CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125521
Drug Name:	TALTZ (ixekizumab) 80 mg subcutaneous injections
Indication(s):	Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant:	Eli Lilly
Date(s):	Letter Date: March 23, 2015
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Review Priority:	Standard
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Keywords:

Psoriasis, superiority, non-inferiority, maintenance

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1 EXECUTIVE SUMMARY

The applicant, Eli Lilly, is seeking approval of TALTZ (ixekizumab) 80 mg subcutaneous injections for the indication of treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The applicant submitted data from three randomized, multicenter, placebo-controlled, parallel-group, pivotal Phase 3 trials (Trials RHAZ, RHBA, and RHBC). The trials enrolled subjects 18 years of age and older who had plaque psoriasis with Psoriasis Area and Severity Index (PASI) score ≥ 12, Static Physician's Global Assessment (sPGA) score of at least 3 (moderate) and body surface area (BSA) involvement ≥ 10%. All three trials evaluated two dose regimens of TALTZ during a 12-week induction period (Weeks 0-12). Subjects randomized to TALTZ 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 (Weeks 12-60).

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 ≥ 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 ≥4-point improvement of itch severity as measured by an itch Numeric Rating Scale (NRS). Table 1 summarizes the efficacy results for the co-primary and secondary efficacy endpoints at Week 12. For all three trials, both dose regimens of TALTZ were statistically superior (p-values < 0.001) to placebo for all of the efficacy endpoints listed in Table 1.

Table 1: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (ITT, NRI)

	Trial RHAZ			Trial RHBA			Trial RHBC		
	TALTZ 80 mg			TALTZ 80 mg			TALTZ 80 mg		
Endpoints	Q2W N=433	Q4W N=432	Placebo N=431	Q2W N=351	Q4W N=347	Placebo N=168	Q2W N=385	Q4W N=386	Placebo N=193
Co-Primary:									
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%
Secondary:									
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%)	258/303 (85%)	225/293 (77%)	19/135 (14%)	264/320 (83%)	250/313 (80%)	33/158 (21%)

Source: Reviewer's Analysis

Trials RHBA and RHBC included etanercept as an active comparator. In both trials, all subjects randomized to etanercept at US study sites received US-licensed Enbrel. Subjects randomized to

etanercept at non-US study sites received EU-approved etanercept (except 30 subjects in Argentina, Chile, and Mexico in Trial RHBC received US-licensed Enbrel). The applicant has not provided an adequate bridge to scientifically justify the relevance of the comparative data generated using EU-approved etanercept. However, 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 for both the overall population and the US only subgroup are presented in Section 3.2.8. In both trials, 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.

2 INTRODUCTION

2.1 Overview

The applicant, Eli Lilly, is seeking approval of TALTZ (ixekizumab) 80 mg subcutaneous injections for the indication of treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that specifically neutralizes IL-17A.

The safety and efficacy of TALTZ was evaluated in three pivotal Phase 3 trials (Trials RHAZ, RHBA and RHBC). All three trials evaluated two dose regimens of TALTZ (160 mg loading dose followed by 80 mg Q2W or 80 mg Q4W) during a 12-week induction period (Weeks 0-12). Trials RHBA and RHBC included etanercept as an active comparator. Trials RHAZ and RHBA evaluated maintenance of efficacy for an additional 48 weeks (Weeks 12-60). An overview of the trials is presented in Table 2.

Table 2: Clinical Study Overview for the Pivotal Phase 3 Trials

Trial	Study Sites	Study Population	Treatment Arms	Number of Subjects	Dates
I1F-MC-RHAZ (UNCOVER 1)	105 International centers	Age ≥ 18 years, diagnosis of chronic plaque psoriasis of at least 6 months prior to randomization, candidates for systemic therapy and/or phototherapy, PASI ≥ 12, sPGA ≥ 3 (moderate), BSA ≥ 10%	TALTZ 80 mg Q2W TALTZ 80 mg Q4W Placebo	433 432 431	12/6/2011 – 8/7/2014(1)
I1F-MC-RHBA (UNCOVER 2)	121 International centers		TALTZ 80 mg Q2W TALTZ 80 mg Q4W Etanercept Placebo	351 347 358 168	5/30/2012 – 10/1/2014(2)
I1F-MC-RHBC (UNCOVER 3)	119 International centers		TALTZ 80 mg Q2W TALTZ 80 mg Q4W Etanercept Placebo	385 386 382 193	8/11/2012 – 5/22/2014(3)

(1) Date of database lock after all subjects completed the maintenance dosing period (Week 60).
(2) Date of database lock after all subjects completed the Week 36 visit of the maintenance dosing period.
(3) Date of database lock after all subjects completed the Week 12 visit.

2.2 Regulatory History

The clinical development program for TALTZ for the treatment of moderate-to-severe plaque psoriasis was conducted under IND 100834. The IND for TALTZ was opened on November 1, 2007. The first meeting held with the applicant was the End-of-Phase 2 (EOP2) meeting on June 22, 2011. For that meeting, the applicant submitted interim results from a Phase 2 dose-ranging trial (Trial RHAJ) and proposed three pivotal Phase 3 trials (Trials RHAZ, RHBA, and RHBC).

Following the EOP2 meeting, the applicant submitted the protocol for Trial RHAZ on September 30, 2011 and the protocol for Trial RHBA on December 9, 2011. The Agency provided comments regarding the protocol for Trial RHAZ in an advice letter sent on February 7, 2012. Following the advice letter, the applicant submitted their responses on March 12, 2012 and noted that some of the Agency's comments could not be implemented because Trial RHAZ was already ongoing. The applicant also noted that the protocols for Trials RHBA and RHBC were amended to include the Agency's comments conveyed in the advice letter. The applicant submitted the protocol amendments for Trials RHAZ and RHBA on March 20, 2012 and for Trial RHBC on April 19, 2012. Comments regarding these protocol amendments were sent in two advice letters, one on July 9, 2012 for Trials RHAZ and RHBA and one on July 18, 2012 for Trial RHBC.

On November 30, 2012, the applicant submitted protocol amendments for Trials RHAZ, RHBA, and RHBC. The statistical analysis plans (SAPs) for the three trials and an integrated efficacy analysis plan were submitted on January 4 and February 6, 2013, respectively. An advice letter for the protocol amendments was sent on April 9, 2013. An advice letter for the SAPs and the integrated efficacy analysis plan was sent on April 17, 2013.

On November 13, 2013, the applicant requested a Type C meeting to obtain guidance on the logistical and formatting aspects of the planned BLA prior to the pre-BLA meeting. Written responses to the applicant's questions were sent to the applicant on January 28, 2014. The pre-BLA meeting was held on October 29, 2014.

