placebo group for the induction period.

**Table 41: Significant Treatment-Emergent Abnormal High or Low Hematology Laboratory Values—Induction Dosing Period Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)**

Laboratory Value	TE High or Low*	Placebo N=791 n/Nx (%)	80 mg Q4W N=1161 n/Nx (%)	80 mg Q2W N=1167 n/Nx (%)	Total Ixe N=2328 n/Nx (%)
Neutrophils (10 <sup>9</sup> /L)	TE low	11/780 (1.4%)	52/1143 (4.5%) <sup>a,b</sup>	56/1148 (4.9%) <sup>a,b</sup>	108/2291 (4.7%) <sup>a,b</sup>
Neutrophils, segmented (10 <sup>9</sup> /L)	TE low	11/780 (1.4%)	52/1143 (4.5%) <sup>a,b</sup>	56/1148 (4.9%) <sup>a,b</sup>	108/2291 (4.7%) <sup>a,b</sup>
Leukocytes (10 <sup>9</sup> /L)	TE low	13/774 (1.7%)	39/1141 (3.4%) <sup>a</sup>	43/1149 (3.7%) <sup>a,b</sup>	82/2290 (3.6%) <sup>a,b</sup>
Platelets (10 <sup>9</sup> /L)	TE low	7/775 (0.9%)	25/1124 (2.2%) <sup>a,b</sup>	22/1148 (1.9%) <sup>a,b</sup>	47/2272 (2.1%) <sup>a,b</sup>
Lymphocyte subsets					
CD19 fraction	TE low	4/689 (0.6%)	13/1048 (1.2%) <sup>b</sup>	16/1050 (1.5%) <sup>b</sup>	29/2098 (1.4%) <sup>b</sup>
CD4/CD8 ratio	TE low	16/695 (2.3%)	9/1024 (0.9%)	22/1040 (2.1%) <sup>c,d</sup>	31/2064 (1.5%)
CD8 fraction	TE low	8/661 (1.2%)	28/967 (2.9%) <sup>a,b</sup>	27/1016 (2.7%) <sup>b</sup>	55/1983 (2.8%) <sup>a,b</sup>
MCV (fL)	TE low	0/777	3/1138 (0.3%)	7/1151 (0.6%) <sup>a,d</sup>	10/2289 (0.4%)

LY = Ixe; MCV = ery. mean corpuscular volume; N = number of patients in the analysis population; n = patients with ≥1 event; Nx = Number of evaluable patients; OR= odds ratio; TE = treatment-emergent; ULN = upper limit of normal.

a Statistically significant compared with placebo.

b Mantel Haenszel OR >2 versus placebo; the absolute count among LY-treated subjects is at least 4; and incidence >1%.

c Statistically significant comparison between Ixe 80 mg Q2W and Ixe 80 mg Q4W.

d OR ≥2 for Ixe 80 mg Q2W versus Ixe 80 mg Q4W.

Source: Applicant’s Summary of Clinical Safety pg.112

*Reviewer Comment: Potential risks based on the class of drug (anti-cytokine) for Ixe include cytopenias. This has been seen with other biologics including other IL-17A inhibitors such as secukinumab. The most meaningful of the cytopenias was seen in the neutrophil counts. There were 4.7% of subjects in the combined Ixe arm that experienced TE-low values for neutrophils vs 1.4% of placebo subjects during the induction period in Pool #1. However, the majority of subjects experienced only grade 1 (76%) or 2 (26%) changes (on CTCAE grade system) in neutrophil counts. The majority of these subjects reverted to normal by the end of the induction period without any change in treatment. There were 3 cases of high grade (≥Grade 3)*

neutropenia, all of which were transient. One case reported as Grade 4 in Ixe Q4W had normal neutrophil count 1 week prior to this report and 48 hours after the report with no associated infection. The Applicant proposes that the low leukocyte counts were predominantly driven by the low neutrophil counts and I agree with this assumption based on evaluation of the findings. The changes in platelet counts were for the most part mild, only three subjects experienced thrombocytopenia with a count below 75,000; two subjects on Ixe and one on placebo. No events of bleeding were associated with low platelet counts. No SAEs or discontinuations due to cytopenias were reported. See Section 8.4.4 **Significant Adverse Events** for the narratives for subjects experiencing grade 3 cytopenias and Section 8.5.3. **Analysis of Submission-Specific Safety Issues** subheading **Cytopenias** for further discussion of this topic.

The findings for the maintenance dosing period are similar in nature (though even less notable in degree) than the changes seen in the induction dosing period. See table below for details:

**Table 42: Treatment-Emergent Abnormal Laboratory Values, Maintenance Dosing Period**

Maintenance Dosing Period  
10:26 04FEB2015 (Maintenance Dosing Period Primary Population)  
PDPM Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)

Parameter (Unit) Category	PBO (N=402) n/Nx (%)	IXE80Q12W (N=408) n/Nx (%)	IXE80Q4W (N=416) n/Nx (%)	Total Ixe (N=824) n/Nx (%)	Total (N=1226) n/Nx (%)
<b>BLOOD Leukocytes (10<sup>9</sup>/L)</b>					
Abnormal	18/ 4.6%)	29/ 398 7.3%)	20/ 407 4.9%)	49/ 805 6.1%)	67/1200 5.6%)
Low	12/ 3.0%)	14/ 400 3.5%)	14/ 411 3.4%)	28/ 811 3.5%)	40/1206 3.3%)
High	6/ 1.5%) 400	15/ 402 3.7%)	6/ 411 1.5%)	21/ 813 2.6%)	27/1213 2.2%)
<b>BLOOD Neutrophils (10<sup>9</sup>/L)</b>					
Abnormal	19/ 4.9%)	34/ 397 8.6%)	32/ 405 7.9%)	66/ 802 8.2%)	85/1189 7.1%)
Low	12/ 3.1%)	16/ 400 4.0%)	19/ 409 4.6%)	35/ 809 4.3%)	47/1198 3.9%)
High	7/ 1.8%) 398	18/ 401 4.5%)	13/ 411 3.2%)	31/ 812 3.8%)	38/1210 3.1%)
<b>BLOOD Platelets (10<sup>9</sup>/L)</b>					
Abnormal	12/ 394 3.0%)	11/ 396 (2.8%)	9/ 405 ( 2.2%)	20/ 801 ( 2.5%)	32/1195 ( 2.7%)
Low	8/ 396 (2.0%)	5/ 398 (	6/ 410 ( 1.5%)	11/ 808 ( 1.4%)	19/1204 ( 1.6%)
High	4/ 397 (1.0%)	6/ 402 (1.5%)	3/ 408 ( 0.7%)	9/ 810 ( 1.1%)	13/1207 ( 1.1%)

Notes: n = number of patients for the named lab parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and N

Source: Applicant's Summary-Clin-Safety-App Pages 2942, 2944 (modified)

*Reviewer Comment: The placebo group experienced a higher incidence of TE-low platelet counts in the maintenance period (placebo 2% vs Ixe 1.4%). With regard to leukocyte counts the combined Ixe group was higher but the difference was small (Ixe 3.5% vs placebo 3%). For neutrophils the difference was more substantial (Ixe 4.3% vs placebo 3.1%). The proposed label*

includes reference to the fact that “neutropenia was observed in clinical trials”. I think this is adequate to convey the findings noted above.

Chemistry

An overview of significant treatment-emergent abnormally high or low chemistry laboratory values for the Primary Psoriasis Placebo-Controlled Integrated Analysis Set is presented below

**Table 43: Percentage of Patients with Notable Treatment-Emergent Abnormal High or Low Clinical Laboratory Values—Induction Dosing Period, Pool#1 (RHAZ, RHBA, and RHBC)**

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

Abbreviations: n = patients with ≥1 event; Nx = Number of evaluable patients; OR = odds ratio; TE = treatment-emergent; ULN = upper limit of normal.

<sup>a</sup> Statistically significant compared with placebo (p<.05) and OR>1.

<sup>b</sup> Mantel Haenszel OR >2 versus placebo; the absolute count among LY-treated subjects is at least 4; and incidence >1% for total Ixe group.

<sup>c</sup> Statistically significant comparison between Ixe 80 mg Q2W and Ixe 80 mg Q4W.

<sup>d</sup> OR ≥2 for Ixe 80 mg Q2W versus Ixe 80 mg Q4W.

Source: Applicant’s Summary of Clinical Safety Page 119

*Reviewer Comment: The statistically significant changes with regard to placebo included low alkaline phosphatase, high AST and high creatinine kinase (CK). The significance of the CK elevation is unclear. Further evaluation for hepatic parameters is presented in the table below.*

**Table 44: Change from Baseline in ALT, AST, Total Bili, Alk Phos, and GGT, Induction Period, Pool#1 (RHAZ, RHBA, and RHBC)**

Parameter	Placebo N=791	80 mg Q4W N=1161	80 mg Q2W N=1167	Total IXE N=2328
<b>Alanine aminotransferase</b>	n=787	n=1154	n=1164	n=2318
Mean baseline (IU/L)	30.3	30.3	30.1	30.2
LSMean change from baseline (SE)	-1.2 (0.55)	0.3 (0.44) <sup>a</sup>	0.0 (0.44)	0.2 (0.31) <sup>a</sup>
<b>Aspartate aminotransferase</b>	n=787	n=1153	n=1163	n=2316
Mean baseline (IU/L)	25.8	25.8	26.2	26.0
LSMean change from baseline (SE)	-0.5 (0.44)	0.3 (0.36)	-0.3 (0.35)	-0.0 (0.25)
<b>Total bilirubin (mg/dL)</b>	n=784	n=1145	n=1155	n=2300
Mean baseline	0.56	0.54	0.53	0.54
LSMean change from baseline (SE)	-0.01 (0.007)	-0.00 (0.006)	0.01 (0.006) <sup>a</sup>	0.00 (0.004) <sup>a</sup>
<b>Alkaline phosphatase</b>	n=788	n=1155	n=1164	n=2319
Mean baseline (IU/L)	74.6	74.9	75.3	75.1
LSMean change from baseline (SE)	-0.6 (0.36)	-2.8 (0.29) <sup>b</sup>	-2.8 (0.29) <sup>b</sup>	-2.8 (0.20) <sup>b</sup>
<b>Gamma glutamyl transferase</b>	n=788	n=1155	n=1163	n=2318
Mean baseline (IU/L)	36.2	39.3	35.8	37.5
LSMean change from baseline (SE)	-1.4 (0.85)	-0.1 (0.69)	-0.2 (0.69)	-0.1 (0.49)

Abbreviations: LSMean = least squares mean; n = number of patients with baseline and post-baseline measurement; SE = standard error.

<sup>a</sup> p<.05 compared to placebo.

<sup>b</sup> p<.001 compared to

Source: Applicant's Summary of Clinical Safety Page 371

*Reviewer Comment: There were statistically significant increases from baseline versus placebo for ALT and total bilirubin (tbili) in the induction period. However the AST was not statistically significantly different than placebo. No patients in the Placebo-Primary Analysis Set met elevated hepatic criteria of maximum ALT ≥ 3xULN, maximum total bilirubin ≥2xULN, and ALP <2xULN (ie Hy's law). See Section 8.5.7 **Analysis of Submission-Specific Safety Issues** subheading **Hepatic** for further discussion of this topic.*

**Table 45: TE Abnormal, High or Low Laboratory Values at Any Time post- baseline, Maintenance Period, Pool#3 (RHAZ and RHBA)**

Parameter (Unit) Category	PBO (N=402) n/Nx (%)	IXE80Q12W (N=408) n/Nx (%)	IXE80Q4W (N=416) n/Nx (%)	Total IXE (N=824) n/Nx (%)	Total (N=1226) n/Nx (%)
<b>SERUM Alanine Aminotransferase (U/L)</b>					
Abnormal	60/ 326 (18.4%)	48/ 336 (14.3%)	83/ 344 (24.1%)	131/ 680 (19.3%)	191/1006 (19.0%)
Low	0/ 398	0/ 405	0/ 414	0/ 819	0/1217
High	60/ 327 (18.3%)	48/ 336 (14.3%)	83/ 345 (24.1%)	131/ 681 (19.2%)	191/1008 (18.9%)
<b>SERUM Alkaline Phosphatase (U/L)</b>					
Abnormal	5/ 386 ( 1.3%)	11/ 394 ( 2.8%)	13/ 409 ( 3.2%)	24/ 803 ( 3.0%)	29/1189 ( 2.4%)
Low	0/ 398	2/ 402 ( 0.5%)	2/ 412 ( 0.5%)	4/ 814 ( 0.5%)	4/1212 ( 0.3%)
High	5/ 388 ( 1.3%)	9/ 398 ( 2.3%)	11/ 412 ( 2.7%)	20/ 810 ( 2.5%)	25/1198 ( 2.1%)
<b>SERUM Aspartate Aminotransferase (U/L)</b>					
Abnormal	55/ 352 (15.6%)	41/ 356 (11.5%)	63/ 377 (16.7%)	104/ 733 (14.2%)	159/1085 (14.7%)
Low	4/ 398 (1.0%)	0/ 404	0/ 414	0/ 818	4/1216 (0.3%)
High	51/ 353 (14.4%)	41/ 356 (11.5%)	63/ 378 (16.7%)	104/ 734 (14.2%)	155/1087 (14.3%)
<b>SERUM Bilirubin (mmol/L)</b>					
Abnormal	47/ 382 (12.3%)	55/ 396 (13.9%)	51/ 398 (12.8%)	106/ 794 (13.4%)	153/1176 (13.0%)
Low	26/ 399 (6.5%)	40/ 405 (9.9%)	36/ 414 (8.7%)	76/ 819 (9.3%)	102/1218 (8.4%)
High	21/ 382 (5.5%)	15/ 396 (3.8%)	15/ 398 (3.8%)	30/ 794 (3.8%)	51/1176 (4.3%)

Notes: n = number of patients for the named lab parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and Nx.

Source: Applicant's Summary-Clin-Safety-App Page 2948, 2950 (modified)

*Reviewer Comment: There were no significant elevations of liver function tests compared with placebo for the maintenance period.*

#### 8.4.7. Vital Signs

Overall, vital signs remained stable throughout the induction and maintenance dosing periods. The table below displays the findings for the induction period.

**Table 46: Vital Signs (VS), TE-Low or High Values at Any Time Post-baseline, Induction Dosing Period, Pool#1 (RHAZ, RHBA, and RHBC)**

Parameter (Unit) Category	PBO (N=791) n/Nx (%)	IXE80Q4W (N=1161) n/Nx (%)	IXE80Q2W (N=1167) n/Nx (%)	Total IXE (N=2328) n/Nx (%)	Total (N=3119) n/Nx (%)
<b>Diastolic Blood Pressure (mmHg)</b>					
Low	3/ 788 ( 0.4%)	2/1157 ( 0.2%)	8/1164 ( 0.7%)	10/2321 ( 0.4%)	13/3109 ( 0.4%)
High	77/ 583 ( 13.2%)	99/ 873 ( 11.3%)	100/ 864 ( 11.6%)	199/1737 ( 11.5%)	276/2320 ( 11.9%)
<b>Pulse Rate (BEATS/MIN)</b>					
Low	4/ 781 ( 0.5%)	1/1151 ( 0.1%)	4/1143 ( 0.3%)	5/2294 ( 0.2%)	9/3075 ( 0.3%)
High	12/ 782 ( 1.5%)	22/1145 ( 1.9%)	11/1157 ( 1.0%)	33/2302 ( 1.4%)	45/3084 ( 1.5%)
<b>Systolic Blood Pressure (mmHg)</b>					
Low	3/ 787 ( 0.4%)	5/1153 ( 0.4%)	5/1161 ( 0.4%)	10/2314 ( 0.4%)	13/3101 ( 0.4%)
High	38/ 538 ( 7.1%)	42/ 809 ( 5.2%)	46/ 816 ( 5.6%)	88/1625 ( 5.4%)	126/2163 ( 5.8%)
<b>Weight (kg)</b>					
Low	13/ 772 ( 1.7%)	15/1135 ( 1.3%)	17/1154 ( 1.5%)	32/2289 ( 1.4%)	45/3061 ( 1.5%)
High	11/ 772 ( 1.4%)	26/1135 ( 2.3%)	21/1154 ( 1.8%)	47/2289 ( 2.1%)	58/3061 ( 1.9%)

Notes: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients for the named lab parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and Nx. See complete footnote on last page of the output.

Dataset: home/lillyce/prd/ly2439821/integrations/ps\_submission/data/adam/adslp\_advsp  
Program: home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/t\_tesm\_safety\_i\_ppc.sas  
Output: home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/tfl\_output/t\_tevssm\_safety\_i\_ppc.rtf

Notes: n = number of patients for the named vitals parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and Nx.

Vital Sign Measurement	Low	High
-----		
--- ----- Systolic BP		
(mmHg)	<= 90 and decrease >= 20	>= 140 and increase >= 20
Diastolic BP (mmHg)	<= 50 and decrease >= 10	>= 90 and increase >= 10
Pulse (bpm)	< 50 and decrease >= 15	> 100 and increase >= 15
Weight (kg)	Decrease from baseline >= 7%	Increase from baseline >= 7%

- [1] Mantel-Haenszel odds ratio. The denominator is Placebo (Ixe vs. placebo) and Ixe Q4W (high dose vs. low dose).
- [2] P-value from Cochran-Mantel-Haenszel (CMH) test stratified by study.
- [3] P-value from Breslow-Day test for homogeneity of odds ratios across studies.
- \*x: p-value (from CMH test) < 0.05 and OR > 1 (when OR is missing, incidence rate higher in Ixe (or IXE80Q2W) than in Placebo (or IXE80Q4W)).\*y: OR >= 2 and Ixe count >= 4.

Source: Applicant's summary-clin-safety-app Page 5075/8171 (modified)

The table below displays the findings for the maintenance period.

Clinical Review  
Jane Liedtka, MD  
BLA 125521  
Taltz (ixekizumab)

**Table 47: Vital Signs, TE- Low or High Values at Any Time Post-baseline, Maintenance Dosing Period, Pool#3, (RHAZ and RHBA)**

Parameter (Unit) Category	PBO (N=402) n/Nx (%)	IXE80Q12W (N=408) n/Nx (%)	IXE80Q4W (N=416) n/Nx (%)	Total IXE (N=824) n/Nx (%)	Total (N=1226) n/Nx (%)
<b>Diastolic Blood Pressure (mmHg)</b>					
Low	4/ 402 ( 1.0%)	8/ 406 ( 2.0%)	9/ 416 ( 2.2%)	17/ 822 ( 2.1%)	21/1224 ( 1.7%)
High	61/ 336 ( 18.2%)	75/ 353 ( 21.2%)	70/ 347 ( 20.2%)	145/ 700 ( 20.7%)	206/1036 ( 19.9%)
<b>Pulse Rate (BEATS/MIN)</b>					
Low	3/ 399 ( 0.8%)	3/ 401 ( 0.7%)	3/ 414 ( 0.7%)	6/ 815 ( 0.7%)	9/1214 ( 0.7%)
High	10/ 395 ( 2.5%)	12/ 407 ( 2.9%)	18/ 414 ( 4.3%)	30/ 821 ( 3.7%)	40/1216 ( 3.3%)
<b>Systolic Blood Pressure (mmHg)</b>					
Low	3/ 399 ( 0.8%)	7/ 406 ( 1.7%)	1/ 416 ( 0.2%)	8/ 822 ( 1.0%)	11/1221 ( 0.9%)
High	39/ 330 ( 11.8%)	55/ 331 ( 16.6%)	58/ 339 ( 17.1%)	113/ 670 ( 16.9%)	152/1000 ( 15.2%)
<b>Weight (kg)</b>					
Low	11/ 352 ( 3.1%)	13/ 383 ( 3.4%)	17/ 398 ( 4.3%)	30/ 781 ( 3.8%)	41/1133 ( 3.6%)
High	10/ 352 ( 2.8%)	17/ 383 ( 4.4%)	23/ 398 ( 5.8%)	40/ 781 ( 5.1%)	50/1133 ( 4.4%)

Notes: PBO = Placebo; IXE80Q12W = Ixekizumab 80 mg Q12W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients for the named lab parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and Nx. See complete footnote on last page of the output.

Dataset: home/lillyce/prd/ly2439821/integrations/ps\_submission/data/adam/adslp, advsp  
Program: home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/t\_team\_safety\_i\_ppc.sas  
Output: home/lillyce/prd/ly2439821/integrations/ps\_submission/programs\_nonsdd/tfl\_output/t\_tevssm\_mpp\_m\_m.rtf

Notes: n = number of patients for the named vitals parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and Nx.

Vital Sign Measurement	Low	High
-----		
--- Systolic BP		
(mmHg)	<= 90 and decrease >= 20	>= 140 and increase >= 20
Diastolic BP (mmHg)	<= 50 and decrease >= 10	>= 90 and increase >= 10
Pulse (bpm)	< 50 and decrease >= 15	> 100 and increase >= 15
Weight (kg)	Decrease from baseline >= 7%	Increase from baseline >= 7%

- [1] Mantel-Haenszel odds ratio. The denominator is Placebo (Ixe vs. placebo), Ixe Q12W (high dose vs. low dose).
- [2] P-value from Cochran-Mantel-Haenszel (CMH) test stratified by study.
- [3] P-value from Breslow-Day test for homogeneity of odds ratios across studies.

Source: Applicant's summary-clin-safety-app Page 5172/8171 (modified)

*Reviewer Comment: Analyses of treatment-emergent low (TE-low) or treatment-emergent high (TE-high) values for vital signs at any time post-baseline and of mean change from baseline for vital signs for the various integrated analysis sets did not reveal any signals of concern.*

#### 8.4.8. Electrocardiograms (ECGs)

The applicant submitted analyses for each of the 5 pooled analysis sets. The induction period ECG analysis is presented below for Pool #1.

**Table 48: ECG Intervals and Heart Rate(HR), TE- Low or High Values at Any Time Post-baseline, Induction Dosing Period, Pool #1 (RHAZ, RHBA, and RHBC)**

Parameter (Unit) Category	PBO (N=791) n/Nx (%)	IXE80Q4W (N=1161) n/Nx (%)	IXE80Q2W (N=1167) n/Nx (%)	Total IXE (N=2328) n/Nx (%)
<b>Heart Rate (BEATS/MIN)</b>				
Low	2/ 687 (0 . 3 %)	1/1016 (0 . 1 %)	2/1018 (0.2%)	3/2034 (0.1%)
High	4/ 716 (0 . 6 %)	2/1044 (0 . 2 %)	2/1053 (0.2%)	4/2097 (0.2%)
<b>QT Large Clinical Trial Population Based Correction (msec)</b>				
Low	0/ 690	0/1029	0/1022	0/2051
High	21/ 609 (3 . 4 %)	34/923 (3.7%)	32/ 903(3.5%)	66/1826(3.6%)
<b>QTcF - Fridericia's Correction Formula (msec)</b>				
Low	0/ 690	0/1029	0/1022	0/2051
High	16/ 648 (2 . 5 %)	9/983 (0.9%)	15/964 (1.6%)	24/1947(1.2%)
<b>Summary (Mean) PR Duration (msec)</b>				
Low	6/ 701 (0 . 9 %)	3/1035 (0.3%)	10/1035(1.0%)	13/2070(0.6%)
High	1/ 711 (0 . 1 %)	2/1034 (0.2%)	3/1048 (0.3%)	5/2082 (0.2%)
<b>Summary (Mean) QRS Duration (msec)</b>				
Low	0/ 721	0/1058	0/1066	0/2124
High	1/ 697 (0 . 1 %)	0/1034	3/1035 (0.3%)	3/2069 (0.1%)

n = number of patients for the named ecg parameter with at least one post baseline value in a given assessment category and for whom baseline value was not in the same assessment category; Nx = number of patients whose baseline result was not in the given assessment category and who provided a post baseline value. Percentages are based on n and Nx.

Percentages are based on n and Nx.

Criteria for Identifying Patients with Potentially Clinically Significant Changes in ECGs		
ECG Measurement	Low	High
Heart Rate (bpm)	Age >=18: <50 and decrease =15	Age >=18: >100 and increase =15
PR Interval (msec)	<120	>=220
QRS Interval (msec)	<60	>=120
QTcF (msec)	Male: <330 Female: <340	Age >=16: Male: >450 Age >=16: Female: >470
QTcLCTPB (msec)	Male: <330 Female: <340	Age <18: Male >444, Female >445 Age 18-25: Male >449, Female >455 Age 26-35: Male >438, Female >455 Age 36-45: Male >446, Female >459 Age 46-55: Male >452, Female >464 Age 56-65: Male >448, Female >469 Age > 65: Male >460, Female >465

Source: Applicant's Summary-clin-safety-app Page 5223/8171

The only significant ECG mean changes from baseline were greater mean increases in PR duration (ms) for Ixe 80 mg Q2W versus placebo and for Ixe 80 mg Q2W versus Ixe 80 mg Q4W. According to the applicant, however, the absolute mean difference was small and likely not clinically meaningful.

Clinical Review  
Jane Liedtka, MD  
BLA 125521  
Taltz (ixekizumab)

*Reviewer Comment: I agree with the applicant that these small changes are not likely to be clinically meaningful.*

There was also an analysis of the proportion of patients in each treatment group with elevated post-baseline QT and QTc values using several elevation cut-offs for the same population during the induction period which is presented below

**Table 49: QT and QTc Interval, Treatment-Emergent Increases at Any Time Post-baseline Induction Dosing Period, Pool #1 (RHAZ, RHBA, and RHBC)**

Table APP.2.7.4.126. QT and QTc Interval, Treatment-Emergent Increases at Any Time Postbaseline Induction Dosing Period  
Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)

Parameter (Unit) Category	PBO (N=791) n/Nx (%)	IXE80Q4W (N=1161) n/Nx (%)	IXE80Q2W (N=1167) n/Nx (%)	Total IXE (N=2328) n/Nx (%)	Total (N=3119) n/Nx (%)
<b>QTcF Interval (msec)</b>					
30 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
60 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
75 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
>500 msec	1/ 694 ( 0.1%)	0/1033	2/1034 ( 0.2%)	2/2067 ( 0.1%)	3/2761 ( 0.1%)
<b>QTcLCTPB</b>					
30 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
60 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
75 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
>500 msec	1/ 694 ( 0.1%)	0/1033	4/1034 ( 0.4%)	4/2067 ( 0.2%)	5/2761 ( 0.2%)
<b>Uncorrected QT</b>					
30 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
60 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
75 msec greater than maximum baseline value	0/ 690	0/1029	0/1022	0/2051	0/2741
>500 msec	3/ 694 ( 0.4%)	1/1033 ( 0.1%)	3/1034 ( 0.3%)	4/2067 ( 0.2%)	7/2761 ( 0.3%)

Source: Summary-Clin-Safety-App1 Pg 5237/8171

*Reviewer Comment: There was a significantly higher incidence of patients with elevated QTcLCTPB values >500 ms for Ixe 80 mg Q2W versus Ixe 80 mg Q4W (4 patients [0.4%] vs no patients), and, although not significant, there was a notable difference between Ixe 80 mg Q2W versus placebo. The clinical significance of this finding is unclear.*

#### 8.4.9. QT

A QT study was not requested of the applicant based on the following recommendation from the QT-IRT Team:

*“In our opinion, monoclonal antibodies do not need to be evaluated in a thorough clinical QT study because:*

- a. as large molecules, monoclonal antibodies cannot access the hERG pore via the intracellular side, which is the target site for most small-molecule QT-prolonging drugs; and*
- b. monoclonal antibodies can have off-target cardiac effects but QT prolongation has not been observed.”*

#### 8.4.10. Immunogenicity

From the draft labeling for Ixe:



The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to TALTZ with the incidences of antibodies to other products may be misleading.

#### 8.5. Analysis of Submission-Specific Safety Issues

Potential risks based on class of drug (anti-cytokine) and of the drug substance (foreign protein) were analyzed. Potential risks associated with immunomodulating biologic therapies may include infections, cytopenias, cardiovascular/cerebrovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity. The sponsor identified the following categories of adverse events as Adverse

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Events of Special Interest (AESI): Depression and Suicidality, Infections, Cytopenias, Allergic Reactions/Hypersensitivities including injection sites reactions, Cerebro-cardiovascular Events, Malignancies, Hepatic events, Autoimmune Disease: Crohn's and Ulcerative Colitis (UC) and Pneumocystis Pneumonia (PCP) and Interstitial Lung Disease (ILD). These will be discussed below in varying degrees of detail depending on the level to which this reviewer felt that these issues were of concern for this application. Appropriate cross-references to other sections of the review (such as SAEs, AEs leading to discontinuation etc.) for narratives and evaluation are included.

### 8.5.1. **Depression and Suicidality**

As was noted in Section 8.1 **Safety Review Approach**, a potential safety concern identified in phase 3 trials for another biologic agent that targets IL-17A, brodalumab (b) (4) was an increase in suicidal thoughts and behaviors. Because of concern about a class effect, an in depth evaluation of this adverse event of special interest was performed for Ixe. DDDP obtained a consult with the Division of Psychiatry Products (DPP) for help in assessing the Ixe development program with regard to this issue. A consult was also obtained from the Division of Epidemiology I (DEPI) to evaluate the results from a retrospective analysis of suicide behavior and ideation in ixekizumab clinical studies and to summarize available information on background suicide rates in psoriasis patients treated with systemic agents in clinical trials.

The evaluation of this issue is complicated by the fact that as previously mentioned in Section 2.1 **Therapeutic Context**, Subsection **Analysis of Condition**, the prevalence of suicidal ideation and depression in patients with psoriasis is higher than that reported in other medical conditions and in the general population.<sup>18</sup> In Sept of 2015 Cohen authored an article entitled "Psoriasis and the Risk of Depression in the US; Population National Health and Nutrition Examination Survey 2009-2012"<sup>19</sup> in which he stated

Fifty-eight (16.5%) patients with psoriasis met criteria for a diagnosis of major depression... Psoriasis was significantly associated with major depression, even after adjustment for sex, age, race, body mass index, physical activity, smoking history, alcohol use, history of myocardial infarction (MI), history of stroke, and history of diabetes mellitus (OR, 2.09 [95%CI, 1.41-3.11], P < .001).

The article referenced an extensive body of literature that supported this finding.

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<sup>18</sup> Kurd SK et al. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol. 2010; 146(8):891-895.

<sup>19</sup> Cohen BE et al. Psoriasis and the Risk of Depression in the US Population: National Health and Nutrition Examination Survey 2009-2012 JAMA Dermatology. Published online September 30, 2015.

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The Phase 3 pivotal clinical trials for Ixe excluded subjects with significant uncontrolled neuro-psychiatric disorder, subjects with a history of a suicide attempt, subjects who scored a 3 on Item 12 (thoughts of death or suicide) on the Quick Inventory of Depressive Symptoms-Subject Rated 16-item scale (QIDS) scale at screening or baseline and subjects who are clinically judged by the investigator to be at risk for suicide.

The sponsor provided an evaluation of depression and suicidality in their clinical development program that included QIDS evaluation and analysis of adverse events in the Depression/Suicidality MedDRA categories. For the pivotal Phase 3 trials, the QIDS was completed at screening, baseline and week 12 (end of the induction period), weeks 24, 36, 52 and 60 (end of maintenance period) and every 6 months thereafter in the long-term extension period. The QIDS includes 16 items rated from 0 to 3. The scoring ranges from 0-27, however not each individual item is scored. Overall depressive symptom severity for QIDS-SR16 total scores is: 0-5 (none), 6-10 (mild), 11-15 (moderate), 16-20 (severe), and 21-27 (very severe).

This scale includes a single item (Item 12 – thoughts of death or suicide) that assesses the presence of suicidal thoughts and behaviors. The responses include

- 0 I do not think of suicide or death
- 1 I feel that life is empty or wonder if it's worth living
- 2 I think of suicide or death several times a week for several minutes
- 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life

The initial psychiatric consultant stated the following in their review dated 8/25/15 in DARRTS;

The QIDS-SR16 is an acceptable rating scale for assessing depressive symptoms in subjects. However, the inclusion of only one item to assess suicidal thoughts and behaviors is not thought to be a comprehensive evaluation for these symptoms. While a rating of 0 would indicate a lack of suicidal thoughts or behaviors, ratings of 1 or 2 could indicate a significant presence of suicidal thoughts. It is unclear whether there was any further follow-up with patients who rated a 1 or 2 on Item 12 to further determine the presence of suicidal thoughts and behaviors.

At the midcycle meeting held on 8/14/15 the applicant was queried regarding follow-up for responses to item #12. The applicant responded with submission of SD#17 on 9/4/15 which stated the following:

From the beginning of a patient's participation in the clinical studies, investigators were expected to manage the treatment of any emerging patient

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safety concern. Patients who scored 2 or less on QIDS-SR16 Item 12 (“Thoughts of Death or Suicide”) were allowed to enter the study with no specific guidance from the sponsor to the investigator, except that, per protocol, a worsening of a patient’s score to 3 on Item 12 at any time during the study would prompt the investigator to take specific action: namely, the patient was to be evaluated at the investigative site for risk of suicide, and/or the patient was to be referred to a mental health provider for assessment. The patient was also to be discontinued from the study (per protocol discontinuation criteria) and enter the post-treatment follow-up period for a minimum of 12 weeks.

The clinical follow-up for patients who had a worsening to a score of 2 or less (whether reported as an AE or as a score higher than a previous assessment noted in database), was determined by the investigator’s medical judgment... The frequency of the follow-up evaluation was left to the discretion of the investigator.

#### Total Score for QIDS Analyses

The treatment groups were balanced with regard to baseline QIDS score as can be seen below for Pool #1 for the induction period.

**Table 50: Mean Baseline QIDS Total Score Induction Period, Pool #1, (RHAZ, RHBA, and RHBC)**

	<b>Placebo N=791</b>	<b>80 mg Q4W N=1161</b>	<b>80 mg Q2W N=1167</b>	<b>Total IXE N=2328</b>
n	789	1160	1165	2325
Mean Baseline (SD)	4.8 (4.31)	4.7 (4.21)	4.5 (3.95)	4.6 (4.08)

Note: QIDS-SR<sub>16</sub> total scores are categorized for severity of depression as follows: None: 0-5; Mild: 6-10; Moderate: 11-15; Severe: 16-20; Very severe: 21-27. Abbreviations: QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptoms-Self Report 16 Items; SD = standard deviation.

Source: Applicant’s Summary of Clinical Safety Pg 401

*Reviewer Comment: The mean QIDS total score for randomized patients was <5 which is categorized as ‘None’ or not depressed.*

In Pool#1, a significantly higher percentage of patients had a last observation QIDS total score of ‘None’ in each of the Ixe treatment groups (Ixe 80 mg Q4W: 78.8% [OR: 1.52], Ixe 80 mg Q2W: 83.6% [OR: 2.14], and total Ixe: 81.3% [OR: 1.78]) compared to placebo (70.8%) at the end of the induction dosing period.

The following table displays the maximum post-baseline score for the QIDS during the induction period for Pool#1

**Table 51: QIDS Total Score, Maximum Post-baseline Category, Induction Period, Pool#1 (RHAZ, RHBA, and RHBC)**

Category	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)	p-value
Nx	762	1123	1141	2264	
Improved	171 (22.4)	305 (27.2)	333 (29.2)	638 (28.2)	>0.999 <sup>a</sup>
Worsened	66 (8.7)	64 (5.7)	65 (5.7)	129 (5.7)	
Stayed the Same	525 (68.9)	754 (67.1)	743 (65.1)	1497 (66.1)	

Abbreviations: Nx = number of patients with a baseline and a post-baseline QIDS-SR<sub>16</sub> total score, n = number of patients within that treatment group and category

<sup>a</sup> p-Value from likelihood ratio Chi-square test.

Source: Applicant’s Summary of Clinical Safety Pg 403

*Reviewer Comment: There was no significant difference among treatment groups in distribution across categories for the QIDS total score maximum post-baseline observation during the induction period. In the lxe treatment groups, a numerically smaller percentage of patients worsened compared to placebo. A numerically larger percentage of patients improved in the lxe treatment groups compared to placebo for maximum post-baseline QIDS total score.*

As was the case with the induction period, in Pool#3 for the maintenance period, a significantly higher percentage of patients had a last observation QIDS total score of ‘none’ in each of the lxe treatment groups (lxe 80 mg Q12W: 83.8% [OR: 1.84], lxe 80 mg Q4W: 88.7% [OR: 2.83], and total lxe: 86.3% [OR: 2.25]) compared to placebo (75.9%). A significantly lower percentage of patients had a QIDS total score in the category of ‘mild’ in lxe 80 mg Q4W (8.3%) and total lxe (10.5%) treatment groups compared to placebo (17.6%). There were no significant differences between lxe and placebo treatment groups in QIDS total score for the categories of ‘moderate,’ ‘severe,’ and ‘very severe.’

As was the case with the induction period, in Pool#3 for the maintenance period, a numerically smaller percentage of patients in the lxe treatment groups worsened compared to placebo in maximum post-baseline QIDS total score (lxe 80 mg Q12W: 15.2%; lxe 80 mg Q4W: 12.8%; total lxe: 14.0%; placebo: 18.2%). The percentage of patients improving was similar across the treatment groups (lxe 80 mg Q12W: 6.8%; lxe 80 mg Q4W: 6.5%; total lxe: 6.7%; placebo: 7.1%).

*Reviewer Comment: These findings would suggest that for the induction and maintenance periods overall, there was not an increase in depression related to lxe treatment.*

Item #12 Analyses

The sponsor included analyses for suicidality by evaluating Item 12 of the QIDS categorically by comparing the percentage of patients categorized as improved, worsened or stayed the same for the induction and maintenance dosing period. In addition, suicide/self-injury AEs were analyzed in the ISS.

The majority of patients continued to endorse the same score on Item 12 from baseline to post-baseline (stayed the same) and the percentages were similar between treatment groups. A similar number of patients worsened, ≈1.5-2% across treatment groups.

**Table 52: QIDS-SR16 Item 12 – Thoughts of Death or Suicide, Maximum Post-baseline Induction Period, Pool #1 (RHAZ, RHBA, and RHBC)**

Category	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)	p-value
Nx	767	1129	1146	2275	
Improved	21 (2.7)	48 (4.3)	43 (3.8)	91 (4.0)	>0.999 <sup>a</sup>
Worsened	17 (2.2)	19 (1.7)	17 (1.5)	36 (1.6)	
Same	729 (95.0)	1062 (94.1)	1086 (94.8)	2148 (94.4)	

Abbreviations: LSMean = least square mean; Nx = number of patients with a baseline observation and a post-baseline observation; QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptoms-Self Report 16 Items.

<sup>a</sup> p-Value from likelihood ratio Chi-square test.

Source: Applicant’s Summary of Clinical Safety, Pg 404

In the equivalent analysis that was performed for the “active comparator” pool #2, a similar percentage of subjects worsened in the etanercept group (2.8%) as in the placebo group (2.6%) with a lesser percentage of subjects worsening in the Ixe groups (total Ixe=1.6%).

The psychiatric consultant noted

One limitation of this type of analysis is that the magnitude of the categorical shift cannot be evaluated. For example, if all patients receiving placebo had a baseline score of 0 that worsened to a score of 1 but all patients receiving IXE had a baseline score of 0 that worsened to a score of 3, this would be a potentially significant difference not evaluated in this particular analysis.

This issue was also addressed at the midcycle meeting and the sponsor response (SD#17) included tables displaying the magnitude of the change from baseline for item #12. There were 187 subjects on Ixe who reported a worsening of item #12, the majority (135 subjects-72%) went from a score of 0 to 1. A summary of these tables created by the statistical reviewer

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shows that the percentage of subjects with increases in score for item #12 during the induction and maintenance period was low.