On May 30, 2014, the applicant requested a Type C meeting to discuss the applicant's plan to provide a bridge between US-licensed Enbrel and EU-approved etanercept. The meeting was scheduled for September 17, 2014; however, the applicant cancelled the meeting. Therefore, the Agency did not have an opportunity to discuss the applicant's plans or provide recommendations prior to the submission of the BLA.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The datasets in this review are archived at the following locations:
\\cdsesub5\EVSPROD\BLA125521\0000\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses and no request for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design

The applicant conducted three pivotal Phase 3 trials (Trials RHAZ, RHBA, and RHBC). For all three trials, the key inclusion criteria that defined the study population were identical and are as follows:

- Male or female 18 years or older
- Have a confirmed diagnosis of chronic plaque psoriasis for at least 6 months prior to randomization
- Have moderate-to-severe plaque psoriasis at screening and baseline defined by:
    - Psoriasis Area Severity Index (PASI) score ≥ 12, see Section 3.2.2 for details on the calculation of PASI
    - Body Surface Area (BSA) ≥ 10%
    - Static Physician's Global Assessment (sPGA) ≥ 3 (moderate), see Section 3.2.2 for details on the sPGA scale
- Must be a candidate for phototherapy and/or systemic therapy

Figures 1, 2, and 3 present the study designs for Trials RHAZ, RHBA, and RHBC. All three are multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials evaluating the safety and efficacy of TALTZ for the treatment of moderate-to-severe plaque psoriasis. All three trials evaluated two dose regimens of TALTZ (160 mg loading dose followed by 80 mg Q2W or 80 mg Q4W) during a 12-week induction period (Weeks 0-12). Trials RHBA and RHBC included etanercept as an active comparator. For Trial RHAZ, subjects were randomized in a 1:1:1 ratio (TALTZ 80 mg Q2W, TALTZ 80 mg Q4W, and placebo) at Week 0. For Trials RHBA and RHBC, subjects were randomized in a 2:2:1:2 ratio (TALTZ 80 mg Q2W, TALTZ 80 mg Q4W, placebo, and etanercept).

Trials RHAZ and RHBA evaluated maintenance of efficacy for an additional 48 weeks (Weeks 12-60). At Week 12, subjects who entered the maintenance dosing period were classified as either responders (sPGA ≤ 1) or non-responder (sPGA ≥ 2). Subjects' responder status at Week 12 and treatment during the induction period determined their treatment for the maintenance period.

- TALTZ during induction period: Responders were re-randomized in a 1:1:1 ratio to 1 of 3 treatment groups (TALTZ 80 mg Q4W, TALTZ 80 mg Q12W, or placebo). Non-responders received TALTZ 80 mg Q4W.

- Placebo during induction period: Responders received placebo and non-responders received TALTZ 80 mg Q4W.
- Etanercept during induction period (Trial RHBA): Responders received placebo and non-responders received TALTZ 80 mg Q4W.

During the maintenance period, all treatments remained in effect until relapse (sPGA ≥ 3). Subjects who relapsed were treated as follows:

- Subjects receiving TALTZ 80 mg Q4W who relapsed continued on 80 mg Q4W in order to maintain the study blind and to see if study response can be regained with continued treatment.
- Subject receiving TALTZ 80 mg Q12W who relapsed switched to 80 mg Q4W.
- Subjects receiving placebo who relapsed switched to TALTZ 80 mg Q4W.

All three trials contain a long-term extension period. Subjects who maintained their efficacy response with adequate overall safety during the maintenance period, as deemed by the investigator, were permitted to enter the long-term extension period. For Trial RHBC, all subjects received TALTZ 80 mg Q4W during this period. For Trials RHAZ and RHBA, the dosing regimen in this period was as follows:

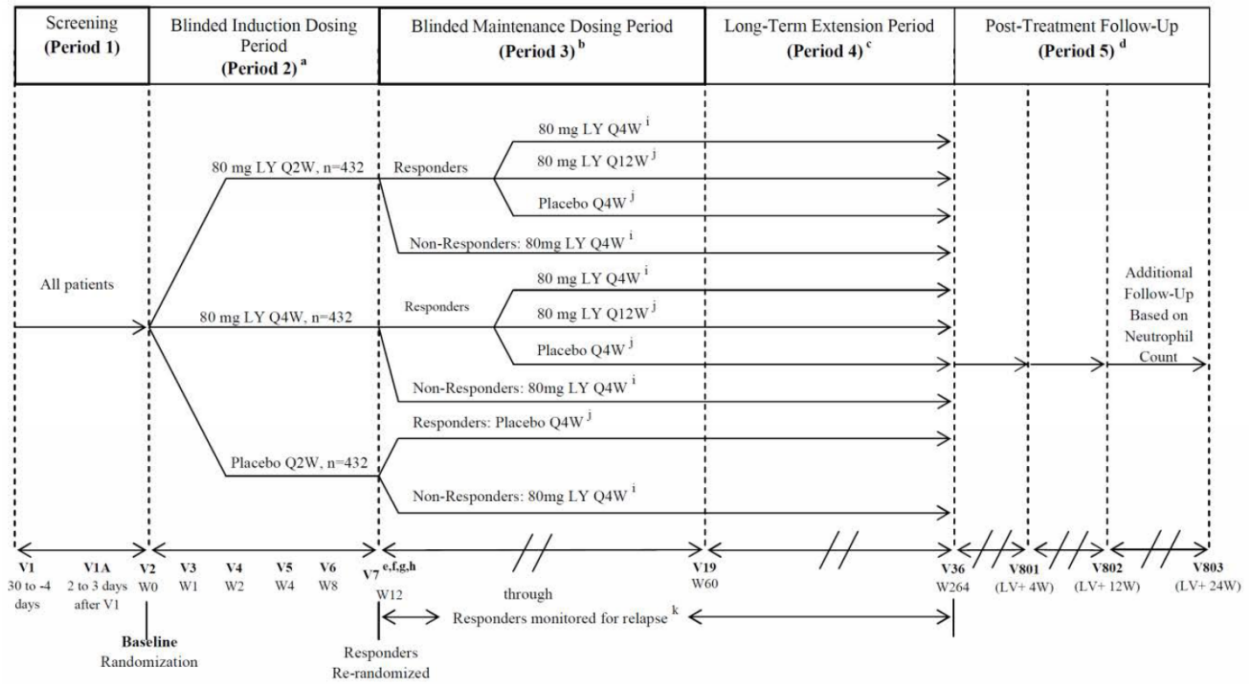
- Responders to TALTZ who were re-randomized at Week 12 but had not relapsed by Week 60 remained on their assigned dosage regimen (80 mg Q4W, 80 mg Q12W, or placebo) until relapse, at which time they were placed on TALTZ 80 mg Q4W.
- Responders to TALTZ who were re-randomized at Week 12 but who relapsed before Week 60 remained on TALTZ 80 mg Q4W following their relapse through the end of the long-term extension period.
- Subjects who were originally randomized to placebo and who were responders at Week 12 but had not relapsed by Week 60 remained on placebo until relapse, at which time they were placed on TALTZ 80 mg Q4W.
- Subjects who were originally randomized to etanercept (Trial RHBA) and who were responders at Week 12 but had not relapsed by Week 60 remained on placebo until relapse (sPGA ≥ 3), at which time they were placed on TALTZ 80 mg Q4W.
- All non-responders, regardless of initial randomization, remained on TALTZ 80 mg Q4W from Week 12 through the end of the long-term extension period.

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 ≥3 conventional systemic therapies), and weight (<100 kg or ≥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).