**Table 53: Shifts from Baseline to Maximum Post-baseline Result for QIDS Item #12 Score, Induction Period (Pool#1) and Maintenance Period (Pool#3)**

**Table 1: Change in QIDS During Induction Period**

Change	TALTZ 80 mg		Placebo
	Q2W	Q4W	
1-point or 2-point increase	17/1146 (1.5%)	19/1129 (1.7%)	17/767 (2.2%)
2-point increase	1/1146 (0.1%)	6/1129 (0.5%)	0
1-point or 2-point decrease	43/1146 (3.7%)	48/1129 (4.3%)	21/767 (2.7%)
2-point decrease	4/1146 (0.3%)	2/1129 (0.2%)	3/767 (0.4%)

**Table 2: Change in QIDS During Maintenance Period**

Change	TALTZ 80 mg		Placebo
	Q4W	Q12W	
1-point or 2-point increase	6/399 (1.5%)	15/383 (3.9%)	9/351 (2.6%)
2-point increase	2/399 (0.5%)	5/383 (1.3%)	1/351 (0.3%)
1-point or 2-point decrease	10/399 (4.5%)	13/383 (3.4%)	12/351 (3.4%)
2-point decrease	1/399 (0.3%)	0	1/351 (0.3%)

Source: Statistical Reviewer's Table

*Reviewer Comment: The percentage of subjects that experienced a 2 point increase during the induction and the maintenance periods was higher for the Ixe groups compared with placebo group. This increase was seen in 7 subjects for each period. It is notable that a larger percentage of Ixe subjects improved their item 12 score (became less depressed) than was seen in the placebo group. The results of this analysis suggest that the risk of suicidality was not increased by Ixe during the induction or maintenance periods for the majority of subjects but does not exclude the possibility that for individual subjects an idiosyncratic increase in suicidal thoughts or behaviors could or did occur. See below discussion of suicide attempts seen in the Ixe development program.*

**Adverse Events Analyses**

**Overall Depression Related Adverse Events**

In Pool #1, the percentage of patients reporting at least 1 TEAE in the Depression (excluding suicide and self-injury) sub-SMQ during induction period was similar among treatment groups as presented below

**Table 54: Overview of TEAEs—Depression, MedDRA Preferred Term by Decreasing Frequency within SMQ, Induction Period for Pool #1 (RHAZ, RHBA, and RHBC)**

<b>SMQ or Sub-SMQ</b>	Placebo N=791	80 mg Q4W N=1161	80 mg Q2W N=1167	Total IXE N=2328
Term Type	n (%)	n (%)	n (%)	n (%)
Preferred Term				
<b>Depression excluding suicide/self-injury</b>	5 (0.6)	5 (0.4)	4 (0.3)	9 (0.4)
Narrow	5 (0.6)	4 (0.3)	4 (0.3)	8 (0.3)
Depression	4 (0.5)	4 (0.3)	4 (0.3)	8 (0.3)
Depressed mood	1 (0.1)	0	0	0 <sup>a</sup>
Broad				
Mood swings	0	1 (0.1)	0	1 (0.0)
<b>Suicide/self-injury</b>	0	1 (0.1)	1 (0.1)	2 (0.1)
Narrow				
Suicide attempt	0	1 (0.1)	1 (0.1)	2 (0.1)

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

Abbreviations: SMQ = Standard MedDRA Query; n=the number of patients with an event in that category.

<sup>a</sup> Statistically significantly (p<.05) different compared to placebo.

Source: Applicant’s Summary of Clinical Safety Pg 413

*Reviewer Comment: In Pool #1, a broad and narrow sub-SMQ search of depression excluding suicide/self-injury identified few patients with depression-related events (placebo: 0.6%; Ixe 80 mg Q4W: 0.4%; Ixe 80 mg Q2W: 0.3%) with no evidence of difference between Ixe and placebo treatment groups during the induction period.*

*It is notable that the rate of depression in the Ixe clinical trials is much lower than the rates reported in the literature for psoriasis patients in general or for psoriasis subjects in clinical trials. This is likely due to poor ascertainment in the Ixe clinical trials. There was no active assessment for depression aside from the previously described QIDS administration which was done at very infrequent intervals (with a 7 day period of recall) and therefore likely missed events.*

Based on the exposure-adjusted analysis in Pool #3, similar incidence rates (events per 100 patient-years) for depression-related events were reported for the Ixe 80-mg Q12W (1.1) treatment group, Ixe 80-mg Q4W treatment group (0.9), total Ixe group (1.0), and the placebo group (1.1) during the maintenance period. No significant differences were noted in the exposure-adjusted incidence rate of any event term.

#### Suicide Attempts

There were 10 suicide attempts in subjects on Ixe reported by the applicant in the Ixe development program. There was one suicide attempt in a placebo treated subject in trial

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RHAG during the post-treatment follow-up period and one report of suicidal ideation in an etanercept treated subject in trial RHBA during induction. No completed suicides occurred. See Section 8.4.2 **Serious Adverse Events** for narratives on these subjects as well as on subjects with depression severe enough to result in hospitalization. According to the applicant, in the pivotal trials, the incidences of depression and suicide/self-injury were low and did not differ between Ixe and placebo or etanercept (Per QIDS-SR16 or reported events).

*Reviewer Comment: The majority of the suicide attempts occurred outside the induction and maintenance periods. Therefore, the analyses performed by the sponsor (mostly limited to the induction and the maintenance periods) did not capture most of these events when comparing to placebo or etanercept.*

Suicide attempts were reported only in patients with multiple risk factors. Two of these patients had undisclosed history of past suicide attempts – a study exclusion criterion. Other risk factors in these patients included: depression and bipolar disorder, anxiety, alcohol or other substance use disorder, and the presence of major, acute psycho-social triggers.

Of the suicide attempts in subjects on Ixe, two occurred during induction (one in each Ixe arm at days 52 and 71 days), 1 occurred during maintenance in the Ixe Q12W arm (after 7 months exposure to Ixe), six occurred during the long term extension period (all after > 200 days of exposure to Ixe) and one was reported during the post-treatment follow-up period. One of the cases was initially categorized as suicidal ideation (RHBC-140-2855- case #10 under Section 8.4.2 **Serious Adverse Events**) in the initial BLA submission but was re-categorized as a suicide attempt after additional information regarding drug intake was discovered during the Columbia Classification Algorithm of Suicide Assessment (C-CASA) analysis that was requested by DDDP. The request for C-CASA retrospective analysis was sent on 6/24/15 and the response from the applicant was received on 8/6/15.

In my review of the SAEs I found two more cases that I think could represent suicide attempts- One is subject RHBA-405-06292 (case #5 under discussion of suicide attempts in Section 8.4.2 **Serious Adverse Events**) who cut his wrist while reportedly intoxicated after being back on Ixe for 4 months after relapse and one (Subject RHAZ-146-02910) who was hospitalized for methanol poisoning after 6 months of exposure to Ixe and was lost to follow-up after this event. In the response to information request submitted by the applicant on 8/6/15 which included the C-CASA retrospective analysis, Subject RHBA-405-06292 was acknowledged by the applicant to represent a 10<sup>th</sup> case of suicide attempt after re-evaluation by the C-CASA team.

The psychiatric consultant expressed concern in her initial consult “It is not clear that the sponsor has identified all potential cases of suicide/self- injury using the methods described to identify the cases”. She recommended a retrospective analysis be performed. DDDP had already requested this and when the results were submitted some additional questions were

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raised which were conveyed to the applicant during the mid-cycle meeting (See above discussion of follow-up for cases with worsening item #12 on QIDS and additional analyses of magnitude of change on item #12 of QIDS).

*Reviewer Comment:*

*My review of the C-CASA analysis reassured me that to the best of our ability all of the cases of possible suicide attempts have been captured. I reviewed the 39 narratives for cases with "not enough information" (code #9 in C-CASA analysis) and was convinced that none of them represented suicide attempts. It is not however possible to exclude that suicidal ideation may have been underestimated since the QIDS evaluation was performed only at infrequent intervals and no other direct inquiry for suicidal ideation (active assessment) was performed during the Ixe trials.*

In response to DDDP's specific questions the psychiatric consultant stated the following:

**1. Is there a signal for suicidality with ixekizumab use?**

It is difficult to definitively answer this question since it is not apparent that the sponsor has provided a comprehensive identification of potential suicide/self-injury adverse events cases. However, given this limitation, identification of nine cases of suicide attempt would suggest that IXE might be associated with suicidal thoughts and behaviors. Interpretation of these data is complex as there appears to be a significant background rate of depression and/or suicidal thoughts and behaviors in patients with psoriasis.

The sponsor cited data indicating that patients with psoriasis have a 39% increased risk of depression and the risk for depression increases with increasing severity with patients with severe psoriasis having a 72% increased risk of depression. The sponsor also cited published psoriasis clinical development programs having a prevalence of depression at baseline ranging from 14.6 to 40.3%. Regarding suicidality, the prevalence of suicidality reported in a population-based cohort study of 146,042 patients with mild psoriasis, 3956 patients with severe psoriasis and 766,950 patients without psoriasis (controls) was 0.71% in the mild psoriasis patients (vs. 0.39% in controls) and 1.01% in the severe psoriasis population (vs. 0.38% in controls). It is beyond the scope of this consult to review all epidemiological data regarding the risk of depression and suicidal thoughts and behaviors in patients with psoriasis and it is noted that DDDP has consulted DEPI for this assessment. It does appear, however, that there is a significant background rate for both depression and suicidal thoughts and behaviors in this population which can complicate the interpretation of data for a new drug treatment/intervention.

**2. If not, could it have been obscured by exclusion of subjects with a prior history of suicidality?**

It is not clear why subjects with any history of suicide attempts were excluded from these clinical trials. DDDP has stated that clinical development programs with other anti-IL-17A antibodies (e.g. brodalumab and secukinumab) have not had this exclusion criterion. In placebo-controlled clinical trials for major depressive disorder or bipolar I disorder, subjects with current suicidal ideation are excluded and subjects with a recent suicide attempt (e.g. within the past 3 months) are excluded. Exclusion of subjects with any history, however remote, of suicide attempt in the clinical development program for IXE may be overly conservative. It is not known whether inclusion of these subjects would impact the overall potential signal of suicidality associated with IXE.

**3. Would you recommend labeling for risk of suicidality?**

The finding of nine cases of suicide attempt in the clinical development program for IXE is of concern. It is also concerning that the identification of potential cases is incomplete and the rating scale used to prospectively assess suicidal thoughts and behaviors is not comprehensive. It is likely that further cases could be identified – e.g. suicidal ideation – that would be of additional concern from a safety perspective. However, it should also be acknowledged that there is a significant background rate of depression and suicidal thoughts and behaviors in patients with psoriasis.

DPP has been involved in the suicidal thoughts and behaviors safety signal for brodalumab. There has also been discussion as to whether this safety signal is a “class effect”. The brodalumab clinical development program included more rigorous prospective assessment of suicidal thoughts and behaviors (e.g. inclusion of eC-SSRS), such that it may be difficult to compare events between the brodalumab and IXE programs.

We note that DDDP has consulted with DEPI to review all epidemiological data regarding the risk of depression and suicidal thoughts and behaviors in patients with psoriasis. If this analysis confirms that the suicide attempt signal in the IXE program is in excess of the background rate, it would be appropriate to include these data in product labeling.

A second consult was requested from DPP to address the new information provided by the sponsor.

The follow-up DPP consult was received on Oct 9, 2015 and included the following comments:

Considering all 9 events that occurred during IXE treatment in any psoriasis trial, the exposure-adjusted reporting rate was 0.14/100 PEYs (9 events/6479.8 PEYs). This overall rate is consistent with the rates in the placebo-controlled studies mentioned above.

The timing of these events did not suggest any temporal association to IXE. The days on IXE at the time of the event were in a wide range (52 to 669 days) with a mean of 380 days, a median of 447 days, and a large standard deviation for the distribution of times to event (SD=221 days).

I examined each of the 39 narrative summaries of cases with a C-CASA classification of "not enough information." In no case did I judge that the event, as described, should have been classified as a suicidal event.

I examined shift tables which displayed the maximum QIDS-SR16 item #12 scores as a function of baseline score for the following study pools... My examination of these tables revealed no major differences between IXE treatment groups and placebo or the active comparator in terms of the proportions of patients with various magnitudes of change in this score. Data from the all IXE study database was comparable to findings from the other three study pools.

#### Conclusions and Recommendations

The sponsor has provided an adequate response to Dr. Alfaro's requests for clarification and additional information. This information yields no solid evidence that IXE treatment is associated with a significantly increased risk of suicidal thoughts or behaviors in the psoriasis patients studied. That said, there are two significant limitations to the available data:

##### 1) Potential for missed events

The QIDS-SR16, as used in these studies, is not an adequate instrument to monitor for the emergence of suicidal thinking or behavior. According to the study protocols, this self-rated instrument asks patients to rate their experience over the previous 7 days. Given that this instrument was rated relatively infrequently in these trials (e.g., at baseline, week 12, and week 24 in study RHAZ), there were huge time gaps in monitoring and, therefore, a large potential to miss suicidal events that occurred since the last visit but more than 7 days

prior to the rating. This difficulty is partially overcome by documentation of suicidal experiences as adverse events independent of the QIDS-SR16 ratings. However, it is not clear that any active solicitation of information regarding those adverse events was performed. Rather, it appears that monitoring for these events was passive and may have resulted in missing suicidal thoughts or behavior that were either not spontaneously recalled by the patient at the visit or were deliberately withheld from the investigator. The use of a scale such as the Columbia-Suicide Severity Rating Scale (C-SSRS), which actively solicits information about suicidal thoughts or behavior since the last visit, should be used in future trials.

2) Study populations may not reflect the target population

As mentioned by Dr. Alfaro, I too am concerned about the exclusion criteria for these trials which resulted in screening out patients with any history of a suicide attempt or any significant uncontrolled neuropsychiatric disorder. As documented in the literature, patients with psoriasis have an increased risk of depression and suicidal thoughts and behaviors. Thus, it can be expected that IXE, if approved, will be used in a number of patients with poorly controlled depression or a history of a suicide attempt. Because these patients were excluded from the clinical trials, it remains unknown whether the risk of suicidal events is increased as a result of IXE treatment in these patients. In addition, I would also note that the use of a highly select population, from a psychiatric perspective, casts a huge shadow of doubt over the sponsor's comparisons of the reporting rates of suicidal events in these trials with rates in the general psoriasis population unselected for psychiatric conditions. Future trials should allow these patients to enter the studies to permit us to reasonably gauge this risk.

In the end, the clinical trials data do not support a causal link between IXE therapy and suicidal events, in my judgment. But the above described deficiencies, which cannot be corrected at this stage, limit the ability to draw an inference regarding IXE and suicidal adverse events.

The consult result from the Division of Epidemiology I (DEPI) was received on 10/15/15 and included the following comments:

In the C-CASA analysis that included 4,209 ixekizumab treated patients, nine patients experienced suicide attempts during treatment (a rate of 0.14 per 100 patients-years), and one patient made a suicide attempt after treatment. No cases of completed suicides or suicide ideation were reported. There was an

imbalance between the ixekizumab and placebo groups, with all suicide behavior occurring in the ixekizumab treated subjects and none in the placebo group. The overall rate of suicide behavior (attempted and completed) for ixekizumab was the same as what was observed in brodalumab treated patients (0.14 per 100 patient-years). However, a key difference is that no completed suicides occurred for ixekizumab, whereas almost half of the suicide behavior events in brodalumab treated patients were completed suicides.

An evaluation of the rate of suicidality in clinical trials of other biologics for moderate to severe psoriasis was also conducted by DEPI. Suicidal behavior (attempts and completed combined) were highest for infliximab (0.24 per 100 patient-years) and apremilast (0.20 per 100 patient-years), a non-biologic for psoriasis that lists depression and suicidal thoughts in the Warning and Precautions section of the label. After omitting brodalumab and apremilast (due to their known suicide and depression safety signals), the pooled incidence rate of suicidality for all other psoriasis biologics was 0.04 per 100 patient-years, much lower than the incidence rate observed for ixekizumab.

In conclusion, data from the retrospective C-CASA analysis of ixekizumab and rates of suicidality in clinical studies of other psoriasis biologics, suggest a possible suicide safety signal for ixekizumab. Although the rate of suicidal behavior for ixekizumab was similar to the observed rate for brodalumab, and higher than the observed rates for most other psoriasis biologics, there were no completed suicides. Based on these findings, DEPI recommends that DDDP consider the potential safety signal for suicidal behavior in their decisions about safety related PMRs and post-marketing safety surveillance for ixekizumab.

*Reviewer Comment:*

*There was active discussion within the Agency involving DDDP, DPP, DEPI and OSE (DRISK, DPVI) regarding the most appropriate path forward to further evaluate this potential signal. See Section 8.10 **Integrated Assessment of Safety** under subheading **Issue Regarding Potential Safety Signal for Suicidal Behavior** for further discussion of this topic.*

### 8.5.2. Infections

IL-17 is thought to play an important role in host defense against extracellular pathogens, particularly the yeast *Candida albicans*.<sup>20</sup> Observations in humans with genetic defects affecting the Th17 pathway and in individuals who have genetic defects in IL-17 signaling

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<sup>20</sup> Peck A, Melins ED. Precarious Balance: TH17 cells in host defense. *Infect Immun.* 2010; 78(1):32-38.

(Hyper-Immunoglobulin E Syndrome, Job's Syndrome) suggest that blockade of IL-17 increases the risk for fungal infections, particularly mucocutaneous candidiasis, as well as staphylococcal skin infections (including abscesses).<sup>21</sup>

### Candidiasis

Complicating the analysis is the fact that underlying psoriasis is a risk factor for mucocutaneous candidiasis. In a case-control study of 200 patients, oral candidiasis was observed in 3% of patients compared with 0% of control patients.<sup>22</sup> In another case-control study of 280 patients, oral candidiasis was observed in 26% of patients with psoriasis compared to 0% among controls<sup>23</sup>.

Risk factors specific for mucocutaneous candidiasis include psoriasis, pregnancy or high-estrogen contraceptive pill, corticosteroid treatment (including topical corticosteroids), DM, immunosuppressive therapy, iron deficiency, general debility (e.g., cancer or malnutrition), obesity, local factors (heat, moisture, skin maceration), and extremes of age.

In trials of another IL-17A inhibitor secukinumab, mucocutaneous *Candida* infections, primarily oral candidiasis, were more frequent at the higher dose of secukinumab than with placebo in the first 12 weeks of the studies, with comparable rates between the lower secukinumab dose and placebo.

The following table displays the treatment emergent *Candida* infections in Pool #1 for the induction period:

**Table 55: Overview of TE Candida Infections, Exploratory Analysis, Pool #1**

Category/Preferred Term	PBO (N=791) n (%)	IXE80Q4W (N=1161) n (%)	IXE80Q2W (N=1167) n (%)	Total IXE (N=2328) n (%)
<b>Candida Infections</b>	4 (0.5%)	7 (0.6%)	16 (1.4%)	23 (1.0%)
Vulvovaginal mycotic infection <sup>a</sup>	1 (0.4%)	2 (0.5%)	2 (0.5%)	4 (0.5%)
Vulvovaginal candidiasis <sup>a</sup>	2 (0.9%)	3 (0.8%)	1 (0.2%)	4 (0.5%)
Oral candidiasis	0	2 (0.2%)	8 (0.7%)	10 (0.4%)

<sup>21</sup> Puel A et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011; 332(6025):65-68.

<sup>22</sup> Bedair AA et al. Oral *Candida* colonization and candidiasis in patients with psoriasis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(5):610-615.

<sup>23</sup> Picciani BL et al. Oral candidiasis in patients with psoriasis: correlation of oral examination and cytopathological evaluation with psoriasis disease severity and treatment. *J Am Acad Dermatol*. 2013; 68(6):986-991.

Skin candida	0	0	2 (0.2%)	2 (0.1%)
Oesophageal candidiasis	0	0	1 (0.1%)	1 (0.0%)
Oral fungal infection	0	0	1 (0.1%)	1 (0.0%)
Otitis externa candida	0	0	1 (0.1%)	1 (0.0%)
Intertrigo candida	1 (0.1%)	0	0	0

<sup>a</sup> Denominator adjusted because gender-specific event for females: N = 232 (Placebo), N = 374 (Ixe 80 mg Q4W), N = 401 (Ixe 80 mg Q2W).

Source: Applicant's Summary of Clinical Safety, Pg 187

*Reviewer Comment: There was a higher incidence of Candida infections in the Ixe Q2W arm versus the placebo arm for the induction period. The incidence in the Ixe Q4W arm was similar to placebo. None of these events were SAEs or led to discontinuation.*

The exposure-adjusted incidence for candida infections for both the induction and the maintenance periods is displayed below.

**Table 56: Exposure-Adjusted Incidence Rate of Candida Infection (Incidence per 100 Patient-Years) by Analysis Set**

Analysis Set	Analysis Sets for Induction Dosing Regimens								
	Primary Ps Placebo-Controlled				Ps Placebo- and Active-Controlled				
Treatment Group	PBO IR	IXE 80 Q4W IR	IXE 80 Q2W IR	Total IXE IR	PBO IR	ETN IR	IXE 80 Q4W IR	IXE 80 Q2W IR	Total IXE IR
<b>Total Patient-Years</b>	180.0	265.9	268.6	534.5	83.2	169.2	167.6	168.9	336.5
<b>Candida Infections</b>	2.2	2.6	6.0	4.3	2.4	3.0	2.4	7.1	4.8
Vulvovaginal mycotic infection*	1.9	2.3	2.2	2.3	4.2	1.9	1.9	3.3	2.7
Vulvovaginal candidiasis *	3.8	3.5	1.1	2.3	0	1.9	3.8	0	1.8
Oral candidiasis	0	0.8	3.0	1.9	0	0.6	0.6	3.0	1.8
Skin candida	0	0	0.7	0.4	0	0	0	1.2	0.6
Oesophageal candidiasis	0	0	0.4	0.2	0	0	0	0.6	0.3
Oral fungal infection	0	0	0.4	0.2	0	0	0	0.6	0.3
Otitis externa candida	0	0	0.4	0.2	0	0	0	0.6	0.3
Genital candidiasis	NR	NR	NR	NR	0	1.2	0	0	0
Intertrigo candida	0.6	0	0	0	1.2	0	0	0	0
Analysis Set	Analysis Sets Inclusive of Maintenance or Longer-Term Dosing								
	Ps Maintenance <sup>a</sup>				All Ps IXE Exposures				
Treatment Group	PBO IR	IXE 80 Q12W IR	IXE 80 Q4W IR	Total IXE IR	IXE (All Doses Pooled) IR				
<b>Total Patient-Years</b>	184.1	269.5	326.7	596.2	4729.7				
<b>Candida infections</b>	2.2	2.2	4.9	3.7	2.7				
Oral candidiasis	0.5	1.9	2.1	2.0	1.2				

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Vulvovaginal mycotic infection <sup>b</sup>	0	1.1	2.0	1.6	1.1
Vulvovaginal candidiasis <sup>b</sup>	1.6	0	1.0	0.5	1.5
Balanitis candida <sup>c</sup>	0	0.6	0.4	0.5	0.1
Skin candida	0.5	0	0.6	0.3	0.2
Oesophageal candidiasis	0.5	0	0.3	0.2	0.1
Intertrigo candida	0	0	0.3	0.2	0.1
Oral fungal infection	0	0	0.3	0.2	0.1
Oropharyngeal candidiasis	0	0	0.3	0.2	<0.1
<i>Candida</i> infection	NR	NR	NR	NR	0.3
Axillary candidiasis	NR	NR	NR	NR	<0.1
Otitis externa candida	NR	NR	NR	NR	<0.1
Nail candida	NR	NR	NR	NR	<0.1

Note: There were no statistically significant differences between treatment groups in any analysis set. Primary Maintenance Integrated Analysis Set: placebo PY=122.3, IXE80Q12W PY=180.6, IXE80Q4W PY=225.9. All Psoriasis Analysis Set: IXE PY=3212.7

a Maintenance Dosing Period Primary Population. b Denominator adjusted because gender-specific event for females. c Denominator adjusted because gender-specific event for males.

Source: Applicant's ISS pg. 189

*Reviewer Comment: The exposure-adjusted incidence rate for candida infections was higher for the Ixe higher dose arm versus placebo for both the induction and the maintenance treatment periods. The majority of cases of Candida infection were oral candidiasis. None of the Candida infection events reported were classified as SAEs, and no Candida infection events led to study discontinuation. The vast majority of events were mild to moderate in severity. Among the 128 patients who reported a Candida infection event, a total of 3 patients had an event classified as severe. A total of 6 patients had an esophageal candidiasis infection event. All subjects recovered without sequelae. The proposed labeling acknowledges an increased incidence of Candida infections in patients receiving Ixe.*

### Tuberculosis

No subjects developed active TB in the Ixe development program. As was noted in Section 8.4.2 **Serious Adverse Events**, there were 26 cases in the original BLA submission of subjects who converted from negative to positive on a TB test. A variety of tests were used including QuantiFERON Gold (14 subjects), T-spot (1 subject) and PPD (3 subjects). In an additional 8 subjects the "test" used was not specified. An additional 28 subjects were reported in the 4 month safety update who converted to positive on a test for TB.

Given these findings I would like to strengthen the warnings in the label regarding TB. The proposed label currently includes the following under (b) (4) **WARNINGS AND PRECAUTIONS**, subsection **Infections**

(b) (4)

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I recommend a separate subsection under **WARNINGS AND PRECAUTIONS** for the tuberculosis warning to read as follows:

#### Reactivation of Latent Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TALTZ. Consider anti-TB therapy prior to initiation of TALTZ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving TALTZ should be monitored closely for signs and symptoms of active TB during and after treatment.

This language is found in precedent labels (such as secukinumab) and reflects clinical trial design.

#### Appendicitis

##### *Reviewer Comment:*

*As was noted in Section 8.4.2 **Serious Adverse Events**, there were 7 cases of appendicitis in the Ixe arms (one of these, subject # RHBA-154-03815 may not have actually been appendicitis) and no cases in placebo. Two of the subjects were RA subjects in trial RHAK and were both on MTX (and one was also on prednisolone) so these subjects were clearly immunosuppressed aside from the Ixe therapy. If we look at just the psoriasis subjects and exclude the subject with a normal appendix on pathology, there were 4 cases out of 4204 subjects with psoriasis exposed to Ixe who developed appendicitis. The proposed labeling does include potential increased risk of infection under warnings and precautions.*

#### 8.5.3. **Cytopenias**

IL-17 is known to play a role in mobilizing neutrophils via release of neutrophil-specific chemokines.<sup>24</sup> There was no evidence of treatment-related cytopenias in the nonclinical toxicology studies in cynomolgus monkeys for Ixe but based on the role of IL-17 in neutrophil mobilization and the known effect of other biologic agents that are anti-cytokines, the development of cytopenias was carefully evaluated in the Ixe development program. See Section 8.4.6 **Laboratory Findings** for an overview of TE-low findings for hematology parameters for both the induction and maintenance periods and for a discussion of the significance of these findings. See Section 8.4.4 **Significant Adverse Events** and Attachment A at

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<sup>24</sup> Witowski et al. IL-17 stimulates intraperitoneal neutrophil infiltration through the release of GRO alpha chemokine from mesothelial cells. J Immunol. 2000; 165(10):5814-5821.

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the end of this document for representative narratives of subjects with grade 3 or higher cytopenias.

*Reviewer Comment:*

*As was noted in Section 8.4.6 **Laboratory Findings**, adverse events of cytopenias were infrequent, generally transient and did not lead to significant sequelae. No SAEs or discontinuations due to cytopenias were reported. Neutropenia is discussed in the proposed labeling.*

#### 8.5.4. Allergic Reactions/Hypersensitivities

As was noted in the introduction to this section, potential risks of a foreign protein such as Ixe may include administration or immune reactions, such as hypersensitivity, injection site /infusion reactions and immunogenicity. Immediate reactions, mediated by IgE are uncommon but may include severe reactions such as anaphylaxis which can be life-threatening. Delayed reactions are more common and usually manifest as exantheams or urticarial eruptions but can include reactions with systemic manifestations such as serum-sickness or vasculitis.

This reviewer has evaluated all of the narratives for potentially serious, life-threatening or severe allergic reactions. See Section 8.4.2 **Serious Adverse Events** for representative narratives for these occurrences. Two cases were labeled as anaphylaxis but on review of the narratives I believe that both represented serious allergic reactions with systemic manifestations without having the acute onset of effect and rapid progression that characterizes anaphylaxis. Two cases were labeled as angioedema but the first RHBA-162-03554 had unilateral eye swelling not consistent with angioedema and the second RHBA-205-04192 was related to a medication other than Ixe (Ixe was restarted without incident in this subject). In my opinion, none of these severe cases were life-threatening and the subjects recovered without sequelae. The issue of hypersensitivity reactions is well described and I think adequately covered in the proposed labeling which states under Section 5 **WARNINGS AND PRECAUTIONS** subsection (b) (4)

#### **Hypersensitivity**

Serious hypersensitivity reactions, including some cases of angioedema and urticaria, (b) (4)

(b) (4)

(b) (4) [see Adverse

Reactions (6.1)].

The incidence of allergic reaction/hypersensitivity reactions reported as AEs for the induction period for Pool#1 is presented in the table below:

**Table 57: Overview of Allergic Reaction/Hypersensitivity AEs, Induction Period, Pool #1**

Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)				
	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)
<b>Potential anaphylaxis (as Defined by Sampson criteria) and nonanaphylaxis TEAEs</b>	17 (2.1%)	46 (4.0%)	41 (3.5%)	87 (3.7%)
<b>Allergic reaction/Hypersensitivity SAEs</b>	1 (0.1%)	1 (0.1%)	3 (0.3%)	4 (0.2%)
<b>Discontinuations due to allergic reaction/hypersensitivity AEs</b>	0 (0%)	2 (0.2%)	2 (0.2%)	4 (0.2%)

Source: Applicant's Summary of Clinical Safety Page 243 (modified)

The applicant provided a table of the incidence of hypersensitivity reactions reported recently for other biologic agents approved for psoriasis which is reproduced below:

**Table 58: Hypersensitivity Reactions Reported in Patients Receiving Treatment with Other Immunomodulating Biologics**

Event	Rate	Source
<i>Adalimumab</i>	~1%	<a href="#">Humira® USPI</a>
Allergic reactions (overall)	3.5%	<a href="#">Puxeddu et al. 2012</a>
Hypersensitivity reaction		
<i>Etanercept</i> Hypersensitivity	1%	<a href="#">Enbrel® USPI</a>
Hypersensitivity reaction	5.3%	<a href="#">Puxeddu et al. 2012</a>
<i>Infliximab</i>	13.8%	<a href="#">Puxeddu et al. 2012</a>
Hypersensitivity reaction		
<i>Secukinumab</i>	4.5%	<a href="#">Secukinumab Ad Com BD</a>
Hypersensitivity <sup>a</sup> (narrow SMQ)		

Abbreviations: Ad Com BD = advisory committee briefing document; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; USPI = United States Prescribing Information.

<sup>a</sup> For secukinumab, the rate of hypersensitivity reactions (narrow SMQ) in the placebo group was 1.3%.

Source: Applicant's Summary of Clinical Safety Page 239

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*Reviewer Comment: I agree with the applicant that this provides a context for the evaluation of hypersensitivity reactions to Ixe. The incidence rate is comparable to other biologic products including the most recently approved secukinumab.*

In assessing exposure-adjusted rates for the induction period, the incidence rate of non-anaphylaxis events per 100 patient-years was 14.8 in the total Ixe treatment group compared to 8.3 in the placebo group (p=.042). For the maintenance period the rate of allergic reactions/hypersensitivity events was lower than for the induction period. The exposure-adjusted incident rate of non-anaphylaxis events per 100 patient-years was 7.9 in the total Ixe treatment group and 6.5 in the placebo group.

With regard to treatment-emergent-antidrug antibody –positivity (TE-ADA+), there were 29 patients with non-anaphylaxis allergic reactions/hypersensitivity events that were temporally associated with TE-ADA+. They included events of eczema, urticaria, contact dermatitis and allergic dermatitis. Only 2 events (both urticaria) were serious and 3 events led to study drug discontinuation. Some individual cases did appear to suggest a temporal relationship to ADA development. See Section 8.4.2 **Serious Adverse Events** for narratives.

### Injection Site Reactions

During the induction period injection site reactions (ISRs) occurred in 12.9% of subjects in the Ixe 80mgQ4w group, in 16.8% of subjects in the Ixe 80mgQ2W group and in 3.3% of subjects in the placebo group. These reactions included erythema, pain, bruising and swelling. The severity of the reactions was predominantly mild (70%) or moderate (27%) with only 3% being severe. A total of 6 subjects in Pool #1 discontinued Ixe due to ISRs during the induction period. There were 53% of subjects who reported a single ISR, 33.5% of subjects reported 2-3 events of ISR and 13% reported > 4 events of ISR. In the maintenance period the rates of ISR were lower with 8.9% of subjects in the Ixe 80mgQ4w group, in 5.1 % of subjects in the Ixe 80mgQ12W group and in 2 % of subjects in the placebo group.

*Reviewer Comment: This is similar to the rates seen with other biologics used for the treatment of moderate to severe psoriasis.*

### 8.5.5. **Cerebro-cardiovascular Events**

There is a higher incidence of cardiovascular risk factors such as DM, HTN, obesity, lipid abnormalities, smoking and a family history (FH) of cardiovascular disease (CVD) in psoriasis patients.<sup>25</sup> Multiple studies have suggested an increased risk of major atherosclerotic events

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<sup>25</sup> Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol. 2008; 159(4):895-902.

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such as MI and ischemic stroke in subjects with psoriasis.<sup>26</sup> In most studies, this association was strongest in those with severe disease and was increased even when controlling for traditional risk factors<sup>27</sup>. The applicant provided a table of incidence rates per 100 patient-years for cardiovascular events compiled from these studies which is provided below:

**Table 59: Incidence Rate of CV Events per 100 Patient-Years**

Country/Data Source	Time Period	Event	Incidence per 100 Patient-Years	Risk Factors Used for Adjustment	Source
UK: Electronic medical records database	1987-2002	MI	Mild psoriasis <sup>b</sup> : 0.40 Severe psoriasis <sup>c</sup> : 0.51	No adjustment	Gelfand et al. 2006a
UK: Electronic medical records database	1994-2005	MI	Newly diagnosed psoriasis: 0.16	No adjustment	Brauchli et al. 2009b
		Stroke	Newly diagnosed psoriasis: 0.17	No adjustment	
UK: Electronic medical records database	1987-2002	Stroke	Mild psoriasis <sup>b</sup> : 0.37 Severe psoriasis <sup>c</sup> : 0.61	No adjustment	Gelfand et al. 2009
UK: Electronic medical records database	1987-2002	CV death	Severe psoriasis <sup>c</sup> : 0.88	No adjustment	Mehta et al. 2010
UK: Electronic medical records database	2000-2010	MI	Early psoriasis <sup>d</sup> : 0.19	No adjustment	Primatesta et al. 2012
		Stroke	Early psoriasis <sup>d</sup> : 0.17	No adjustment	
Netherlands: National hospital and pharmacy records	1997-2008	Ischemic	Psoriasis requiring treatment or hospitalization for psoriasis: 0.61	No adjustment	Wakkee et al. 2010
United States: Administrative claims	2000-2008	MI	Phototherapy: 0.38 Traditional therapy: 0.64 Biologic therapy: 0.43	Age, sex, comorbid diagnoses of depression, hypertension, hyperlipidemia and	Abuabara et al. 2011
United States: Regional administrative claims	2004-2010	MI	TNF inhibitor treatment: 0.31 Oral/phototherapy treatment: 0.39 Topical treatment: 0.67 Overall: 0.52	No adjustment	Wu et al. 2012b
Denmark: Danish population records linked to biologic registry	2007-2009	CV death, MI, and stroke	Biologic therapy: 0.40 Methotrexate therapy: 0.68 Other therapies <sup>e</sup> : 2.22	Unknown	Ahlehoff et al. 2013
International psoriasis registry	2007-2012	CV death, MI, stroke	Psoriasis patients on systemic therapy: 0.36	No adjustment	Gottlieb et al. 2013

**Incidence Rate of CV Events per 100 Patient-Years**

Abbreviations: MI = myocardial infarction; TNF = tumor necrosis factor.

<sup>a</sup> Cardiovascular death defined as diagnoses consistent with MI, stroke, peripheral vascular disease, arrhythmia, or left ventricular thrombus entered on or very close to the entry of death.

<sup>b</sup> All patients with a first-time recorded diagnosis of psoriasis without the use of systemic therapy at any time point.

<sup>26</sup> Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. *J Am Heart Assoc.* 2013;2:e000062.

<sup>27</sup> Gelfand JM, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA.* 2006a;296(14):1735-1741.

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<sup>c</sup> All patients who received a code consistent with severe disease (eg, treatment with psoralen or phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea, or mycophenolate), as determined by the British National Formulary and the opinion of 2 dermatologists. During the time period that this study was conducted, biologic therapies were not approved for use for psoriasis in the UK.

<sup>d</sup> All patients with a first-time recorded diagnosis of psoriasis.

<sup>e</sup> Other therapies include retinoids, cyclosporine, phototherapy, and/ or climate therapy.

Source: Applicant's Summary of Clinical Safety, Page 310 (modified)

*Reviewer Comment: This table provides a helpful context for the following evaluation of incidence rates for MACE in the Ixe development program.*

According to the Applicant, in the Phase 3 studies (Studies RHAT, RHAZ, RHBA, RHBC, and RHBL) in patients with psoriasis, cardiovascular events were reported by investigators for adjudication according to criteria specified in the study protocols (based on the selected MedDRA PTs). An independent, external clinical events committee (CEC) [REDACTED] <sup>(b) (4)</sup> adjudicated all investigator-reported CV events according to criteria in the CEC Charter and in compliance with the Standard Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials<sup>28</sup>. The ATTC subset of CEC-confirmed events was prespecified for selected analyses because they more specifically reflect acute atherothrombotic complications (see PSAP). ATTC events included:

- Vascular death (including cardio-vascular and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system)
- Nonfatal MI
- Nonfatal stroke (ischemic, hemorrhagic, unknown stroke type).

The composite of ATTC events (from this point on in this document referred as "Major Adverse Cardiovascular Events or abbreviated as "MACE") was the basis of the primary analyses of the effect of Ixe on acute atherothrombotic complications. Non-MACE events in the CV category were also analyzed.

The following table displays the exposure-adjusted incidence rates for MACE for the induction and the maintenance periods.

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<sup>28</sup> Hicks KA, et al; on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized definitions for cardiovascular and stroke endpoint events in clinical trials. Draft definitions for [REDACTED] <sup>(b) (4)</sup> August 20, 2014.

**Table 60: Overview of TE MACE, Exposure-Adjusted Incidence Rate**

Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)				
	Placebo PY=180.0 n (IR)	80 mg Q4W PY=265.9 n (IR)	80 mg Q2W PY=268.6 n (IR)	Total IXE PY=534.5 n (IR)
<b>MACE</b>	1 (0.6)	2 (0.8)	0	2 (0.4)
Vascular death	0	0	0	0
Nonfatal MI	1 (0.6)	1 (0.4)	0	1 (0.2)
Nonfatal stroke	0	1 (0.4)	0	1 (0.2)

Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)				
	Placebo PY=184.1 n (IR)	80 mg Q12W PY=269.5 n (IR)	80 mg Q4W PY=326.7 n (IR)	Total IXE PY=596.2 n (IR)
<b>MACE</b>	1 (0.5)	0	3 (0.9)	3 (0.5)
Vascular death	0	0	2 (0.6)	2 (0.3)
Nonfatal MI	0	0	1 (0.3)	1 (0.2)
Nonfatal stroke	1 (0.5)	0	0	0

Source: Applicant’s Summary of Clinical Safety pg. 317 (modified)

The onset of MACEs from the start of treatment during the induction period was 72 days for the patient in the placebo group, and the median time to onset was 70 days for the 2 patients in the Ixe 80-mg Q4W treatment group. During the induction dosing period, all MACEs were reported as SAEs. Two patients with confirmed MI were discontinued from treatment: 1 patient in the Ixe 80-mg Q4W group (0.1%) and 1 patient in the etanercept group (0.1%).

The median time to onset of MACEs from the start of treatment during the maintenance period was 61.0 days for the 1 patient in the placebo group, and the median time to onset was 162.0 days for the 3 patients in the Ixe 80-mg Q4W treatment group. One patient with MI was discontinued from treatment in the Ixe 80-mg Q4W group (0.2%). There were 2 patients in the Ixe 80-mg Q4W group who discontinued due to vascular death (0.5%). See Section 8.4.1 **Deaths** for narratives on these subjects. See Section **8.4.2 Serious Adverse Events** and Attachment A at the end of this document for narratives on representative subjects with SAEs of MACE.