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

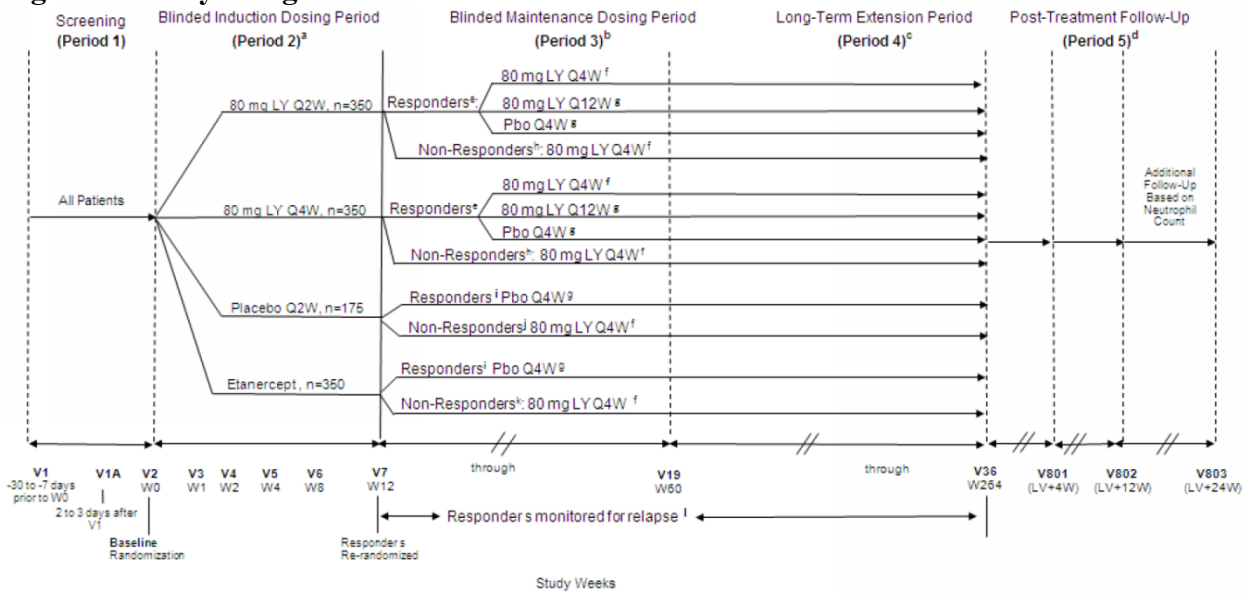
contains all data collected up to a database lock (October 1, 2014) that occurred after all subjects enrolled completed the Week 36 visit of the maintenance dosing period. For Trial RHBC, the BLA application contains all data up to Week 12 and all safety data up to the database lock (May 22, 2014).

Figure 1: Study Design Schematic for Trial RHAZ



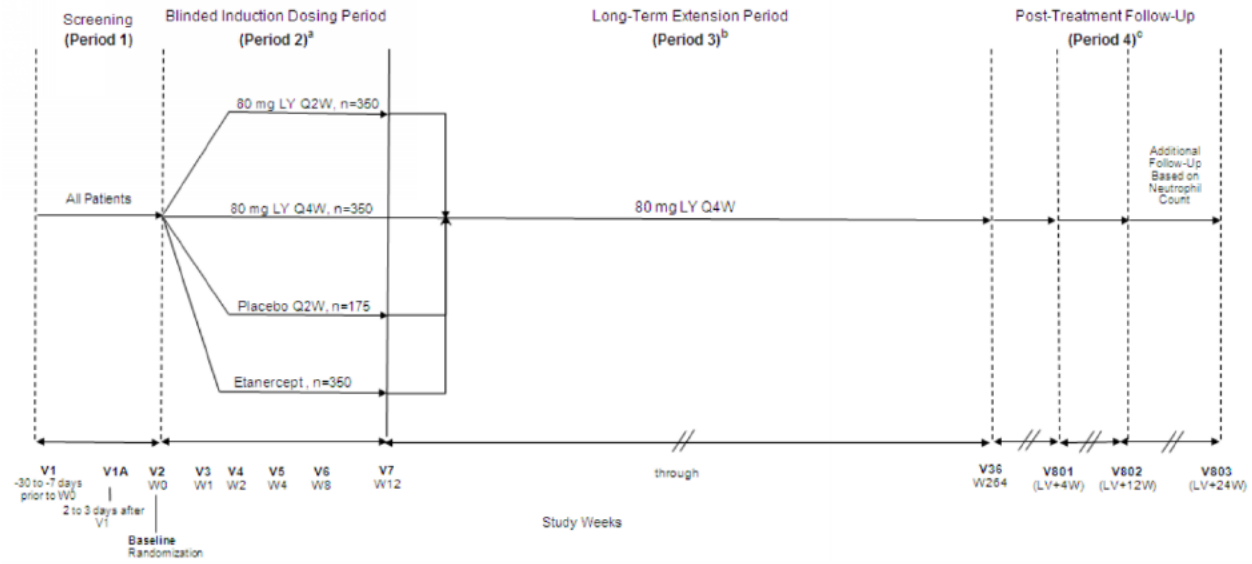
Source: Study Report for Trial RHAZ

Figure 2: Study Design Schematic for Trial RHBA



Source: Study Report for Trial RHBA

Figure 3: Study Design Schematic for Trial RHBC



Source: Study Report for Trial RHBC

3.2.2 Endpoints

For all three trials, the protocol-specified co-primary efficacy endpoints were:

- 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
- Proportion of subjects achieving a ≥ 75% improvement in PASI (PASI-75) from baseline at Week 12

There were some differences regarding the protocol-specified secondary efficacy endpoints between the three trials. Table 3 presents the secondary endpoints along with the trials that specified them. In the advice letter dated February 7, 2012, the Agency stated that (b) (4) (b) (4) and cannot agree that it is well-defined with adequate content validity in the targeted patient population with moderate-to-severe plaque psoriasis to support labeling and advertising. Therefore, the results (b) (4) are not presented in this review.

Table 3: Secondary Efficacy Endpoints

Endpoint	Trial
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

For all three trials, the protocols specified many "other" secondary efficacy endpoints; however, those endpoints were not included in the multiplicity testing strategy. Therefore, these "other" secondary efficacy endpoints are not presented in this review. Section 3.2.3 provides details on how the co-primary and secondary efficacy endpoints listed above were analyzed across the various treatment arms (i.e., superiority vs. non-inferiority and multiplicity control).

Table 4: Static Physician's Global Assessment (sPGA) Scale

Numerical score	Description	Criteria
0	Clear	Plaque elevation = 0 (no elevation over normal skin), Scaling = 0 (no scale), Erythema = 0 (residual post-inflammatory hyperpigmentation or hypopigmentation may be present)
1	Minimal	Plaque elevation = +/- (possible but difficult to ascertain whether there is a slight elevation above normal skin), Scaling = +/- (surface dryness with some white coloration), Erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped), Scaling = fine (fine scale partially or mostly covering lesions), Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges), Scaling = coarser (coarse scale covering most of all of the lesions), Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard sharp edges), Scaling = coarse (coarse, non tenacious scale predominates covering most or all of the lesions), Erythema = severe (very bright red coloration)
5	Very Severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges), Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface), Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Source: Protocols for Trials RHAZ, RHBA, and RHBC

Psoriasis Area Severity Index (PASI):

PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The index ranges from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

Itch Numeric Rating Scale (NRS):
The Itch NRS is a single-item, patient-reported outcome (PRO) measure designed to capture information on the overall severity of a patient's itching due to their psoriatic skin condition by having the patient circle the integer that best describes the worst level of itching in the past 24 hours on an 11-point NRS anchored at 0 representing "no itching" and 10 representing "worst itch imaginable."