*Reviewer Comment: The exposure-adjusted incidence rates appear to be in line with what has been seen in other programs for biologics for moderate to severe psoriasis. According to the Applicant, in patients exposed to at least 1 dose of Ixe for any length of time (1 day up to 1591 days) and to any Ixe regimen (Ixe 80 mg Q12W, 80 mg Q4W, 80 mg Q2W or their sequential combinations), the overall exposure-adjusted incidence rate of adjudicated MACE was 0.72 per 100 patient-years (CI: 0.50 to 1.02). Even after including 2 MACEs reported outside of the database lock in the calculation, the overall MACE exposure-adjusted incidence rate (0.76 per*

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*100 patient-years [CI: 0.54 to 1.07]) is consistent with the exposure-adjusted incidence rate reported in clinical trials conducted with secukinumab, recently approved for the treatment of moderate-to-severe psoriasis. The exposure-adjusted incidence rate of MACE with Ixe is also consistent with the incidence rate of non-adjudicated CV events of MI and stroke reported for observational studies in a similar patient population. The evaluations and analyses performed by the applicant do not reveal evidence of an increased risk of MACE in subjects treated with Ixe over placebo. I agree with their analysis and conclusions.*

**Non-MACE cardiovascular events**

The following tables display information regarding the Non-MACE cardiovascular events that occurred in the induction and maintenance periods for Ixe:

**Table 61: Overview CEC-Confirmed TE Cardiovascular Events other than MACE—Unadjusted and Exposure-Adjusted Incidence Rate, Induction Period**

**Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)**

	Placebo N=791, PY=180.0 n (%) [IR]	80 mg Q4W N=1161 PY=265.9 n (%) [IR]	80 mg Q2W N=1167 PY=268.6 n (%) [IR]	Total IXE N=2328 PY=534.5 n (%) [IR]
Cardiogenic shock due to MI	0	0	0	0
Resuscitated cardiac death	0	0	0	0
Hospitalization due to UA	0	0	0	0
Coronary revascularization	1 (0.1%) [0.6]	1 (0.1%) [0.4]	0	1 (0.0%) [0.2]
Hospitalization due to HF	0	0	0	0
Hospitalization due to HPT	0	0	0	0
Peripheral arterial event	0	0	0	0
Peripheral revascularization	0	0	0	0
Serious arrhythmia	0	2 (0.2%) [0.8]	0	2 (0.1%) [0.4]

Source: Applicant’s Summary of Clinical Safety Page 345 (modified)

**Table 62: Overview CEC-Confirmed TE Cardiovascular Events other than MACE—Unadjusted and Exposure-Adjusted Incidence Rate, Maintenance Period**

<b>Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)</b>					
	Placebo N=402 PY =184.1 n (%) [IR]	80 mg Q12W N=408 PY =269.5 n (%) [IR]	80 mg Q4W N=416 PY =326.7 n (%) [IR]	Total IXE N=824 PY =596.2 n (%) [IR]	
Cardiogenic shock due to MI	0	0	0	0	
Resuscitated cardiac death	0	0	0	0	
Hospitalization due to UA	0	0	0	0	
Coronary revascularization	0	3 (0.7%) [1.1]	1 (0.2%) [0.3]	4 (0.5%) [0.7]	
Hospitalization due to HF	0	0	1 (0.2%) [0.3]	1 (0.1%) [0.2]	
Hospitalization due to HPT	0	0	0	0	
Peripheral arterial Event	0	0	0	0	
Peripheral revascularization	1 (0.2%) [0.5]	0	0	0	
Serious arrhythmia	1 (0.2%) [0.5]	0	0	0	

Source: Applicant’s Summary of Clinical Safety Page 346 (modified)

*Reviewer Comment: The absolute number of events was small. There does not appear to be a signal for any specific Non-MACE cardiovascular event in the Ixe development program.*

### 8.5.6. Malignancies

There were 46 patients in the All Psoriasis Ixe-Exposure Analysis Set (Pool#4) who experienced a malignancy or potential malignancy. Non-melanoma skin cancer (NMSC) comprised half of these cases with 16 basal cell carcinomas (BCCs) and 8 Squamous Cell carcinomas (SCCs). Of the 23 malignancies that were not NMSC, no predominant cell type was identified, and malignancy types for which more than 1 event was reported included prostate cancer (n=3), thyroid neoplasm (n=4), B-cell lymphoma (n=2), and colon cancer (n=2). In the All Psoriasis Ixe Analysis Set, the incidence rate of malignancy was 1.0 per 100 patient-years (0.5 per 100 patient-years for both NMSCs and malignancies excluding NMSCs).

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**Table 63: TEAEs – Malignancies, MedDRA Preferred Term by Decreasing Frequency within Category, Pool #4, All Ps Ixe Exposure Integrated Analysis Set**

Category Preferred Term (%)	Pooled Ixe (N=4204) n
Patients with >=1 TEAE - Malignancies	46 ( 1.1%)
Non-Melanoma Skin Cancer (NMSC)	23 ( 0.5%)
Basal Cell Carcinoma	16 ( 0.4%)
Basal cell carcinoma	16 ( 0.4%)
Basosquamous carcinoma	0
Basosquamous carcinoma of skin	0
Squamous Cell Carcinoma	8 ( 0.2%)
Squamous cell carcinoma of skin	7 ( 0.2%)
Bowen's disease	1 ( 0.0%)
Malignancies Excluding NMSC	23 (0 . 5 %)
Prostate cancer *a	3 ( 0.1%)
Thyroid neoplasm	4 ( 0.1%)
B-cell lymphoma	2 ( 0.0%)
Colon cancer	2 ( 0.0%)
Breast cancer	1 ( 0.0%)
Invasive ductal breast carcinoma	1 ( 0.0%)
Lung neoplasm malignant	1 ( 0.0%)
Metastatic neoplasm	1 ( 0.0%)
Non-small cell lung cancer metastatic	1 ( 0.0%)
Rectal adenocarcinoma	1 ( 0.0%)
Renal cell carcinoma	1 ( 0.0%)
Renal neoplasm	1 ( 0.0%)
Small intestine adenocarcinoma	1 ( 0.0%)
Squamous cell carcinoma of lung	1 ( 0.0%)

Notes: IXE = Ixe; N = number of patients in the analysis population; NMSC = non-melanoma skin cancer; n = number of patients with at least one treatment-emergent adverse event (TEAE) in the specified category; Percentage is calculated by n/N\*100%

\*a - Denominator adjusted because gender-specific event for males: N = 2846 (Pooled IXE).

Synovial sarcoma	1 (0.0%)
Thyroid cancer	1 (0.0%)
Tonsillar neoplasm	1 (0.0%)

Source: Applicant's summary-clin-safety-app Page 17436-37/18215.

*Reviewer Comment: The distribution of malignancies across body systems does not reveal any specific signal. The malignancies that occurred are common in the general population. The evaluation is complicated by the fact that there is evidence of a possible increase in the risk of cancer in psoriasis patients relative to the general population. Additional confounders include behavioral risk factors (high incidence of alcohol use, smoking and obesity in psoriasis patients)*

*as well as the past use of immunomodulatory agents to treat the disease. The relative risk has been estimated to be between 1.3<sup>29</sup> and 1.78<sup>30</sup> and the increase seems largely based on increases in NMSCs and lymphoproliferative malignancies. Margolis<sup>18</sup> found the risk increased with the severity of the disease (2.9% per 100 patient-years in severe disease vs 1.9% in subjects with less severe involvement). Brauchli<sup>31</sup> in examining a large UK database found an increased risk for lympho-hematopoietic and pancreatic cancers, but did not find a significant difference in the incidence of all cancers. See Section 8.4.2 **Serious Adverse Events** and Attachment A at the end of this document for some representative narratives for individual cases of subjects who developed malignancy.*

The incidence of malignancies was similar for placebo and Ixe during induction (0.3% each), which corresponds to an exposure-adjusted incidence of 1.1 per 100 patient-years in both groups. The exposure adjusted incidence rate (IR) for malignancy with NMSC excluded was 0.6 per 100 patient-years for both the Ixe and placebo groups. The exposure-adjusted incidence (by exposure-adjusted incidence rate per 100 patient-years) was 1.5 in the Ixe 80-mg Q12W group; 0.3 in the Ixe 80-mg Q4W group, and 0.5 in the placebo group. There were no significant differences between any treatment groups.

The incidence rate of malignancy (excluding NMSC) is also available from psoriasis treatment registries. The rate of malignancy reported after approximately 4 years of observation from the PSOLAR (31 818 total patient-years of follow up with 12 095 patients [95% CI: 0.59, 0.77]) was 0.68 events per 100 patient-years. The rates of malignancy (excluding NMSC) by treatment were reported as

- ustekinumab: 0.51 per 100 patient-years [95% CI: 0.37, 0.68]
- infliximab/golimumab (almost exclusively infliximab): 0.64 per 100 patient-years [95% CI: 0.42, 0.93]
- other biologics (almost exclusively etanercept and adalimumab): 0.74 per 100 patient-years [95% CI: 0.60, 0.91]; and
- non-biologic therapy 0.81 per 100 patient-years [95% CI: 0.59, 1.08].<sup>32</sup>

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<sup>29</sup> Hannuksela-Svahn et al. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol.* 2000;114(3):587-590.

<sup>30</sup> Margolis et al. The risk of malignancy associated with psoriasis. *Arch Dermatol.* 2001;137(6):778-783.

<sup>31</sup> Brauchli YB et al. Psoriasis and risk of incident cancer: an inception cohort study with a nested case-control analysis. *J Invest Dermatol.* 2009a; 129(11):2604-2612.

<sup>32</sup> Fiorentino et al. Malignancies in the psoriasis longitudinal assessment and registry (PSOLAR) study: current status of observations. *Exp Dermatol.* 2014; 23(Suppl 2):4.

### 8.5.7. Hepatic

Psoriasis patients have a higher risk of hepatic dysfunction due to the inflammatory nature of the disease and comorbidities associated with the disease such as diabetes, metabolic syndrome, obesity, and fatty liver which can lead to serious liver conditions. In the PSOLAR registry, which is a prospective 8-year, longitudinal, disease-based registry designed to collect safety, clinical outcome, quality of life, and comorbidity data from patients with psoriasis, patients are included who are receiving, or are eligible to receive, conventional systemic or biologic therapies. In a total of 11,900 patients (mean age: 48.6), hepatic disease was reported in 4.1% of patients.<sup>33</sup>

There was no evidence of treatment-related hepatic injury in the nonclinical toxicology studies in cynomolgus monkeys in the Ixe development program, including a 39-week repeat-dose toxicity study in which Ixe was administered weekly at doses up to 50 mg/kg.

Patients were excluded from enrollment for evidence of Hepatitis B or C from the pivotal phase 3 trials. In the original protocols for the Phase 3 trials, patients were to be discontinued from the study if they met any of the following criteria:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks;
- ALT or AST >3xULN and total bilirubin >2xULN or International Normalized Ratio >1.5
- ALT or AST >3xULN with concurrent appearance or worsening of, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, eosinophilia.

In 2012, protocols were amended; discontinuation of the Ixe for abnormal liver tests were to be considered by the investigator when a study patient met one of the above criteria, after consultation with the Lilly designated medical monitor.

An overview of significant treatment-emergent abnormally high or low chemistry laboratory values for the Primary Psoriasis Placebo-Controlled Integrated Analysis Set is presented in Section 8.4.6 **Laboratory Findings**. This is followed by a table of specific abnormal hepatic parameters. There were statistically significant increases from baseline versus placebo for ALT and total bilirubin (tbili) in the induction period. There were no statistically significant increases from baseline versus placebo for any liver function tests for the maintenance period.

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<sup>33</sup> Kimball AB et al. PSOLAR Steering Committee. Demography, baseline disease characteristics and treatment history of patients with psoriasis enrolled in a multi-center, prospective, disease-based registry (PSOLAR). *Br J Dermatol*. 2014a; 171(1):137-147.

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Looking at the hepatic enzymes in another way, the table below compares proportions of patients in each treatment group with elevated post-baseline hepatic values using several elevation cut-offs for each parameter in Pool #1.

**Table 64: Serum Alanine Aminotransferase (ALT) (U/L) Elevation, Abnormal Post-Baseline Categories, Induction Period, Pool#1 (RHAZ, RHBA and RHBC)**

Maximum Baseline Category	PBO (N=791) n/Nx(%)	IXE80Q4W (N=1161) n/Nx(%)	IXE80Q2W (N=1167) n/Nx(%)	Total IXE (N=2328) n/Nx(%)	Total (N=3119) n/Nx(%)
<b>Patients with Maximum Post Baseline &gt;= 3x ULN</b>					
Total*	7/ 787 ( 0.9%)	12/1154 ( 1.0%)	16/1164 ( 1.4%)	28/2318 ( 1.2%)	35/3105 ( 1.1%)
<=1x ULN	2/ 606 ( 0.3%)	2/ 860 ( 0.2%)	4/ 902 ( 0.4%)	6/1762 ( 0.3%)	8/2368 ( 0.3%)
>1 to <3x ULN	3/ 173 ( 1.7%)	4/ 286 ( 1.4%)	8/ 255 ( 3.1%)	12/ 541 ( 2.2%)	15/ 714 ( 2.1%)
>=3x ULN	2/ 8 (25.0%)	6/ 8 (75.0%)	4/ 7 (57.1%)	10/ 15 (66.7%)	12/ 23 (52.2%)
Missing	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
<b>Patients with Maximum Post Baseline &gt;= 5x ULN</b>					
Total*	1/ 787 ( 0.1%)	3/1154 ( 0.3%)	3/1164 ( 0.3%)	6/2318 ( 0.3%)	7/3105 ( 0.2%)
<=1x ULN	0/ 606	1/ 860 ( 0.1%)	2/ 902 ( 0.2%)	3/1762 ( 0.2%)	3/2368 ( 0.1%)
>1 to <3x ULN	1/ 173 ( 0.6%)	1/ 286 ( 0.3%)	0/ 255	1/ 541 ( 0.2%)	2/ 714 ( 0.3%)
>=3 to <5x ULN	0/ 7	0/ 7	1/ 6 (16.7%)	1/ 13 (7.7%)	1/ 20 (5.0%)
>=5x ULN	0/ 1	1/ 1 (100.0%)	0/ 1	1/ 2 (50.0%)	1/ 3 (33.3%)
Missing	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
<b>Patients with Maximum Post Baseline &gt;= 10x ULN</b>					
Total*	0/ 787	1/1154 ( 0.1%)	0/1164	1/2318 ( 0.0%)	1/3105 ( 0.0%)
<=1x ULN	0/ 606	1/ 860 ( 0.1%)	0/ 902	1/1762 ( 0.1%)	1/2368 ( 0.0%)
>1 to <3x ULN	0/ 173	0/ 286	0/ 255	0/ 541	0/ 714
>=3 to <5x ULN	0/ 7	0/ 7	0/ 6	0/ 13	0/ 20
>=5 to <10x ULN	0/ 1	0/ 1	0/ 1	0/ 2	0/ 3
>=10x ULN	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0

Notes: n = number of patients in the specified category; Nx = number of patients within each baseline category and have at least one post-baseline measure; Percentage is calculated by n/Nx\*100%; ULN = Upper limit normal from Covance reference limits; vs = versus.

Source: Applicant's Summary-Clin-Safety-App Pg 17567

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**Table 65: Serum Aspartate Aminotransferase (U/L)(AST ) Elevation, Abnormal Post-Baseline Categories, Induction Period, Pool#1 (RHAZ, RHBA and RHBC)**

Maximum Baseline Category	PBO (N=791) n/Nx(%)	IXE80Q4W (N=1161) n/Nx(%)	IXE80Q2W (N=1167) n/Nx(%)	Total IXE (N=2328) n/Nx(%)	Total (N=3119) n/Nx(%)
<b>Patients with Maximum Post Baseline &gt;= 3x ULN</b>					
Total*	7/ 787 ( 0.9%)	13/1154 (1.1%)	12/1164 (1.0%)	25/2318 (1.1%)	32/3105 (1.0%)
<=1x ULN	3/ 664 ( 0.5%)	7/ 974 (0.7%)	5/ 991 (0.5%)	12/1965 (0.6%)	15/2629 (0.6%)
>1 to <3x ULN	3/ 121 ( 2.5%)	5/ 176 (2.8%)	5/ 163 (3.1%)	10/ 339 (2.9%)	13/ 460 (2.8%)
>=3x ULN	1/ 2 (50.0%)	1/ 3 (33.3%)	2/ 9 (22.2%)	3/ 12 (25.0%)	4/ 14 (28.6%)
Missing	0/ 0	0/ 1	0/ 1	0/ 2	0/ 2
<b>Patients with Maximum Post Baseline &gt;= 5x ULN</b>					
Total*	2/ 787 ( 0.3%)	3/1154 ( 0.3%)	3/1164 ( 0.3%)	6/2318 ( 0.3%)	8/3105 ( 0.3%)
<=1x ULN	0/ 664	3/ 974 ( 0.3%)	3/ 991 ( 0.3%)	6/1965 ( 0.3%)	6/2629 ( 0.2%)
>1 to <3x ULN	1/ 121 ( 0.8%)	0/ 176	0/ 163	0/ 339	1/ 460 (0.2%)
>=3 to <5x ULN	1/ 2 (50.0%)	0/ 1	0/ 7	0/ 8	1/ 10 (10.0%)
>=5x ULN	0/ 0	0/ 2	0/ 2	0/ 4	0/ 4
Missing	0/ 0	0/ 1	0/ 1	0/ 2	0/ 2
<b>Patients with Maximum Post Baseline &gt;= 10x ULN</b>					
Total*	0/ 787	1/1154 ( 0.1%)	1/1164 ( 0.1%)	2/2318 ( 0.1%)	2/3105 (0.1%)
<=1x ULN	0/ 664	1/ 974 ( 0.1%)	1/ 991 ( 0.1%)	2/1965 ( 0.1%)	2/2629 (0.1%)
>1 to <3x ULN	0/ 121	0/ 176	0/ 163	0/ 339	0/ 460
>=3 to <5x ULN	0/ 2	0/ 1	0/ 7	0/ 8	0/ 10
>=5 to <10x ULN	0/ 0	0/ 2	0/ 2	0/ 4	0/ 4
>=10x ULN	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0

Notes: n = number of patients in the specified category; Nx = number of patients within each baseline category and have at least one post-baseline measure; Percentage is calculated by n/Nx\*100%; ULN = Upper limit normal from Covance reference limits; vs = versus.

Source: Applicant's Summary-Clin-Safety-App Pg 17571

**Table 66: Serum Bilirubin (umol/L) Elevation, Abnormal Post-Baseline Categories, Induction Period, Pool#1 (RHAZ, RHBA and RHBC)**

Maximum Baseline Category	PBO (N=791) n/Nx(%)	IXE80Q4W (N=1161) n/Nx(%)	IXE80Q2W (N=1167) n/Nx(%)	Total IXE (N=2328) n/Nx(%)	Total (N=3119) n/Nx(%)
<b>Patients with Maximum Post Baseline &gt;= 1.5x ULN</b>					
Total*	10/ 787 ( 1.3%)	15/1151 (1.3%)	12/1162 (1.0%)	27/2313 (1.2%)	37/3100 (1.2%)
<=1x ULN	1/ 732 ( 0.1%)	2/1101 (0.2%)	3/1116 (0.3%)	5/2217 (0.2%)	6/2949 (0.2%)
>1 to <1.5x ULN	4/ 40 (10.0%)	5/ 31 (16.1%)	3/ 29 (10.3%)	8/ 60 (13.3%)	12/ 100 (12.0%)
>=1.5x ULN	5/ 12 (41.7%)	8/ 13 (61.5%)	6/ 10 (60.0%)	14/ 23 (60.9%)	19/ 35 (54.3%)
Missing	0/ 3	0/ 6	0/ 7	0/ 13	0/ 16
<b>Patients with Maximum Post Baseline &gt;= 2x ULN</b>					
Total*	2/ 787 ( 0.3%)	3/1151 ( 0.3%)	2/1162 ( 0.2%)	5/2313 ( 0.2%)	7/3100 ( 0.2%)
<=1x ULN	0/ 732	0/1101	0/1116	0/2217	0/2949
>1 to <1.5x ULN	1/ 40 ( 2.5%)	2/ 31 ( 6.5%)	0/ 29	2/ 60 ( 3.3%)	3/ 100 ( 3.0%)
>=1.5 to <2x ULN	0/ 10	1/ 11 ( 9.1%)	0/ 5	1/ 16 ( 6.3%)	1/ 26 ( 3.8%)
>=2x ULN	1/ 2 (50.0%)	0/ 2	2/ 5 (40.0%)	2/ 7 (28.6%)	3/ 9 (33.3%)
Missing	0/ 3	0/ 6	0/ 7	0/ 13	0/ 16

Notes: n = number of patients in the specified category; Nx = number of patients within each baseline category and have at least one post-baseline measure; Percentage is calculated by n/Nx\*100%; ULN = Upper limit normal from Covance reference limits; vs = versus.

Source: Applicant's Summary-Clin-Safety-App Pg 17575

**Table 67: Serum Alkaline Phosphatase (U/L)**

Maximum Baseline Category	PBO (N=791) n/Nx(%)	IXE80Q4W (N=1161) n/Nx(%)	IXE80Q2W (N=1167) n/Nx(%)	Total IXE (N=2328) n/Nx(%)	Total (N=3119) n/Nx(%)
<b>Patients with Maximum Post Baseline &gt; 1.5x ULN</b>					
Total*	1/ 788 ( 0.1%)	1/1155 ( 0.1%)	3/1164 ( 0.3%)	4/2319 ( 0.2%)	5/3107 (0.2%)
<=1x ULN	0/ 764	0/1104	2/1122 ( 0.2%)	2/2226 ( 0.1%)	2/2990 (0.1%)
>1 to <=1.5x ULN	0/ 22	1/ 49 ( 2.0%)	1/ 42 ( 2.4%)	2/ 91 ( 2.2%)	2/ 113 (1.8%)
>1.5x ULN	1/ 2 (50.0%)	0/ 2	0/ 0	0/ 2	1/ 4 (25.0%)
Missing	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0

Notes: n = number of patients in the specified category; Nx = number of patients within each baseline category and have at least one post-baseline measure; Percentage is calculated by n/Nx\*100%; ULN = Upper limit normal from Covance reference limits; vs = versus.

Source: Applicant's Summary-Clin-Safety-App Pg 17577

*Reviewer Comment: There were no significant differences between Ixe treatment groups and placebo in proportions of patients with elevations, for any of the cut-offs or parameters.*

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### Individual cases

In Pool#1 for induction there were 6 subjects (0.3%) in the Ixe arms (3 per group) who experienced ALT  $\geq$  5X ULN compared to 1 subject in the placebo arm. See Section 8.4.4 **Significant Adverse Events** for some representative narratives for some of these subjects.

No subject treated with Ixe during the development program met the criteria for Hy's law (maximum ALT  $\geq$  3xULN, maximum total bilirubin  $\geq$ 2xULN, and ALP  $<$ 2xULN (ie Hy's law). I examined the narratives for the individual subjects who experienced either an ALT and/or an AST  $>$  10X ULN. See Section 8.4.4 **Significant Adverse Events** and Attachment A at the end of this document for some representative narratives for some of these subjects.

According to the sponsor, two independent Lilly physician reviewers, who were blinded to study drug treatment, conducted a case review of patients who were treated with Ixe and met the criterion either of ALT  $\geq$ 5xULN or maximum ALT  $\geq$ 3xULN with maximum total bilirubin  $\geq$ 2xULN. They assessed subjects and placed them in the following categories: excluded (not a liver injury-ie clearly muscle injury etc.), unlikely related, possibly related (25-49% likelihood), probably related ( $\geq$  50% likelihood) and Indeterminate (insufficient data to decide).

There were 34 cases and I reviewed the narratives for all of them. I had the advantage of knowing the treatment arms at the times for the hepatic events. The independent Lilly reviewers (ILRs) assessed 2 as excluded, 20 as unlikely, 9 as possible and 3 as probable with regard to the relationship with Ixe. For the three cases the ILR assessed as probable I agreed on 2 and felt the third was only possible (rather than probable) based on the persistence of elevation of the LFTs 5 months off Ixe treatment.

There were 9 cases assessed by the ILRs as possible, of these I upgraded 2 cases to probable (based on the timing of elevations with regard to treatment arm), I downgraded 2 to unlikely (again based on timing and knowing the treatment arm) and the rest I agreed were possible. I agreed with the unlikely and excluded determinations made by the ILRs.

*Reviewer Comment: There were a small number of cases of substantially increased transaminases (ie 10X ULN), see Section 8.4.4 **Significant Adverse Events** for narratives. There were also a small number of cases with moderately elevated transaminases (ie 3-5X ULN) associated with elevated bilirubin values (see above discussion of cases reviewed by ILRs and Section 8.4.4 **Significant Adverse Events** and Attachment A at the end of this document for some representative narratives.). None of these cases resulted in sequelae and most normalized with either an interruption in treatment or while on continued therapy. I did not detect a signal for serious or life-threatening hepatic events in the Ixe development program.*

### 8.5.8. Autoimmune Disease: Crohn's and Ulcerative Colitis (UC)

Several studies demonstrate an increased prevalence of inflammatory bowel disease (IBD), that is, Crohn's disease and Ulcerative Colitis, among patients with psoriasis when compared to a matched control population.<sup>34, 35</sup> One hypothesized pathway is through IL-17-producing T-cells.<sup>36</sup> There is evidence to suggest that treatment of Crohn's disease with an IL-17A inhibitor may exacerbate existing disease<sup>37</sup>. In the development program for recently approved IL-17A inhibitor secukinumab there were 9 cases of IBD in the secukinumab arm yielding an exposure-adjusted rate per 100 patient-years of 0.26 for the 300mg dose, 0.35 for the 150mg dose, 0.34 for the active comparator etanercept and no cases for placebo.

The following table displays the adverse events of auto-immune related AEs reported during the Induction (Pool 1) and Maintenance periods (Pool #3) for Ixe.

**Table 68: Overview of Autoimmune Disorder-Related AEs of Special Interest, Induction (Pool # 1) and Maintenance periods (Pool #3)**

<b>Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)</b>				
	<b>Placebo N=791 n (%)</b>	<b>80 mg Q4W N=1161 n (%)</b>	<b>80 mg Q2W N=1167 n (%)</b>	<b>Total IXE N=2328 n (%)</b>
<b>Autoimmune disorder-related TEAEs</b>	0 (0%)	1 (0.1%)	4 (0.3%)	5 (0.2%)
Crohn's disease	0 (0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Ulcerative colitis	0 (0%)	0 (0%)	2 (0.2%)	2 (0.1%)
Rheumatic disorder	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)
<b>Autoimmune disorder-related SAEs</b>				
Crohn's disease	0 (0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Ulcerative colitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Discontinuations due to autoimmune disorder -related AEs</b>				
Crohn's disease	0 (0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Ulcerative colitis	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)

<sup>34</sup> Weng X et al. Clustering of inflammatory bowel disease with immune mediated diseases among members of a northern California-managed care organization. *Am J Gastroenterol.* 2007; 102(7):1429-1435.

<sup>35</sup> Cohen AD et al.. Psoriasis associated with ulcerative colitis and Crohn's disease. *J Eur Acad Dermatol Venereol.* 2009; 23(5):561-565.

<sup>36</sup> Geremia A, Jewell DP. The IL-23/IL-17 pathway in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol.* 2012; 6(2):223-237.

<sup>37</sup> Targan SR et al. A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AMG 827 in subjects with moderate to severe Crohn's disease. *Gastroenterology.* 2012;143(3):e26.

<b>Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)</b>					
	<b>Placebo N=402 n [IR]</b>	<b>80 mg Q12W N=408 n [IR]</b>	<b>80 mg Q4W N=416 n [IR]</b>	<b>Total IXE N=824 n [IR]</b>	<b>Total N=1226 n [IR]</b>
Total patient-years	184.1	269.5	326.7	596.2	780.3
<b>Autoimmune Disorder -related TEAEs</b>	3 [1.6]	2 [0.7]	1 [0.3]	3 [0.5]	6 [0.8]
Crohn's disease	3 [1.6]	0	0	0	3 [0.4]
Ulcerative colitis	0	1 [0.4]	1 [0.3]	2 [0.3]	2 [0.3]
Multiple sclerosis	0	1 [0.4]	0	1 [0.2]	1 [0.1]
<b>Autoimmune Disorder -related SAEs</b>					
Crohn's disease	2 [1.1]	0	0	0	2 [0.3]
Ulcerative colitis	0	1 [0.4]	0	1 [0.2]	1 [0.1]
<b>Discontinuations due to autoimmune disorder-related AEs</b>					
Crohn's disease	2 [1.1]	0	0	0	2 [0.3]
Ulcerative colitis	0	1 [0.4]	0	1 [0.2]	1 [0.1]

Source: Applicant's Summary of Clinical Safety Pgs 428- 429

For the induction period, there were 2 cases of newly diagnosed Crohn's disease, one in each Ixe treatment arm. Both were SAEs and resulted in discontinuation from the trial. Both cases of UC were exacerbations of previously diagnosed disease, neither were SAEs but one did result in discontinuation.

For the maintenance period, 3 subjects in the placebo group experienced Crohn's disease. Two of these were SAEs and resulted in discontinuation. These subjects had previously been on Ixe and had been switched to placebo 23, 70 and 134 days before the adverse events occurred. Given the long half-life it is not possible to r/o potential influence of the IP on these adverse events. The other 2 subjects experienced UC one in each Ixe arm, one of these was a SAE and led to discontinuation.

In the All Psoriasis Ixe-Exposure Analysis Set there were 13 subjects who experienced events characterized as IBD. In addition, there were 4 subjects who experienced AEs whose preferred terms are potentially related to Crohn's disease (2 anal abscess, 1 anal fistula, and 1 rectal abscess). See Section 8.4.2 **Serious Adverse Events** for some representative narratives of these subjects.

*Reviewer Comment: As was stated in Section 8.4.2 **Serious Adverse Events**, it appears possible given the cases presented above (narratives for SAEs of IBD) that the use of Ixe may exacerbate*

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*or result in new onset of IBD. This issue has been seen with another IL-17A antagonist secukinumab. The proposed labeling for Ixe adequately addresses this issue.*

### 8.5.9. **Pneumocystis Pneumonia (PCP) and Interstitial Lung Disease (ILD)**

There were no cases of Pneumocystis Pneumonia (PCP) in the clinical development for Ixe. In the All Psoriasis Ixe Exposure Integrated Analysis Set, there were 3 patients (0.1%) with TEAEs related to Interstitial Lung Disease (one case each of moderate bronchiolitis, mild pulmonary sarcoidosis and moderate sarcoidosis).

*Reviewer Comment: I agree with the sponsor that there is no safety signal for PCP or ILD identified in the Ixe development program.*

### 8.6. **Specific Safety Studies/Clinical Trials**

There were no specific safety studies in the development program for Ixe.

### 8.7. **Additional Safety Explorations**

#### 8.7.1. **Human Carcinogenicity or Tumor Development**

From the draft labeling for Ixe:

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TALTZ. Some published literature suggests that IL-17A directly promotes cancer cell invasion (b) (4) whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

The pharmacology-toxicology reviewer had the following comments regarding carcinogenicity:

There are no carcinogenic concerns related to ixekizumab structure or metabolism. Since ixekizumab is a monoclonal antibody, this large protein is not expected to gain access to the nucleus and directly interact with DNA. It will be catabolized to peptides and constituent amino acids via normal metabolic pathways.

The literature supports a pro-tumor role for IL-17A based on its high expression in a variety of tumor types and its ability to promote angiogenesis, attract pro-inflammatory cells and provide pro-survival signals to tumor cells. A strong association between chronic inflammation and increased incidence of malignancy is well established... Conversely, several researchers have observed an anti-tumor effect of IL-17A. Kryzcek studied the effect of IL-17 on tumor

growth in IL-17-deficient mice.<sup>38</sup> MC38, a murine colon cancer cell line, was subcutaneously inoculated into the wild-type and IL-17-deficient mice. The IL-17-deficient mice exhibited an accelerated tumor growth compared with the control mice ( $P < 0.01$ ). They also compared the metastatic potential of MC38 cells by intravenously inoculating cells into wild-type and IL-17-deficient mice and observed more metastatic foci of tumors in the lungs of IL-17-deficient mice ( $59 \pm 8$ ) than in control mice ( $12 \pm 5$ ;  $P = 0.01$ ). The effect was accompanied by reduced IFN- $\gamma$  levels in tumor-infiltrating NK cells and T cells. These data suggest that endogenous IL-17 may play a protective role in tumor immunity... Other investigations of tumorigenesis in IL-17A-deficient mice have produced mixed results. Martin-Orozco found that in IL-17A-deficient mice, adaptive T cell therapy with tumor-specific Th17 cells prevented the development of poorly immunogenic lung melanoma tumors as well as helped control growth of established lung melanoma tumors; the Th17 cells maintained their Th17 cell cytokine production and did not convert to Th1 cells.<sup>39</sup> The proposed anti-tumor mechanism was Th17-cell mediation of dendritic cell recruitment and subsequent activation of CD8+ T cells against the tumor. According to the authors, their data indicated an active role of IL-17A in immunosurveillance since IL-17A deficiency resulted in reduced leukocyte infiltration into the tumor and increased tumor development. The authors further commented that their findings were consistent with the notion that the effects of IL-17A on tumor development are directly influenced by the existence of an adaptive immune system; in the presence of lymphocytes, IL-17A promotes tumor rejection, while in their absence, IL-17A favors tumor growth and angiogenesis.

The overall weight-of-evidence suggests that neutralization of IL-17A with ixekizumab is expected to create a less favorable environment for tumor growth. Assessment of the frequency of malignancy reports during postmarketing surveillance in comparison to the background rates in patient populations will ultimately provide the most accurate determination of cancer risk for ixekizumab.

### 8.7.2. Human Reproduction and Pregnancy

From the draft labeling for Ixe:

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<sup>38</sup> Kryzcek et al. (2009). Endogenous IL-17 contributes to reduced tumor growth and metastasis. *Blood* 114(2):357-359.

<sup>39</sup> Martin-Orozco et al. 2009. T helper 17 cells promote cytotoxic T cell activation in tumor immunity. *Immunity* 31:787-798.

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### Risk Summary

There are no available data on TALTZ use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. An embryofetal development study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the fetus due to ixekizumab [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### Data

#### *Animal Data*

An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis at doses up to 19 times the MRHD (on a mg/kg basis (b) (4) of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the (b) (4) of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). The (b) (4) clinical significance of these findings are unknown. No ixekizumab-related effects on (b) (4) functional or immunological development were observed in the infants from birth through six months of age.

### Risk Summary for Lactation

There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TALTZ and any potential adverse effects on the breastfed infant from TALTZ or from the underlying maternal condition.

### Impairment of Fertility

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No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm were observed in sexually mature cynomolgus monkeys that were administered ixekizumab for 13 weeks at a subcutaneous dose of 50 mg/kg/week (19 times the MRHD on a mg/kg basis). The monkeys were not mated to evaluate fertility.

### 8.7.3. **Pediatrics and Assessment of Effects on Growth**

There were no pediatric subjects in the development program for Ixe. See Section 12 **Postmarketing Requirements and Commitments** for discussion of the plan for pediatric development of Ixe.

### 8.7.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

#### Overdose

Limited information is available regarding overdose of Ixe from the Ixe development program. According to the applicant, in the pivotal Phase 3 studies, a total of 2328 patients were randomized and received at least 1 injection of Ixe. Of these patients, 11 (0.5%) reported taking double (160 mg), and in 1 case triple (240 mg) of the designated 80-mg dose. Events reported following these overdoses were flu-like symptoms, tinea pedis, upper respiratory tract infection, and seasonal allergy, some of which have also been attributed to Ixe at normal doses. The severity of these events was classified as mild (3 events) to moderate (one event), and none were classified as severe. None of the reported events were considered “serious.”

#### Withdrawal and Rebound

According to the applicant, no withdrawal symptoms were observed in the clinical trials of Ixe. Rebound [Defined as a subject experiencing a significant worsening of their psoriasis over their baseline severity: sPGA score > baseline sPGA score, PASI score >125% of baseline PASI score, or a change in psoriasis phenotype (e.g., erythrodermic)] was observed in < 1% of subjects upon treatment withdrawal (as assessed during maintenance within 8 weeks of re-randomization to placebo).

## 8.8. **Safety in the Postmarket Setting**

### 8.8.1. **Safety Concerns Identified Through Postmarket Experience**

Ixe is not a marketed product so this section is not applicable.

### 8.8.2. **Expectations on Safety in the Postmarket Setting**

Not Applicable.

## 8.9. Additional Safety Issues From Other Disciplines

The potential safety issues have all been discussed in previous sections of the review.

## 8.10. Integrated Assessment of Safety

Overall, the safety profile for Ixe was similar to that of other biologics approved for moderate to severe plaque psoriasis. The most common TEAEs were injection site reactions, upper respiratory tract infections, nausea and tinea infections, which were reported in  $\geq 1\%$  in the pivotal trials. The expected findings for an immunomodulatory biologic agent such as increased risk of infection (including reactivation of TB) and hypersensitivity were also seen and are discussed below under the subsection heading Contraindications and Warnings and Precautions. The major area of uncertainty with regard to safety was the possible increased risk of suicidal behavior.

### Issue Regarding Potential Safety Signal for Suicidal Behavior

There was an active discussion within the Agency involving DDDP, DPP, DEPI and OSE (DRISK, DPVI) regarding the most appropriate path forward to further evaluate a potential signal for an increased risk of suicidal behavior. Multiple possibilities were under consideration as a means of addressing this area of uncertainty including inclusion in labeling, safety related PMRs, REMS and pharmacovigilance.

I agree with the DPP reviewer Dr. Alfaro that “The finding of nine cases of suicide attempt in the clinical development program for IXE is of concern”. However, I do not believe, at this time, that we have convincing evidence of a signal for an increased rate of suicidal behavior for patients treated with Ixe for moderate to severe plaque psoriasis. Therefore, I recommend ongoing monitoring through pharmacovigilance in the post-market setting as the primary method to further assess this potential signal. I have outlined my reasoning below with regard to incidence rates and plausibility.

With regard to data from the development program, there is no increased incidence rate of either depression or suicidality during the placebo-controlled induction portion of the pivotal trials nor was there an increased rate in the exposure-adjusted data for the maintenance period. The overall rates of depression were low and in most analyses the rates in the placebo group exceeded that seen in the Ixe arms. No negatively impacting dose-response with regard to Ixe was seen. Over the course of the induction period Ixe subjects tended to improve at a higher rate than placebo subjects. See Section 8.5.1 **Analysis of Submission-Specific Safety Issues**; subsection **Depression and Suicidality** for details.

Examining the program in its entirety, there were 9 suicide attempts in the Ixe treated arms over a period of 6480 person-years for Ixe versus either one or none (depending on whether you

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choose to count the subject who attempted suicide 2-3 months after being in the placebo group for a phase 1 Ixe trial) over a period of 421 person-years for placebo. The point estimate for the incidence rate ratio is 0.58, consistent with Ixe having a lower rate than placebo. However, the 95% confidence interval goes all the way from 0.08 to 25.6, the degree of uncertainty reflecting the sparseness of the data. Given the increased background rate of depression and suicide known to exist in the population of subjects with moderate to severe psoriasis it is difficult to determine if the number of attempts exceeds what would be expected for the population and causality to the treatment with Ixe is difficult to assess. See discussion of the DEPI consult from Section 8.5.1 **Analysis of Submission-Specific Safety Issues**, subsection **Depression and Suicidality** for a discussion of the background rates of depression and suicidality in psoriasis and in psoriasis clinical trials.

I suspect that the incidence of depression and possibly suicidal ideation was grossly underestimated in the Ixe clinical trials based on its low incidence both at baseline and throughout the course of the trials in comparison to what is reported in the literature for psoriasis patients in general and psoriasis subjects in clinical trials. (Again, See DEPI consult referenced in the paragraph above) What I believe was not underestimated is the number of suicide attempts (with the possible exception of the “methanol poisoning case”). Based on the C-CASA review and the evaluations of the “not enough information” cases from that review (performed by both myself and the DEPI reviewer) I do believe we have captured all of the suicide attempts.

Another factor to consider with regard to whether the suicide attempts in the Ixe program were causally related to the drug is the timing of the suicide attempts. The timing does not suggest a causal relationship. As per the DEPI reviewer

The timing of these events did not suggest any temporal association to IXE. The days on IXE at the time of the event were in a wide range (52 to 669 days) with a mean of 380 days, a median of 447 days, and a large standard deviation for the distribution of times to event (SD=221 days).

With regard to plausibility of the mechanism for an increased risk of suicidality for IL-17 blockers we have some contradictory data to consider. Secukinumab, a recently approved biologic agent for psoriasis, has an identical mechanism of action as Ixe, both bind to the IL-17A cytokine. There is no discernable signal from the Secukinumab development program with no completed suicides and only one suicide attempt in a safety database that covers 3225 person-years of data. However there is a potential signal of concern for brodalumab, a biologic that binds to the IL-17 receptor (and therefore blocks the actions of IL-17A, IL-17C and IL-17F) that is in development for psoriasis. There were 4 completed suicides and 7 additional suicide attempts in a database that covers 7895 person-years of data. The possibility of a class effect

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associated with IL-17 blockade has not been ruled out. However, it is difficult to explain the entirely benign database for secukinumab under this scenario.

Another factor to consider with regard to plausibility is the potential for Ixe to pass through the blood-brain barrier (BBB). The conventional wisdom holds that large molecules such as biologics are unlikely to pass through the BBB. There is recent literature that suggests however, that IL-17 may disrupt BBB tight junctions and that IL-17 receptors are present on BBB endothelial cells.<sup>40</sup> It is possible that by altering the amount of IL-17 available (particularly after discontinuing the drug) the use of anti-IL17 agents may impact this system.