Nail Psoriasis Severity Index (NAPSI):
The fingernail is divided with imaginary horizontal and longitudinal lines into quadrants, and examined for two distinct assessments: nail matrix assessment and nail bed assessment. Each assessment is graded depending on the presence or absence of any of the features of fingernail bed and fingernail matrix psoriasis in each quadrant, as follows: 0 = none, 1 = present in one quadrant of nail, 2 = present in two quadrants of nail, 3 = present in three quadrants of nail, 4 = present in four quadrants of nail. The NAPSI score of a fingernail is the sum of scores in fingernail bed and fingernail matrix from each quadrant (maximum of 8). The sum of the fingernail scores will be added, resulting in a NAPSI total score with a range of 0 to 80. If an individual fingernail assessment is missing (not done), the average of the remaining measured digits will be imputed and added to the sum. If <50% of the fingernail assessments are missing the imputation will be performed. If more than 50% of the assessments are missing, then the sum of the scores will be left as missing.

Dermatology Life Quality Index (DLQI):
The DLQI is a patient-administered, 10-question, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment, as assessed over the past week. Response categories include "not at all", "a little", "a lot" and "very much", with corresponding numerical scores of 0, 1, 2, and 3 respectively and unanswered ("not relevant") responses scored as 0. A DLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment).

3.2.3 Statistical Methodologies

The primary analysis population specified in the protocols was the intent-to-treat (ITT) population, defined as randomized subjects. The protocols also specified supportive analyses using the per-protocol (PP) population, defined as all randomized subjects who are compliant with therapy, who do not have significant protocol violations, and whose investigator site does not have significant GCP issues that require 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 subjects participated in the trial and prior to Week 12.

For Trials RHBA and RHBC, the protocols specified pooling centers with fewer than 5 subjects per treatment arm. Starting with the smallest center, pooling began with the next smallest center(s) within each country until the criteria for at least 5 subjects per treatment group have been met. If this results in a center with fewer than 5 subjects per treatment group, the protocol

specified that these centers will be pooled together with the next smallest center in another country within the same region. Pooling for Trial RHAZ was not specified in the protocol.

For Trial RHAZ, the protocol-specified analysis method for the co-primary efficacy endpoints (both binary) was a logistic regression with treatment, geographic region, previous non-biologic therapy, and weight (i.e., the factors used to stratify the randomization) in the model. The effects of study center for the co-primary efficacy endpoints was evaluated using logistic regression with treatment, center, and the interaction of treatment-by-center as factors in the model. The protocol specified that if a significant treatment-by-center interaction is found at the 0.10 level, then "further investigations will be performed in an attempt to explain the interaction in terms of patient characteristics." However, it should be noted that a significant treatment-by-center interaction was not found in Trial RHAZ.

For Trials RHBA and RHBC, the protocol-specified analysis method for the co-primary efficacy endpoints was a Cochran-Mantel-Haenszel (CMH) test stratified by pooled center. The protocols specified that the effects of center on the co-primary efficacy endpoints will be investigated based on the actual centers as well as the pooled centers. The protocols specified using logistic regression with treatment, center, and the interaction of treatment-by-center as factors in the model. The protocols specified that if a significant treatment-by-center interaction is found at the 0.10 level, then "further investigations will be performed in an attempt to explain the interaction in terms of patient characteristics." However, it should be noted that a significant treatment-by-center (actual centers and pooled centers) interaction was not found in Trials RHBA and RHBC.

The protocols specified analyzing binary secondary efficacy endpoints in the same manner as the co-primary efficacy endpoints (i.e., logistic regression for Trials RHAZ and CMH test for Trials RHBA and RHBC). The protocol specified analyzing the continuous secondary efficacy endpoints (i.e., change from baseline in DLQI and NAPSI at Week 12) with a mixed effect for repeated measures (MMRM) model. As noted in Section 3.2.2, only Trials RHAZ and RHBC included these endpoints as "major" secondary efficacy endpoints.

- For Trial RHAZ, the protocol specified the MMRM model to include treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, baseline value, visit, and treatment-by-visit interaction as fixed effects. The covariance structure to model the within-subject errors was specified to be unstructured; however, if the unstructured covariance matrix resulted in lack of convergence, the protocol specified using the Toeplitz covariance structure.
- For Trial RHBC, the protocol specified the MMRM model to include treatment, pooled center, baseline value, visit, and the interaction of treatment-by-visit as fixed effects. The covariance structure to model the within-subject errors was specified to be unstructured; however, if the unstructured covariance matrix resulted in lack of convergence, the protocol specified using the Toeplitz covariance structure.

In addition to the MMRM model, the protocols specified analyzing the continuous secondary endpoints using analysis of covariance (ANCOVA). For Trial RHAZ, the protocol specified including treatment, geographic region, previous non-biologic systemic therapy, weight, and baseline value in the model. For Trial RHBC, the protocol specified including treatment, pooled center and baseline value.

The protocols specified a sequential gatekeeping approach based on the Bonferroni test to control the Type I error rate for testing multiple primary and secondary efficacy endpoints and two dose regimens of TALTZ (i.e., Q2W and Q4W). Tables 5, 6, and 7 list the primary and secondary efficacy endpoints for Trials RHAZ, RHBA and RHBC, respectively. The protocols specified two parallel branches, one for each dose regimen of TALTZ, where the tests listed in the following tables will be sequentially tested at the $\alpha = 0.025$ level (i.e., α was split between the two dose regimens of TALTZ). For the secondary endpoint of maintaining sPGA of 0 or 1 from Week 12 to Week 60 (i.e., Test 6 for Trial RHAZ and Test 13 for Trial RHBA), there are two comparisons (i.e., maintenance dose regimens of Q4W and Q12W vs. placebo) for each branch (i.e., induction dose regimens of Q2W and Q4W); therefore, the protocols specified conducting tests at the $\alpha = 0.0125$ level.

Table 5: Multiplicity Testing Strategy for Trial RHAZ

Test Set	Endpoint	Comparison
Test 1 (Primary 1)	sPGA of 0 or 1 at Week 12	Superiority to placebo
Test 2 (Primary 2)	PASI-75 at Week 12	Superiority to placebo
Test 3 (Secondary 1)	sPGA of 0 at Week 12	Superiority to placebo
Test 4 (Secondary 2)	PASI-90 at Week 12	Superiority to placebo
Test 5 (Secondary 3)	PASI-100 at Week 12	Superiority to placebo
Test 6 (Secondary 4)	Maintaining sPGA of 0 or 1 from Week 12 to Week 60	Superiority to re-randomized placebo
Test 7 (Secondary 5)	≥ 4-point reduction in Itch NRS from baseline at Week 12	Superiority to placebo
Test 8 (Secondary 6)	Change from baseline in DLQI at Week 12	Superiority to placebo
Test 9 (Secondary 7)	Change from baseline in NAPSI (for fingernails) at Week 12	Superiority to placebo

Table 6: Multiplicity Testing Strategy for Trial RHBA

Test Set	Endpoint	Comparison
Test 1 (Primary 1)	sPGA of 0 or 1 at Week 12	Superiority to placebo
Test 2 (Primary 2)	PASI-75 at Week 12	Superiority to placebo
Test 3 (Primary 3)	sPGA of 0 or 1 at Week 12	Non-inferiority to etanercept
Test 4 (Primary 4)	PASI-75 at Week 12	Non-inferiority to etanercept
Test 5 (Primary 5)	sPGA of 0 or 1 at Week 12	Superiority to etanercept
Test 6 (Primary 6)	PASI-75 at Week 12	Superiority to etanercept
Test 7 (Secondary 1)	sPGA of 0 at Week 12	Superiority to placebo
Test 8 (Secondary 2)	PASI-90 at Week 12	Superiority to placebo
Test 9 (Secondary 3)	PASI-100 at Week 12	Superiority to placebo
Test 10 (Secondary 4)	sPGA of 0 at Week 12	Superiority to etanercept
Test 11 (Secondary 5)	PASI-90 at Week 12	Superiority to etanercept
Test 12 (Secondary 6)	PASI-100 at Week 12	Superiority to etanercept
Test 13 (Secondary 7)	Maintaining sPGA of 0 or 1 from Week 12 to Week 60	Superiority to re-randomized placebo

Table 7: Multiplicity Testing Strategy for Trial RHBC

Test Set	Endpoint	Comparison
Test 1 (Primary 1)	sPGA of 0 or 1 at Week 12	Superiority to placebo
Test 2 (Primary 2)	PASI-75 at Week 12	Superiority to placebo
Test 3 (Primary 3)	sPGA of 0 or 1 at Week 12	Non-inferiority to etanercept
Test 4 (Primary 4)	PASI-75 at Week 12	Non-inferiority to etanercept
Test 5 (Primary 5)	sPGA of 0 or 1 at Week 12	Superiority to etanercept
Test 6 (Primary 6)	PASI-75 at Week 12	Superiority to etanercept
Test 7 (Secondary 1)	sPGA of 0 at Week 12	Superiority to placebo
Test 8 (Secondary 2)	PASI-90 at Week 12	Superiority to placebo
Test 9 (Secondary 3)	PASI-100 at Week 12	Superiority to placebo
Test 10 (Secondary 4)	sPGA of 0 at Week 12	Superiority to etanercept
Test 11 (Secondary 5)	PASI-90 at Week 12	Superiority to etanercept
Test 12 (Secondary 6)	PASI-100 at Week 12	Superiority to etanercept
Test 13 (Secondary 7)	≥ 4-point reduction in Itch NRS from baseline at Week 12	Superiority to placebo
Test 14 (Secondary 8)	Change from baseline in DLQI at Week 12	Superiority to placebo
Test 15 (Secondary 9)	Change from baseline in NAPSI (for fingernails) at Week 12	Superiority to placebo

For the non-inferiority analysis against etanercept (Trials RHBA and RHBC), the protocol specified using a non-inferiority margin of -12% for each co-primary efficacy endpoint. The applicant stated "this non-inferiority margin represents a ≥70% preservation of the etanercept effect (based upon the difference between etanercept and placebo) observed in historical Phase 3 studies for etanercept 50 mg twice weekly compared with placebo (Leonardi et al. 2003; Papp et al. 2005)." The protocol specified testing for non-inferiority by using a 2-sided 97.5% confidence interval for the difference in the proportion of responders between TALTZ and etanercept, claiming non-inferiority if the lower bound is greater than the non-inferiority margin of -12%. If the lower bound is greater than 0, then TALTZ was deemed to be superior to etanercept.

The protocol-specified primary imputation method for the handling of missing binary data was non-responders imputation (NRI). For the co-primary efficacy endpoints (both binary), the applicant conducted a sensitivity analysis for the handling of missing data using the placebo multiple imputation (pMI) approach. The approach assumes that the statistical behavior of drug- and placebo-treated subjects after discontinuing study product becomes that of the placebo-treated subjects. For this approach, missing data for both subjects on active and placebo will be imputed based on only the placebo arm data using a regression model with visit and baseline value as covariates.

For continuous endpoints, the primary analysis method specified in the protocols is the MMRM approach, which does not impute missing data. The protocol specified the following as sensitivity analyses for the handling of missing data:

- Modified baseline observation carried forward (mBOCF): subjects discontinuing investigational product due to an AE, the baseline observation will be carried forward to the corresponding endpoint for evaluation. For subjects discontinuing investigational product for any other reason, the last non-missing post-baseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. Randomized subjects without at least one post-baseline observation will not be included

for evaluation with the exception of subjects discontinuing study treatment due to an AE.

- Last observation carried forward (LOCF): this approach is identical to the mBOCF approach, with one exception. For subjects discontinuing investigational product due to an AE, the last non-missing post-baseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. Randomized subjects without at least one post-baseline observation will not be included for evaluation.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Trial RHAZ enrolled a total of 1296 subjects from 105 centers. Trial RHBA enrolled a total of 1224 subjects from 121 centers. Trial RHBC enrolled a total of 1346 subjects from 119 centers. Tables 8, 9, and 10 present the disposition of subjects during the induction period for Trials RHAZ, RHBA, and RHBC, respectively. The discontinuation rates were generally similar between treatment arms within each trail and between each trial. The demographics and baseline disease characteristics are displayed in Tables 11, 12 and 13 for Trials RHAZ, RHBA, and RHBC, respectively. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial; however, for Trial RHBA, subjects in the TALTZ 80 mg Q2W had on average a slightly lower weight compared to the other treatment arms.