Another fact that hinders an argument for the plausibility of Ixe causing increased suicidal behavior is the lack of any signal regarding other neuropsychiatric events (NPEs) such as anxiety, depression or cognitive disorders such as confusion, memory loss and disorientation. These other NPEs would most commonly accompany a drug induced change in mental status. I have mentioned my concern about a lack of ascertainment of depression-related events in the Ixe trials. Some of the other NPEs such as cognitive disorders are less subtle however, and I would expect them to have been reported through spontaneous adverse event reporting if they had occurred. These types of other events were seen in trials of TNF inhibitors and are discussed in the previously mentioned OSE Review of NPE in subjects on TNF Inhibitors. See Section 8.4.2 **Serious Adverse Events** subsection **Depression/Suicidality: Ideation/Attempt** example #12 pg. 120 for discussion of the OSE review. This lack of other NPEs reported in the Ixe trials argues against a role for Ixe in causing increased suicidal behavior.

In conclusion, I agree with the author of the second DPP consult Dr. Dubitsky who stated

In the end, the clinical trials data do not support a causal link between Ixe therapy and suicidal events, in my judgment. But the above described deficiencies, which cannot be corrected at this stage, limit the ability to draw an inference regarding IXE and suicidal adverse events.

Due to the limitations of the Ixe trials with regard to assessing suicidal behavior and due to the possible signal seen in another biologic agent that blocks the actions of IL-17A, I recommend ongoing monitoring through pharmacovigilance in the post-market setting as the primary method to further assess this potential signal.

#### Contraindications and Warnings and Precautions

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<sup>40</sup> Kebir et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. Nature Medicine. 2007.Vol 13 #10. 1173-1175.

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The items below will be included in Section 4 Contraindications and Section 5 Warnings and Precautions in the product label.

### Infections

In clinical trials, (b) (4) Ixe had a higher rate of infections than placebo (b) (4) (b) (4) (27% vs. 23%). Upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections occurred more frequently in the Ixe than the placebo group.

(b) (4)

### Hypersensitivity

Serious hypersensitivity (b) (4) (b) (4) .

*Reviewer Comment:*

*This is an expected adverse event in development programs for a biologic foreign protein product. The incidence rate is comparable to other biologic products including the most recently approved secukinumab. See Section 8.5.4 **Allergic Reactions/Hypersensitivities** for further discussion of this topic.*

### Inflammatory Bowel disease

Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in Ixe- (Crohn's disease 0.1%, ulcerative colitis (b) (4) %) than in placebo-treated patients (0%) during the 12-week, placebo-controlled period. During Ixe treatment, monitor for onset or exacerbation of inflammatory bowel disease.

## **9 Advisory Committee Meeting and Other External Consultation**

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No Advisory committee was held for Ixe.

## **10 Labeling Recommendations**

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### 10.1. Prescribing Information

Labeling recommendations are contained within the body of the document. Labeling negotiations are ongoing at the time of this review.

### 10.2. Patient Labeling

A medication guide and instructions for use were included with the submission of the BLA for Ixe. Labeling negotiations are ongoing at the time of this review.

### 10.3. Non-Prescription Labeling

Not applicable.

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

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Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.”

## **12 Postmarketing Requirements and Commitment**

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### Pediatric PMR

On March 30, 2014 an agreed upon Pediatric Study Plan (PSP) letter was sent to the applicant. The PSP included the following statement by the Applicant:

The details of the planned pediatric studies will be included in the pediatric plan proposal which is tentatively planned to be submitted by December 1, 2022.

In this letter the Agency stated the following:

We have completed our review of the submission and acknowledge your plan to request a waiver for subjects 0 to (b) (4) years old and to defer your pediatric study plan (PSP) in subjects (b) (4) to 17 years old until such time as adult safety experience can be evaluated. We also acknowledge your intent to conduct trials in pediatric subjects outside the United States (US) to satisfy regulatory requirements for non-US jurisdictions. The adequacy of these trial(s) to address the US regulatory requirements for pediatric safety and efficacy data (i.e., PREA) cannot be determined at this time, as safety and efficacy for adults has not yet been

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evaluated by the Agency.

DDDP thinking regarding the timing for development of systemic agents for the pediatric population for the treatment of serious conditions such as moderate to severe psoriasis has evolved since this agreement was made. In light of the positive risk-benefit profile of Ixe relative to other currently available treatments (MTX, CSA, TNF Inhibitors), I recommend beginning development in the pediatric population in the US. A revised pediatric development plan should be requested from the sponsor to include a PK study and a study assessing safety and activity in all relevant pediatric populations. I agree that the relevant age should be subjects ages <sup>(b)</sup><sub>(4)</sub> years and older and that below 7 years can be waived based on an insufficient number of subjects with disease of a severity requiring systemic agents as was previously negotiated in the PSP dated March 30, 2014.

#### Clinical Pharmacology PMC

The clinical pharmacology reviewer recommends the following PMC:

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 pro-inflammatory 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.

## 13 Appendices

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### 13.1. References

References are footnoted at the bottom of the page throughout the text of the review.

### 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number):**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
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Total number of investigators identified: RHAJ-23 investigators, RHAZ-117 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S-0 Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>RHAZ-116</u> <u>RHAJ-22</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/> see below	No <input type="checkbox"/> (Request explanation from Applicant)

PI (b) (6) reported that he received other payments from Lilly in the amount of \$41,647 for Honorarium during his participation in RHAJ and the RHAZ Ixe studies.

RHAJ

His site screened (Visit 1) 17 patients; this was 7.3% of the total patients screened in the study (N=232). His site randomized 16 patients; this was 11.3% of the total patients randomized in the study (N=142). A statistical analysis was completed repeating the study's primary analysis excluding data from this site (by the applicant). No meaningful difference was seen between the primary analysis and this new analysis excluding Dr. (b) (6) site data; both analyses support the same scientific conclusion.

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RHAZ

His site screened (Visit 1) 42 patients; this was 2.5% of the total patients entered in the study (N=1660). His site randomized 40 patients; this was 3.1% of the total patients randomized in the study (N=1296). A statistical analysis was completed repeating the study's primary analysis excluding data from this site (This was performed by both the applicant and by the Agency's statistical reviewer). No meaningful difference was seen between the primary analysis and this new analysis excluding Dr. (b) (6) site data; both analyses support the same scientific conclusion.

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## **Attachment A**

### **Narratives 1: Representative cases of SAEs - Cerebro-cardiovascular Events**

RHAZ-101-01013: MI

57 yo white male with psoriasis and a h/o COPD, DM, HTN, ↑ lipids, angina, 120 pk-yr smoker, cardiomegaly, MI, FH CAD, partial colectomy in 2005 was treated with Ixe from 4/26/12 through at least 8/7/14 (when BLA submission cut-off date occurred). On [REDACTED] (b) (6) months of exposure) he was hospitalized with an MI and underwent catheterization with stent placement during which he experienced ventricular fibrillation and atrial fibrillation. In the opinion of the investigator the event was not related to the IP.

*Reviewer Comment: I agree with the investigator that given the multiple risk factors it is unlikely that the IP was the cause.*

RHAZ-202-04043: MI

45 yo white male with psoriasis and a h/o morbid obesity, DM, HTN, ↑ lipids and a FH of MI was treated with Ixe from 8/6/12 through 11/7/12. On [REDACTED] (b) (6) weeks of exposure) he was admitted to the intensive care unit for non-ST-elevation myocardial infarction (NSTEMI). Acute coronary angiography revealed a recent thrombotic occlusion of the medial right coronary artery and a stent was placed. In the opinion of the investigator, the MI was possibly related to the IP.

*Reviewer Comment: Thought I think it is unlikely related I do not believe that a contribution to the event from the IP can be ruled out.*

RHAZ-206-04202: CVA, atrial septal defect

53 yo white male with psoriasis and a h/o HTN, ↑ lipids, smoking, CAD, MI and stent placement was treated with Ixe from 2/18/13 through at least 7/17/14. On [REDACTED] (b) (6) months of exposure) he experienced an ischemic stroke. On 13-Jun-2014 trans-esophageal heart echo showed evidence of persistent foramen ovale with atrial septal aneurysm therefore a paradoxical embolic ischemia origin was assumed. In the opinion of the investigator, the CVA was possibly related to the IP.

*Reviewer Comment: Thought I think it is unlikely related I do not believe that a contribution to the event from the IP can be ruled out.*

### **Reviewer Comment Regarding Cerebro-cardiovascular Events**

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*See Section 8.5.5 Analysis of Submission Specific Safety Issues; subsection Cerebro-cardiovascular Events for discussion of this issue within the context of the Ixe development program.*

## **Narratives 2: Representative cases of SAEs - Malignancies**

RHAZ-203-04113: B Cell Lymphoma

49 yo white male with psoriasis and a h/o MTX use for 6 months in 2009 as well as other “biologics” use from 2009 through 2011 was treated with Ixe from 4/9/13 through 2/11/14. On 2/11/14 he was noted to have inguinal lymphadenopathy. On 4/1/14 (~ 12 months of exposure) he was diagnosed with follicular non-Hodgkin B cell lymphoma stage 3 and the IP was discontinued. In the opinion of the investigator, the event was related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution to the above event by the investigational product.*

RHAZ-153-03126: B cell lymphoma, colon cancer

56 yo white female with psoriasis and a h/o treatment with multiple other biologic agents X 2 years was treated with Ixe from 11/12/12 through 3/11/13. On 3/18/13 (~ 4 months of exposure) she was diagnosed with colon cancer. On 3/29/13 she was diagnosed with B cell lymphoma. In retrospect she reported loose stools and abdominal pain dating from 9/12 with a 10 kg weight loss. Adenocarcinoma was found on colonoscopy at two sites. The colon cancers were resected. Multiple lymph nodes were noted on CT scan including in the neck and mediastinum. Palpable lymph nodes were present in the neck area. Biopsy revealed large B cell lymphoma. The investigator considered the events were not related to the IP.

*Reviewer Comment: I do not agree, it is not possible to rule out a contribution to the above events by the investigational product.*

RHBA-131-01860: Prostate Cancer

72 yo white male with psoriasis and a h/o BPH and prostate nodule was treated with Ixe from 4/1/13 through 8/25/14. On 4/14/14 (~ 12 months of exposure) bx of the nodule in the prostate (felt on digital exam) revealed prostate cancer. In the opinion of the investigator, the event was related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution to the above event by the investigational product.*

RHAZ-402-06163: Breast cancer

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50 yo white female with psoriasis was treated with Ixe from 3/14/13 through 6/6/14. On 7/18/14 (≈ 16 months of exposure) she was diagnosed with invasive ductal carcinoma of the breast. She was discontinued from the trial. In the opinion of the investigator, the event was related to the IP.

*Reviewer Comment: I agree with the investigator, it is not possible to rule out a contribution to the above event by the investigational product.*

Reviewer Comment Regarding Malignancy

See Section 8.5.6 **Analysis of Submission Specific Safety Issues**; subsection **Malignancies** for discussion of malignancy within the context of the Ixe development program.

**Narratives 3: Representative cases of SAEs - Miscellaneous**

RHAZ-102-01068: Multiple Sclerosis (MS)

48 yo obese white female with psoriasis and a h/o hypothyroidism, urinary frequency (12/11) and was treated with Ixe from 12/22/11 through 9/13/12. She began to c/o vertigo/balance issues and numbness in 2/12 and was diagnosed with MS on 5/2/12 (≈4 months of exposure) which worsened in 6/12. In the opinion of the investigator, the event of multiple sclerosis was not related to the IP.

*Reviewer Comment: I do not agree with the investigator. Given the timing I do not believe that a contribution to the event from the IP can be ruled out.*

RHBA-259-06027: Pustular psoriasis flare

47 yo white male with psoriasis entered trial RHBA and was treated with placebo for the 3 month induction period. He started Ixe on 7/9/13. On 9/3/13 (≈2 months of exposure) he had a change in disease phenotype and developed pustular psoriasis. He was discontinued from the IP and cyclosporine was instituted. In the opinion of the investigator, the events were related to the IP.

*Reviewer Comment: I agree with the investigator that it is not possible to rule out a contribution from the IP to this event. It is unclear from the narrative (which lacks detail) whether the plaque psoriasis improved and then a paradoxical flare of pustular psoriasis occurred or whether the subject just never responded to the IP and his psoriasis progressed to a pustular type of flare due to lack of response. I looked at the efficacy parameters for this subject and after starting Ixe on 7/9/13 he did respond with a decrease in PGA from a score of 2 to a score of 1 between*

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*7/12/13 and 8/16/13. His PASI went from 12 to 1.4 over the same one month period of treatment. He maintained a PGA of 1 (PASI=1.8) through till his next date of assessments on 9/20/13 but had meanwhile developed pustular lesions on his palms and soles without fever. Biopsy revealed pustular psoriasis and IP was discontinued and CSA was started. This event is unusual and I will monitor for other cases with a similar presentation.*

#### **Narratives 4: Cases of Grade 3 Neutropenia**

RHAK 551-7494

59 yo Asian female with RA on concomitant MTX, ASA and sulfasalazine was treated with Ixe 3 mg SCT for the induction period and was then switched to Ixe 160 mg SQ for the LTE on 8/3/10. On 4/11/10, her baseline leukocyte count was low at  $3.79 \times 10^9/L$  (LLN  $3.8 \times 10^9/L$ ) but her ANC was WNL. On 3/15/11 ( $\approx 338$  days of exposure) She developed Grade 3 neutropenia with a ANC of  $0.65 \times 10^9/L$ . The Grade 3 neutropenia persisted with a count of  $0.84 \times 10^9/L$  on 3/20/11 and  $.65 \times 10^9/L$  on 5/10/11. There were no concurrent infections (She had pharyngitis on 10/21/10 and 10/28/10). Her last dose of Ixe was on 6/7/11 as per protocol. She completed the trial with an ANC=1.61 on 8/30 11, off treatment with Ixe for 2 months.

*Reviewer Comment: The timing of this subject's neutropenia does not seem to correlate with IP treatment nor with any infectious complications.*

RHBC-103-01736

40 yo white female was started on Ixe 80 mgQ2W on 10/15/13. Her baseline CBC was WNL. On 12/10/13 ( $\approx 57$  days of exposure) she developed leukopenia [ $1.48 \times 10^9/L$  (LLN  $3.8 \times 10^9/L$ )] and Grade 3 neutropenia with an ANC of  $0.71 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ). She reverted to an ANC WNL on the next blood draw on 1/7/14 and maintained a normal ANC throughout the rest of the trial (through at least 5/27/14). No infectious events occurred.

*Reviewer Comment: This seems to be an isolated occurrence of neutropenia with no sequelae.*

RHBC-219-09081

29 yo white male was started on Ixe 80 mgQ4W on 1/8/13. His baseline CBC was WNL. He entered the LTE period on 4/3/13. He experienced a mild AE of nasopharyngitis on 10/11/13. On 10/18/13 ( $\approx 284$  days of exposure) the patient's leukocytes, neutrophils and blood platelets count were below the lower limits of normal measuring  $0.73 \times 10^9/L$  (LLN  $3.8 \times 10^9/L$ ),  $0.55 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ) and  $11 \times 10^9/L$  (LLN  $140 \times 10^9/L$ ), respectively. On re-test (10/22/13), the leukocytes, neutrophils and blood platelets counts were within normal limits. The nasopharyngitis resolved on 10/19/13. On 3/6/14 he had another low ANC of  $1.38 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ).

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*Reviewer Comment: This subject did experience an infectious event associated with his neutropenia but it was mild and both the AE and the neutropenia resolved rapidly without sequelae.*

RHBA 119-01918

48 yo African American female was started on Ixe 80 mg Q4W on 9/3/13. On 8/27/13 (Visit 1), her screening neutrophil and leukocytes counts were low,  $1.77 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ) and  $3.28 \times 10^9/L$  (LLN  $3.8 \times 10^9/L$ ), respectively. On 9/3/13 (Visit 2), her baseline neutrophil and leukocytes counts were WNL. Her ANC fluctuated below the LLN for most of the induction period with the lowest value  $1.57 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ) on 10/1/13. She entered the maintenance period on 12/3/13 assigned to the Ixe 80mg Q12W arm. Throughout the maintenance period her ANC was below the LLN varying from a low of  $0.90 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ) on 6/17/14 ( $\approx$  288 days of exposure) to  $1.92 \times 10^9/L$  (LLN  $1.96 \times 10^9/L$ ) on 4/15/14. She experienced AEs of URI and mild gastroenteritis during this period.

*Reviewer Comment: It is not possible to r/o a contribution to this event from the IP. However, this subject had a low neutrophil count at baseline and recovered without sequelae from the two infectious AEs that occurred. About 5% of African American patients are known to have "benign ethnic neutropenia" which is defined as a neutrophil count below  $1.5 \times 10^9/L$  without overt cause or complications.<sup>41</sup>*

RHAZ-138-02880

Patient RHAZ 138-2880 on Ixe 80 mg Q4W reported a TEAE of severe diverticulitis on Day 266, and Grade 3 neutropenia preceded the event on Day 249 with a value of  $0.64 \times 10^9/L$ . On Day 259 (prior to reported event), total ANC was  $3.03 \times 10^9/L$ , and the patient was reported as recovered from the event on Day 275.

*Reviewer Comment: This subject did experience an infectious event associated with his neutropenia but it was mild and both the AE and the neutropenia resolved rapidly without sequelae. More detail was requested from the applicant who informed DDDP that the AE of diverticulitis did not have onset within the 14 day window which was used to define concurrent infection for the patient narrative criteria. They also updated status; the patient is ongoing in the study without problems.*

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<sup>41</sup> Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? J Lab Clin Med 1999; 133:15–22.

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/s/  
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JANE E LIEDTKA  
11/13/2015

JILL A LINDSTROM  
11/20/2015

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA  
CONSULT #11-549**

**Consultant Reviewer:** Gregory M. Dubitsky, M.D.  
Division of Psychiatry Products

**Consultation Requestor:** Jane Liedtka, M.D.  
Jill Lindstrom, M.D.  
J. Paul Phillips, RPM  
Division of Dermatology and Dental Products

**Subject of Request:** BLA 125521 (ixekizumab)/Suicidal Events

**Date of Request:** September 11, 2015

**Date Received:** October 1, 2015

**Desired Completion Date:** October 9, 2015

**I. Background**

Ixekizumab (IXE) is a humanized monoclonal antibody that blocks interleukin-17A (IL-17A), a proinflammatory cytokine. BLA 125521, sponsored by Eli Lilly, is intended to support the use of subcutaneous IXE in the treatment of moderate to severe plaque psoriasis and is currently under review by the Division of Dermatology and Dental Products (DDDP).

DDDP requested consultation with the Division of Psychiatry Products (DPP) on June 11, 2015, to evaluate the potential of IXE to be associated with suicidal behavior or thoughts in the development program. A consultative review was completed by Cara Alfaro, Pharm.D., on August 25, 2015. Dr. Alfaro focused her examination on 3 pivotal Phase 3 placebo-controlled trials:

- RHAZ (N=1296) - this trial consisted of a 12-week induction dosing phase followed by a 48-week maintenance dosing phase, and finally a 204-week open-label extension. IXE induction dosing regimens were 80mg q2wks or 80mg q4wks. Week 12 IXE responders during the induction phase were re-randomized 1:1:1 to IXE 80mg q4wks, 80mg q12wks, or placebo for maintenance treatment. Week 12 IXE or placebo non-responders were assigned to IXE 80mg q4wks (b) (4) were not included in the maintenance analysis population. Patients who relapsed during maintenance were assigned to IXE 80mg q4wks and also were not included in the maintenance analysis population.
- RHBA (N=1224) - this trial had essentially the same design as RHAZ.
- RHBC (N=1346) - this trial consisted of a 12-week induction period with IXE doses of 80mg q2wks or 80mg q4wks followed by a 252-week extension.

The latter two trials also included an active control arm (etanercept 50mg twice weekly) during the induction phase. These trials excluded subjects with a

significant uncontrolled psychiatric disorder or any history of a suicide attempt, subjects judged by the investigator to be at risk for suicide, and subjects who scored a “3” on item #12 of the Quick Inventory of Depressive Symptoms-Subject Rated 16-item (QIDS-SR16) scale (see below).

Suicidal thoughts or behavior were monitored during these trials using item #12 of the QIDS-SR16, which was scored as follows:

0 = I do not think of suicide or death.

1 = I feel that life is empty or wonder if it’s worth living.

2 = I think of suicide or death several times/week for several minutes.

3 = I think of suicide or death several times/day in some detail or I have made specific plans for suicide or have actually tried to take my own life.