Table 8: Disposition of Subjects for Induction Period in Trial RHAZ (ITT)

	TALTZ 80 mg		
	Q2W (N=433)	**Q4W (N=432)**	**Placebo (N=431)**
Discontinued	18 (4%)	24 (6%)	24 (6%)
Adverse Event	10	10	6
Investigator Decision	1	0	0
Lack of Efficacy	0	1	7
Lost to Follow-Up	2	0	1
Protocol Violation	0	6	3
Sponsor Decision	1	1	1
Subject Decision	5	6	6

Source: Reviewer's Analysis (same as Applicant's Analysis)

Table 9: Disposition of Subjects for Induction Period in Trial RHBA (ITT)

	TALTZ 80 mg			
	Q2W (N=351)	**Q4W (N=347)**	**Etanercept (N=358)**	**Placebo (N=168)**
Discontinued	9 (3%)	19 (5%)	25 (7%)	10 (6%)
Adverse Event	4	5	5	1
Investigator Decision	1	0	0	1
Lack of Efficacy	0	1	3	3
Lost to Follow-Up	0	2	5	1
Protocol Violation	2	5	4	2
Subject Decision	2	6	8	2

Source: Reviewer's Analysis (same as Applicant's Analysis)

Table 10: Disposition of Subjects for Induction Period in Trial RHBC (ITT)

	TALTZ 80 mg			
	Q2W (N=385)	Q4W (N=386)	Etanercept (N=382)	Placebo (N=193)
Discontinued	22 (6%)	26 (7%)	13 (3%)	10 (5%)
Adverse Event	8	9	4	2
Investigator Decision	2	1	2	1
Lack of Efficacy	1	2	0	0
Lost to Follow-Up	0	2	2	3
Protocol Violation	7	8	3	1
Subject Decision	4	4	2	3

Source: Reviewer's Analysis (same as Applicant's Analysis)

Table 11: Demographics and Baseline Disease Characteristics in Trial RHAZ (ITT)

	TALTZ 80 mg		
	Q2W (N=433)	Q4W (N=432)	Placebo (N=431)
Age (years)			
Mean (SD)	45 (12)	46 (13)	46 (13)
Median	45	46	47
Range	17 – 75	18 – 88	18 – 79
Gender			
Male	291 (67%)	289 (67%)	303 (70%)
Female	142 (33%)	143 (33%)	128 (30%)
Race			
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%)
Weight (kg)			
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%)
Country			
US	159 (37%)	156 (36%)	146 (34%)
Non-US	274 (63%)	276 (64%)	285 (66%)
sPGA			
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%)
PASI			
Mean (SD)	20 (8)	20 (7)	20 (9)
Median	17.5	17.8	17.2
Range	12 – 60	12 – 61.2	12 – 69.2
Percent BSA			
Mean (SD)	28 (18)	27 (16)	27 (18)
Median	22.0	21.0	20.0
Range	10 – 95	10 – 92	10 – 95

Source: Reviewer's Analysis (same as Applicant's Analysis)

Table 12: Demographics and Baseline Disease Characteristics in Trial RHBA (ITT)

	TALTZ 80 mg		

	Q2W (N=351)	Q4W (N=347)	Etanercept (N=358)	Placebo (N=168)
Age (years)				
Mean (SD)	45 (13)	45 (14)	45 (13)	45 (12)
Median	44	45	46	46
Range	18 – 84	18 – 82	18 – 79	20 – 76
Gender				
Male	221 (63%)	244 (70%)	236 (66%)	120 (71%)
Female	130 (37%)	103 (30%)	122 (34%)	48 (29%)
Race[(1)]				
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%)
Weight (kg)				
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%)
Country				
US	104 (30%)	105 (30%)	111 (31%)	49 (29%)
Non-US	247 (70%)	242 (70%)	247 (69%)	119 (71%)
sPGA				
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%)
PASI				
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
Percent BSA				
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 (same as Applicant'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.

Table 13: Demographics and Baseline Disease Characteristics in Trial RHBC (ITT)

	TALTZ 80 mg		

	Q2W (N=385)	Q4W (N=386)	Etanercept (N=382)	Placebo (N=193)
Age (years)				
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
Gender				
Male	254 (66%)	258 (67%)	269 (70%)	137 (71%)
Female	131 (34%)	128 (33%)	113 (30%)	56 (29%)
Race				
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%)
Weight (kg)				
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%)
Country				
US	141 (37%)	147 (38%)	146 (38%)	69 (36%)
Non-US	244 (63%)	239 (62%)	236 (62%)	124 (64%)
sPGA				
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%)
PASI				
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
Percent BSA				
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: Reviewer's Analysis (same as Applicant's Analysis)

3.2.5 Co-Primary Efficacy Results at Week 12

Table 14 presents the results for the co-primary efficacy endpoints at Week 12 for all three pivotal Phase 3 trials in the ITT population. Both dose regimens of TALTZ were statistically superior (p-values < 0.001) to placebo for both co-primary efficacy endpoints in all three trials. The response rates for both co-primary efficacy endpoints were slightly higher for the Q2W dose regimen compared to the Q4W dose regimen in all three trials. The results in the PP population are presented in Table 15. For Trials RHBA and RHBC, the response rates were slightly higher for the TALTZ treatment arms in the PP population compared to the ITT population.

Table 14: Results for the Co-Primary Efficacy Endpoints at Week 12 (ITT, NRI)

	TALTZ 80 mg		
	Q2W	**Q4W**	**Placebo**
Trial RHAZ	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%)
Trial RHBA	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%)
Trial RHBC	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: Reviewer's Analysis (same as Applicant's Analysis)

Table 15: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

	TALTZ 80 mg		
	Q2W	**Q4W**	**Placebo**
Trial RHAZ	N=406	N=391	N=404
sPGA of 0 or 1	333 (82%)	306 (78%)	13 (3%)
PASI-75	363 (89%)	331 (85%)	16 (4%)
Trial RHBA	N=291	N=292	N=133
sPGA of 0 or 1	246 (84%)	221 (76%)	3 (2%)
PASI-75	267 (92%)	231 (79%)	3 (2%)
Trial RHBC	N=338	N=338	N=165
sPGA of 0 or 1	284 (84%)	271 (80%)	11 (7%)
PASI-75	306 (91%)	303 (90%)	10 (6%)

Source: Reviewer's Analysis (same as Applicant's Analysis)

Table 16 provides the number of subjects with missing data for the co-primary efficacy endpoints by treatment arm in each trial. The proportion of subjects with missing data at Week 12 was generally similar between each treatment arm and between each trial; however, in Trial RHBA, the proportion of subjects with missing data in the TALTZ 80 mg Q2W was smaller than the other treatment arms in that trial and in the other two trials.

Table 16: Missing Data for the Co-Primary Efficacy Endpoints at Week 12 (ITT)

	TALTZ 80 mg		
Trial	**Q2W**	**Q4W**	**Placebo**

RHAZ	16/433 (4%)	23/432 (5%)	24/431 (6%)
RHBA	7/351 (2%)	18/347 (5%)	8/168 (5%)
RHBC	20/385 (5%)	23/386 (6%)	10/193 (5%)

Source: Reviewer's Analysis

Table 17 presents the results for the co-primary efficacy endpoints at Week 12 for the applicant's primary imputation method of non-responder imputation (NRI) and the applicant's sensitivity analysis using placebo multiple imputation (pMI). The results between NRI and pMI were very similar. This reviewer conducted an additional sensitivity analysis under the worst case scenario (i.e., missing data for TALTZ is imputed as non-responders and missing data for placebo is imputed as responders). In this extreme case, both dose regimens of TALTZ 80 mg were still statistically superior (p-values < 0.001) to placebo for both co-primary efficacy endpoints in all three trials.

Table 17: Results for Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data (ITT)

		TALTZ 80 mg		
	Endpoint	**Q2W**	**Q4W**	**Placebo**
Trial RHAZ		N=433	N=432	N=431
	sPGA of 0 or 1			
	NRI (Primary)	82%	76%	3%
	pMI[(1)]	83%	77%	3%
	Worst Case	82%	76%	9%
	PASI-75			
	NRI (Primary)	89%	83%	4%
	pMI[(1)]	91%	84%	4%
	Worst Case	89%	83%	10%
Trial RHBA		N=351	N=347	N=168
	sPGA of 0 or 1			
	NRI (Primary)	83%	73%	2%
	pMI[(1)]	83%	73%	2%
	Worst Case	83%	73%	7%
	PASI-75			
	NRI (Primary)	90%	78%	2%
	pMI[(1)]	91%	79%	2%
	Worst Case	90%	78%	7%
Trial RHBC		N=385	N=386	N=193
	sPGA of 0 or 1			
	NRI (Primary)	81%	75%	7%
	pMI[(1)]	81%	76%	7%
	Worst Case	81%	75%	12%
	PASI-75			
	NRI (Primary)	87%	84%	7%
	pMI[(1)]	88%	84%	8%
	Worst Case	87%	84%	12%

Source: Reviewer's Analysis (NRI and pMI same as Applicant's Analysis)
(1) The rates displayed are the averages over the 100 imputed datasets.

3.2.6 Secondary Efficacy Results at Week 12

Table 18 presents the results for the secondary efficacy endpoints at Week 12 in the ITT population. Both dose regimens of TALTZ were statistically superior (p-values < 0.001) to placebo for all presented secondary endpoints in all three trials. The results for the PP population (not shown) were similar to those in the ITT population.

Table 18: Results for the Secondary Efficacy Endpoints at Week 12 (ITT, NRI, LOCF[1])

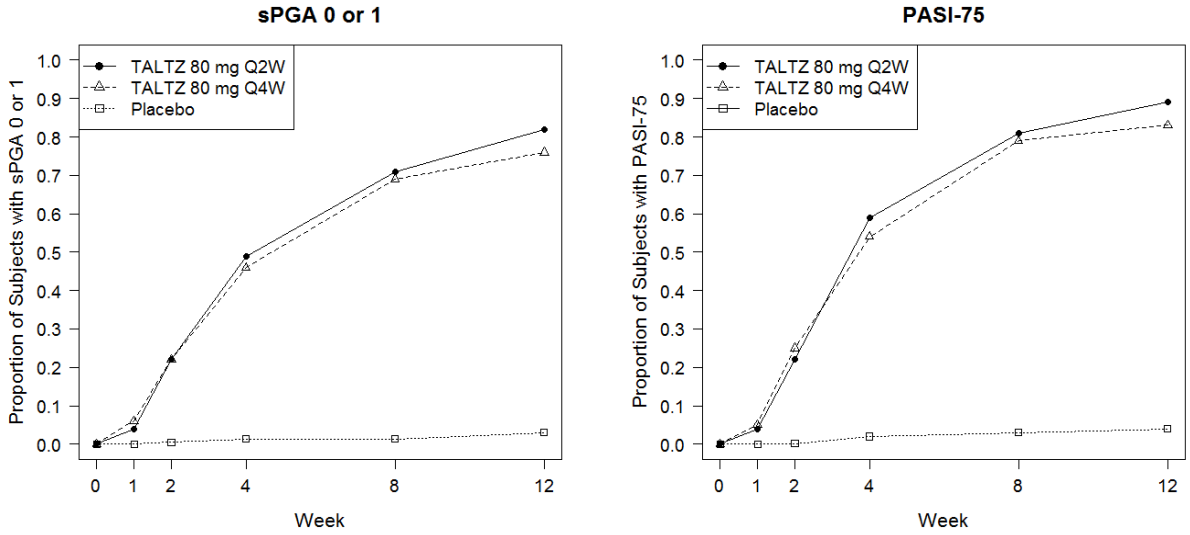
	TALTZ 80 mg		
	Q2W	**Q4W**	**Placebo**
Trial RHAZ	N=433	N=432	N=431
sPGA of 0	160 (37%)	149 (34%)	0
PASI-90	307 (71%)	279 (65%)	2 (1%)
PASI-100	153 (35%)	145 (34%)	0
≥ 4-point reduction in Itch NRS from baseline	336/391 (86%)	305/379 (80%)	58/374 (16%)
Change from baseline in NAPSI			
N[2]	283	279	281
Mean (SD)	-7.1 (11.9)	-7.0 (11.2)	1.9 (9.0)
Trial RHBA	N=351	N=347	N=168
sPGA of 0	147 (42%)	112 (32%)	1 (1%)
PASI-90	248 (71%)	207 (60%)	1 (1%)
PASI-100	142 (40%)	107 (31%)	1 (1%)
≥ 4-point reduction in Itch NRS from baseline[3]	258/303 (85%)	225/293 (77%)	19/135 (14%)
Change from baseline in NAPSI[3]			
N[2]	208	216	113
Mean (SD)	-8.3 (11.9)	-7.0 (12.0)	-0.5 (13.0)
Trial RHBC	N=385	N=386	N=193
sPGA of 0	155 (40%)	139 (36%)	0
PASI-90	262 (68%)	252 (65%)	6 (3%)
PASI-100	145 (38%)	135 (35%)	0
≥ 4-point reduction in Itch NRS from baseline	264/320 (83%)	250/313 (80%)	33/158 (21%)
Change from baseline in NAPSI			
N[2]	229	227	115
Mean (SD)	-10.1 (12.9)	-9.7 (12.7)	1.6 (11.2)

Source: Reviewer's Analysis (same as Applicant's Analysis)
(1) The last observation carried forward (LOCF) even if it was baseline was used to impute missing data for NAPSI.
(2) The number of subjects with baseline nail involvement.
(3) Endpoint was not specified as a secondary endpoint in the multiplicity testing strategy, see Table 6.

3.2.7 Efficacy Over Time

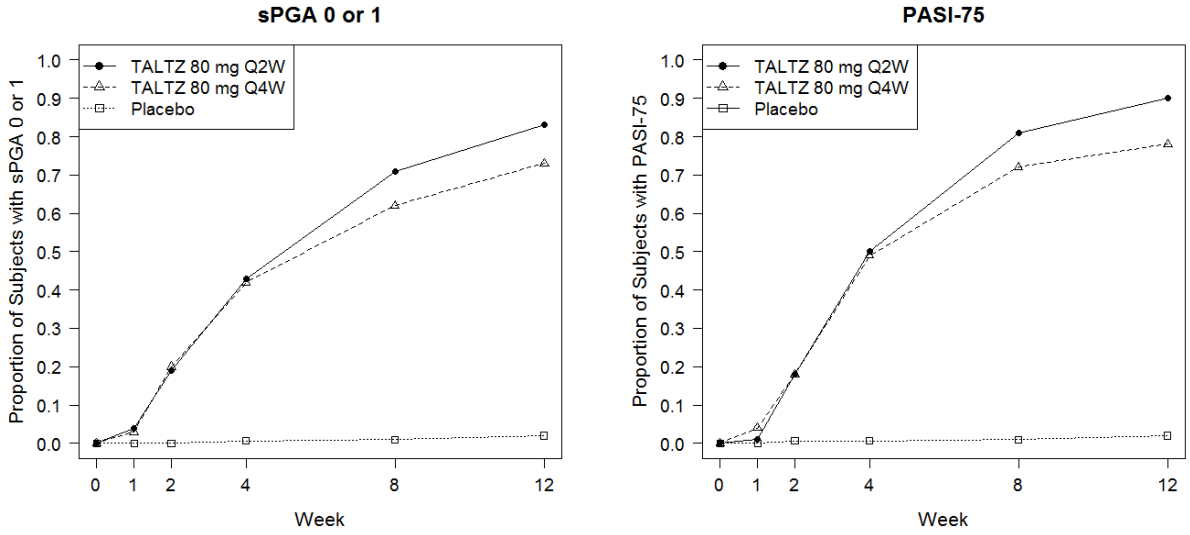
For the induction period, subjects were evaluated for sPGA and PASI at Weeks 1, 2, 4, 8, and 12. Figures 4, 5, and 6 present the results of the co-primary efficacy endpoints during the induction period for Trials RHAZ, RHBA, and RHBC, respectively.