This scale is self-rated and is answered by the patient depending on how they have felt within the past 7 days, according to the study protocols.

Dr. Alfaro examined the maximum post-baseline item 12 scores in the following data pools (presented in Tables 1, 2, and 3 of her review, respectively):

- induction phases of studies RHAZ, RHBA, and RHBC.
- induction phases of studies RHBA and RHBC.
- maintenance phases of studies RHAZ and RHBA.

In general, the proportions of patients who experienced worsening on item #12 were not significantly different between the IXE-treated patients and placebo. However, Dr. Alfaro expressed a concern that simply looking at rates of worsening may mask differences in the magnitude of worsening. Therefore, she recommended that the sponsor provide shift tables which present the proportions of patients by maximum item #12 scores stratified by baseline score.

Regarding suicidal adverse events, Dr. Alfaro noted that the sponsor had identified 2 suicide attempts during the induction periods of the pool of the 3 Phase 3 trials and an additional attempt during the maintenance phases of studies RHAZ and RHBA. An additional 6 events (5 attempts and one case of suicidal ideation) were reported in the extension phases of all psoriasis trials. All events occurred in IXE-treated patients. (In addition, there was one suicide attempt during the post-treatment follow-up period that occurred more than 2 months after the last dose of IXE.) There were no completed suicides.

After adjustment for exposure, the rates of suicide attempts in the induction phases of the primary psoriasis placebo-controlled integrated analysis set and in the maintenance phases of the psoriasis maintenance integrated analysis set were not significantly different between IXE and placebo:<sup>1</sup>

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<sup>1</sup> Data are from pages 20 and 41 of the sponsor’s August 6, 2015 submission (Sequence #0012).

### Primary PC Induction Phases

IXE rate = 0.29/100 PEYs (95% CI -0.11, +0.70)

p-value vs. placebo=0.157

### Maintenance Phases

IXE rate = 0.16/100 PEYs (95% CI -0.15, +0.47)

p-value vs. placebo=0.317

Considering all 9 events that occurred during IXE treatment in any psoriasis trial, the exposure-adjusted reporting rate was 0.14/100 PEYs (9 events/6479.8 PEYs).<sup>2</sup> This overall rate is consistent with the rates in the placebo-controlled studies mentioned above.

The timing of these events did not suggest any temporal association to IXE. The days on IXE at the time of the event were in a wide range (52 to 669 days) with a mean of 380 days, a median of 447 days, and a large standard deviation for the distribution of times to event (SD=221 days).<sup>3</sup>

However, Dr. Alfaro was concerned that suicidal events may have been missed because this enumeration appeared to count only cases that resulted in drug discontinuation. She recommended that Lilly perform a retrospective review of all potential cases of suicidal thoughts or behaviors based on a text string search (e.g., suic, overdos, attempt) and classification of such cases using the Columbia-Classification Algorithm of Suicide Assessment (C-CASA). As a postscript to her review, Dr. Alfaro noted that the sponsor had submitted a retrospective C-CASA analysis on August 6, 2015, based on a previous request from DDDP. She was satisfied that the sponsor appeared to use appropriate methodology to identify all potential cases. No additional cases of suicidal thoughts or behaviors were identified by this process. But the fact that 39 cases were classified as “not enough information” was of concern to her and, thus, she recommended a review of these 39 narrative summaries.

In response to Dr. Alfaro’s recommendations, DDDP requested and the sponsor submitted the following items (Serial #0016 received September 4, 2015):

- narrative summaries for the 39 cases for which the C-CASA classification was “not enough information” to determine if any actually represented suicidal events.
- shift tables for the QIDS-SR16 item #12 data to evaluate the magnitude of observed changes in this score.
- description of the follow-up provided to subjects who experienced a worsening score on the QIDS item #12.

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<sup>2</sup> Total exposure is based on information contained in the 4-Month Safety Update Report dated July 21, 2015 (#0007). No new events were reported in the update.

<sup>3</sup> Data are from page 44 of submission #0012. I derived the statistics using JMP 11.

- clarification regarding whether the reviewers for the C-CASA analysis were blinded to study segment to determine whether this could have biased the findings of this analysis.

DDDP has re-consulted DPP to evaluate this submitted information and provide an opinion on how it affects previous findings regarding suicidality with IXE.

## **II. Review Of Clinical Issues**

### **A. Narrative Summaries of Cases with C-CASA Classification of “Not Enough Information”**

I examined each of the 39 narrative summaries of cases with a C-CASA classification of “not enough information.” In no case did I judge that the event, as described, should have been classified as a suicidal event.

### **B. QIDS-SR16 Item #12 Shift Tables**

I examined shift tables which displayed the maximum QIDS-SR16 item #12 scores as a function of baseline score for the following study pools:

- induction phases of studies RHAZ, RHBA, and RHBC.
- induction phases of studies RHBA and RHBC.
- maintenance phases of studies RHAZ and RHBA.
- all IXE clinical trials in psoriasis.

These shift tables are provided as Appendix Tables 1, 2, 3, and 4, respectively, in the appendix to this review. My examination of these tables revealed no major differences between IXE treatment groups and placebo or the active comparator in terms of the proportions of patients with various magnitudes of change in this score. Data from the all IXE study database was comparable to findings from the other three study pools.

### **C. Follow-up on Subjects with QIDS Item #12 Worsening**

Lilly states that patients who experienced worsening on item #12 to a score of “3” were to be evaluated at the investigative site for risk of suicide and/or to be referred to a mental health provider for assessment. These patients also were discontinued from the trial. Patients who had worsening to a score of “1” or “2” had follow-up that was deemed appropriate by the investigator; the investigator may have terminated these patients from the study. No other follow-up was required by the sponsor.

## D. Blinding of C-CASA Reviewers to Study Segment

Lilly indicates that the reviewers who performed the C-CASA categorization were not familiar with the design and visit structure of the studies and, thus, were not familiar with the segments of the studies and were not informed of the treatment received during blinded phases of the trials. For some serious adverse events (SAEs), the study segment was included in the SAE narrative summary. Overall, the reports were evaluated by reviewers unfamiliar with the study segments.

## III. Conclusions and Recommendations

The sponsor has provided an adequate response to Dr. Alfaro's requests for clarification and additional information. This information yields no solid evidence that IXE treatment is associated with a significantly increased risk of suicidal thoughts or behaviors in the psoriasis patients studied. That said, there are two significant limitations to the available data:

1) Potential for missed events The QIDS-SR16, as used in these studies, is not an adequate instrument to monitor for the emergence of suicidal thinking or behavior. According to the study protocols, this self-rated instrument asks patients to rate their experience over the previous 7 days. Given that this instrument was rated relatively infrequently in these trials (e.g., at baseline, week 12, and week 24 in study RHAZ), there were huge time gaps in monitoring and, therefore, a large potential to miss suicidal events that occurred since the last visit but more than 7 days prior to the rating. This difficulty is partially overcome by documentation of suicidal experiences as adverse events independent of the QIDS-SR16 ratings. However, it is not clear that any active solicitation of information regarding those adverse events was performed. Rather, it appears that monitoring for these events was passive and may have resulted in missing suicidal thoughts or behavior that were either not spontaneously recalled by the patient at the visit or were deliberately withheld from the investigator. The use of a scale such as the Columbia-Suicide Severity Rating Scale (C-SSRS), which actively solicits information about suicidal thoughts or behavior since the last visit, should be used in future trials.

2) Study populations may not reflect the target population As mentioned by Dr. Alfaro, I too am concerned about the exclusion criteria for these trials which resulted in screening out patients with any history of a suicide attempt or any significant uncontrolled neuropsychiatric disorder. As documented in the literature, patients with psoriasis have an increased risk of depression and suicidal thoughts and behaviors.<sup>4</sup> Thus, it can be expected that IXE, if approved, will be used in a number of patients with poorly controlled depression or a history of a suicide attempt. Because these patients were excluded from the clinical trials, it remains unknown whether the risk of suicidal events is increased as a

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<sup>4</sup> Kurd SK, et al. The Risk of Depression, Anxiety, and Suicidality in Patients With Psoriasis. Arch Dermatol 2010;146(8):891-895.

result of IXE treatment in these patients. In addition, I would also note that the use of a highly select population, from a psychiatric perspective, casts a huge shadow of doubt over the sponsor's comparisons of the reporting rates of suicidal events in these trials with rates in the general psoriasis population unselected for psychiatric conditions. Future trials should allow these patients to enter the studies to permit us to reasonably gauge this risk.

In the end, the clinical trials data do not support a causal link between IXE therapy and suicidal events, in my judgment. But the above described deficiencies, which cannot be corrected at this stage, limit the ability to draw an inference regarding IXE and suicidal adverse events.

Please let us know if DPP can be of further assistance.

Gregory M. Dubitsky, M.D.  
Medical Officer  
Division of Psychiatry Products

**APPENDIX**  
**QIDS-SR16 ITEM #12 SHIFT TABLES<sup>5</sup>**

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<sup>5</sup> Tables were copied from pages 38-39, 41-42, 44, and 47 of the sponsor's September 4, 2015, submission (#0016).

**Appendix Table 1: QIDS-SR16 Item #12: Shifts From Baseline To Maximum Post-Baseline Score  
Induction Dosing Period  
Primary Psoriasis Placebo-Controlled Integrated Analysis Set (RHAZ, RHBA, and RHBC)**

Treatment	Maximum Baseline score	Maximum Post Baseline Score				Total n (%)
		0 n (%)	1 n (%)	2 n (%)	3 n (%)	
Placebo (N=791) (Nx=767)	0	708 ( 92.3%)	16 ( 2.1%)	0	0	724 ( 94.4%)
	1	14 ( 1.8%)	18 ( 2.3%)	1 ( 0.1%)	0	33 ( 4.3%)
	2	3 ( 0.4%)	4 ( 0.5%)	3 ( 0.4%)	0	10 ( 1.3%)
	3	0	0	0	0	0
	Total	725 ( 94.5%)	38 ( 5.0%)	4 ( 0.5%)	0	767 (100.0%)
IXE80Q4W (N=1161) (Nx=1129)	0	1043 ( 92.4%)	12 ( 1.1%)	6 ( 0.5%)	0	1061 ( 94.0%)
	1	46 ( 4.1%)	15 ( 1.3%)	1 ( 0.1%)	0	62 ( 5.5%)
	2	2 ( 0.2%)	0	4 ( 0.4%)	0	6 ( 0.5%)
	3	0	0	0	0	0
	Total	1091 ( 96.6%)	27 ( 2.4%)	11 ( 1.0%)	0	1129 (100.0%)
IXE80Q2W (N=1167) (Nx=1146)	0	1077 ( 94.0%)	14 ( 1.2%)	0	0	1091 ( 95.2%)
	1	38 ( 3.3%)	8 ( 0.7%)	2 ( 0.2%)	1 ( 0.1%)	49 ( 4.3%)
	2	4 ( 0.3%)	1 ( 0.1%)	1 ( 0.1%)	0	6 ( 0.5%)
	3	0	0	0	0	0
	Total	1119 ( 97.6%)	23 ( 2.0%)	3 ( 0.3%)	1 ( 0.1%)	1146 (100.0%)

Note: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; Nx = number of patients with baseline and at least one post baseline value; n = number of patients in category.

**Appendix Table 1 (cont'd): QIDS-SR16 Item #12: Shifts From Baseline To Maximum Post-Baseline Score  
 Induction Dosing Period  
 Primary Psoriasis Placebo-Controlled Integrated Analysis Set (RHAZ, RHBA, and RHBC)**

		Maximum Post Baseline Score				
Treatment	Maximum Baseline score	0 n (%)	1 n (%)	2 n (%)	3 n (%)	Total n (%)
Total IXE (N=2328) (Nx=2275)	0	2120 ( 93.2%)	26 ( 1.1%)	6 ( 0.3%)	0	2152 ( 94.6%)
	1	84 ( 3.7%)	23 ( 1.0%)	3 ( 0.1%)	1 ( 0.0%)	111 ( 4.9%)
	2	6 ( 0.3%)	1 ( 0.0%)	5 ( 0.2%)	0	12 ( 0.5%)
	3	0	0	0	0	0
	Total	2210 ( 97.1%)	50 ( 2.2%)	14 ( 0.6%)	1 ( 0.0%)	2275 (100.0%)
Total (N=3119) (Nx=3042)	0	2828 ( 93.0%)	42 ( 1.4%)	6 ( 0.2%)	0	2876 ( 94.5%)
	1	98 ( 3.2%)	41 ( 1.3%)	4 ( 0.1%)	1 ( 0.0%)	144 ( 4.7%)
	2	9 ( 0.3%)	5 ( 0.2%)	8 ( 0.3%)	0	22 ( 0.7%)
	3	0	0	0	0	0
	Total	2935 ( 96.5%)	88 ( 2.9%)	18 ( 0.6%)	1 ( 0.0%)	3042 (100.0%)

**Appendix Table 2: QIDS-SR16 Item #12: Shifts From Baseline To Maximum Post-Baseline Score  
Induction Dosing Period  
Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (RHBA and RHBC)**

Treatment	Maximum Baseline score	Maximum Post Baseline Score				Total n (%)
		0 n (%)	1 n (%)	2 n (%)	3 n (%)	
Placebo (N=360) (Nx=346)	0	316 ( 91.3%)	8 ( 2.3%)	0	0	324 ( 93.6%)
	1	8 ( 2.3%)	8 ( 2.3%)	1 ( 0.3%)	0	17 ( 4.9%)
	2	2 ( 0.6%)	2 ( 0.6%)	1 ( 0.3%)	0	5 ( 1.4%)
	3	0	0	0	0	0
	Total	326 ( 94.2%)	18 ( 5.2%)	2 ( 0.6%)	0	346 (100.0%)
ETN (N=739) (Nx=722)	0	671 ( 92.9%)	14 ( 1.9%)	5 ( 0.7%)	0	690 ( 95.6%)
	1	16 ( 2.2%)	9 ( 1.2%)	1 ( 0.1%)	0	26 ( 3.6%)
	2	2 ( 0.3%)	0	4 ( 0.6%)	0	6 ( 0.8%)
	3	0	0	0	0	0
	Total	689 ( 95.4%)	23 ( 3.2%)	10 ( 1.4%)	0	722 (100.0%)
IXE80Q4W (N=729) (Nx=711)	0	654 ( 92.0%)	7 ( 1.0%)	4 ( 0.6%)	0	665 ( 93.5%)
	1	32 ( 4.5%)	9 ( 1.3%)	1 ( 0.1%)	0	42 ( 5.9%)
	2	2 ( 0.3%)	0	2 ( 0.3%)	0	4 ( 0.6%)
	3	0	0	0	0	0
	Total	688 ( 96.8%)	16 ( 2.3%)	7 ( 1.0%)	0	711 (100.0%)
IXE80Q2W (N=734) (Nx=721)	0	674 ( 93.5%)	9 ( 1.2%)	0	0	683 ( 94.7%)
	1	28 ( 3.9%)	3 ( 0.4%)	1 ( 0.1%)	1 ( 0.1%)	33 ( 4.6%)
	2	4 ( 0.6%)	0	1 ( 0.1%)	0	5 ( 0.7%)
	3	0	0	0	0	0
	Total	706 ( 97.9%)	12 ( 1.7%)	2 ( 0.3%)	1 ( 0.1%)	721 (100.0%)

Note: PBO = Placebo; ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; Nx = number of patients with baseline and at least one post baseline value; n = number of patients in category.

**Appendix Table 2 (cont'd): QIDS-SR16 Item #12: Shifts From Baseline To Maximum Post-Baseline Score  
 Induction Dosing Period  
 Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (RHBA and RHBC)**

		Maximum Post Baseline Score				
Treatment	Maximum Baseline score	0 n (%)	1 n (%)	2 n (%)	3 n (%)	Total n (%)
Total IXE (N=1463) (Nx=1432)	0	1328 ( 92.7%)	16 ( 1.1%)	4 ( 0.3%)	0	1348 ( 94.1%)
	1	60 ( 4.2%)	12 ( 0.8%)	2 ( 0.1%)	1 ( 0.1%)	75 ( 5.2%)
	2	6 ( 0.4%)	0	3 ( 0.2%)	0	9 ( 0.6%)
	3	0	0	0	0	0
	Total	1394 ( 97.3%)	28 ( 2.0%)	9 ( 0.6%)	1 ( 0.1%)	1432 (100.0%)
Total (N=2562) (Nx=2500)	0	2315 ( 92.6%)	38 ( 1.5%)	9 ( 0.4%)	0	2362 ( 94.5%)
	1	84 ( 3.4%)	29 ( 1.2%)	4 ( 0.2%)	1 ( 0.0%)	118 ( 4.7%)
	2	10 ( 0.4%)	2 ( 0.1%)	8 ( 0.3%)	0	20 ( 0.8%)
	3	0	0	0	0	0
	Total	2409 ( 96.4%)	69 ( 2.8%)	21 ( 0.8%)	1 ( 0.0%)	2500 (100.0%)

**Appendix Table 3: QIDS-SR16 Item #12: Shifts From Baseline To Maximum Post-Baseline Score  
Maintenance Dosing Period  
Psoriasis Maintenance Integrated Analysis Set (RHAZ and RHBA)**

Treatment	Baseline score	Maximum Post Baseline Score				Total n (%)
		0 n (%)	1 n (%)	2 n (%)	3 n (%)	
Placebo (N=402) (Nx=351)	0	326 ( 92.9%)	5 ( 1.4%)	1 ( 0.3%)	0	332 ( 94.6%)
	1	10 ( 2.8%)	4 ( 1.1%)	3 ( 0.9%)	0	17 ( 4.8%)
	2	1 ( 0.3%)	1 ( 0.3%)	0	0	2 ( 0.6%)
	3	0	0	0	0	0
	Total	337 ( 96.0%)	10 ( 2.8%)	4 ( 1.1%)	0	351 (100.0%)
IXE80Q12W (N=408) (Nx=383)	0	351 ( 91.6%)	9 ( 2.3%)	5 ( 1.3%)	0	365 ( 95.3%)
	1	13 ( 3.4%)	4 ( 1.0%)	1 ( 0.3%)	0	18 ( 4.7%)
	2	0	0	0	0	0
	3	0	0	0	0	0
	Total	364 ( 95.0%)	13 ( 3.4%)	6 ( 1.6%)	0	383 (100.0%)
IXE80Q4W (N=416) (Nx=399)	0	375 ( 94.0%)	4 ( 1.0%)	2 ( 0.5%)	0	381 ( 95.5%)
	1	8 ( 2.0%)	8 ( 2.0%)	0	0	16 ( 4.0%)
	2	1 ( 0.3%)	1 ( 0.3%)	0	0	2 ( 0.5%)
	3	0	0	0	0	0
	Total	384 ( 96.2%)	13 ( 3.3%)	2 ( 0.5%)	0	399 (100.0%)
Total IXE (N=824) (Nx=782)	0	726 ( 92.8%)	13 ( 1.7%)	7 ( 0.9%)	0	746 ( 95.4%)
	1	21 ( 2.7%)	12 ( 1.5%)	1 ( 0.1%)	0	34 ( 4.3%)
	2	1 ( 0.1%)	1 ( 0.1%)	0	0	2 ( 0.3%)
	3	0	0	0	0	0
	Total	748 ( 95.7%)	26 ( 3.3%)	8 ( 1.0%)	0	782 (100.0%)

Note: PBO = Placebo; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE = Ixekizumab; N = number of patients in the analysis population; Nx = number of patients with baseline and at least one post baseline value; n = number of patients in category.

**Appendix Table 4: QIDS-SR16 Item #12: Shifts From Baseline To Maximum Post-Baseline Score  
All Dosing Periods  
All Psoriasis IXE Exposure Integrated Analysis Set (All IXE Trials in Psoriasis)**

Treatment	Baseline score	Maximum Post Baseline Score				Total n (%)
		0 n (%)	1 n (%)	2 n (%)	3 n (%)	
Pooled IXE	0	3705 ( 90.5%)	135 ( 3.3%)	33 ( 0.8%)	1 ( 0.0%)	3874 ( 94.6%)
(N=4209)	1	106 ( 2.6%)	67 ( 1.6%)	17 ( 0.4%)	1 ( 0.0%)	191 ( 4.7%)
(Nx=4093)	2	10 ( 0.2%)	1 ( 0.0%)	17 ( 0.4%)	0	28 ( 0.7%)
	3	0	0	0	0	0
	Total	3821 ( 93.4%)	203 ( 5.0%)	67 ( 1.6%)	2 ( 0.0%)	4093 (100.0%)

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/s/  
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