Figure 4: Co-Primary Efficacy Results for the Induction Period in Trial RHAZ (ITT, NRI)



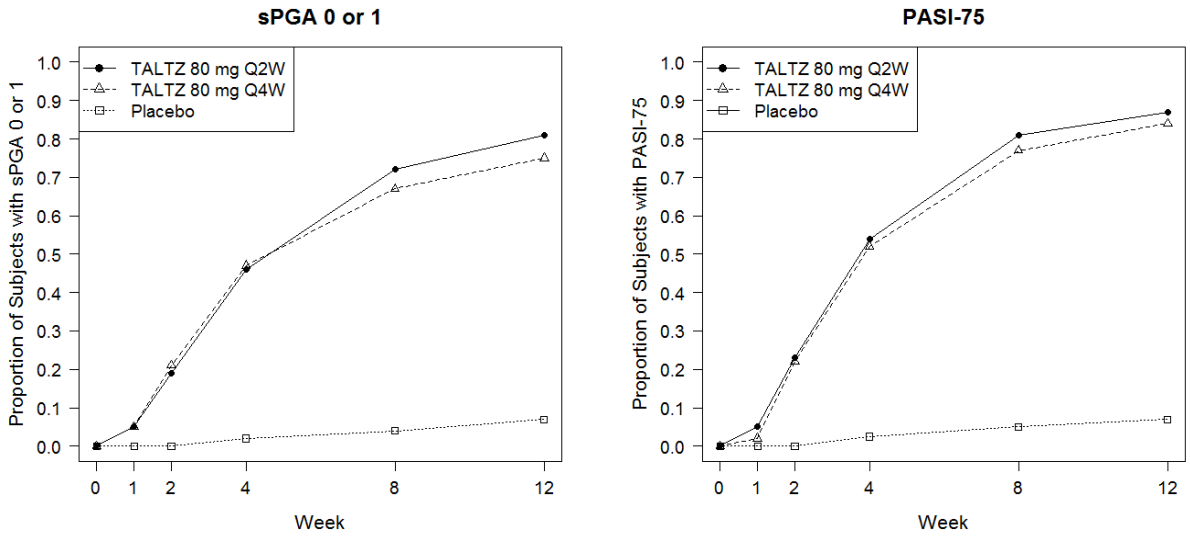
Source: Reviewer's Analysis

Figure 5: Co-Primary Efficacy Results for the Induction Period in Trial RHBA (ITT, NRI)



Source: Reviewer's Analysis

Figure 6: Co-Primary Efficacy Results for the Induction Period in Trial RHBC (ITT, NRI)



Source: Reviewer's Analysis

Trials RHAZ and RHBA evaluated maintenance of efficacy for an additional 48 weeks (Weeks 12-60). At Week 12, subjects who entered the maintenance dosing period were classified as either responders (sPGA 0 or 1) or non-responder (sPGA ≥ 2). Subjects' responder status at Week 12 and treatment during the induction period determined their treatment for the maintenance period, see Section 3.2.1. Table 19 presents the proportion of Week 12 responders (sPGA of 0 or 1) who were responders at Week 60. The proportion of subjects that maintain their response at Week 60 was higher for subjects who received TALTZ 80 mg Q4W during the maintenance period compared to TALTZ 80 mg Q12W and placebo. The proportion of subjects that relapsed (sPGA ≥ 3) and the median time to relapse for subjects who were re-randomized to placebo at Week 12 are presented in Table 20.

Table 19: Maintenance of Response (sPGA of 0 or 1) at Week 60

Treatment Arm (Induction → Maintenance)	Trial RHAZ	Trial RHBA
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: Reviewer's Analysis (same as Applicant's Analysis)

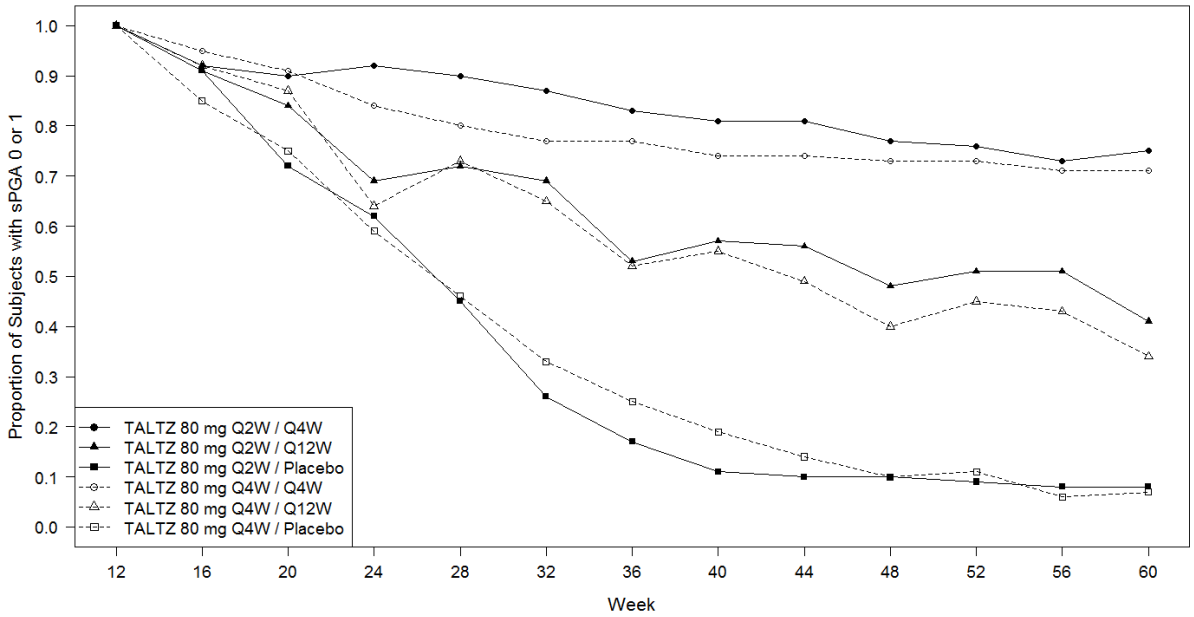
Table 20: Relapse (sPGA ≥ 3) During Maintenance Period

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

Source: Reviewer's Analysis (same as Applicant's Analysis)

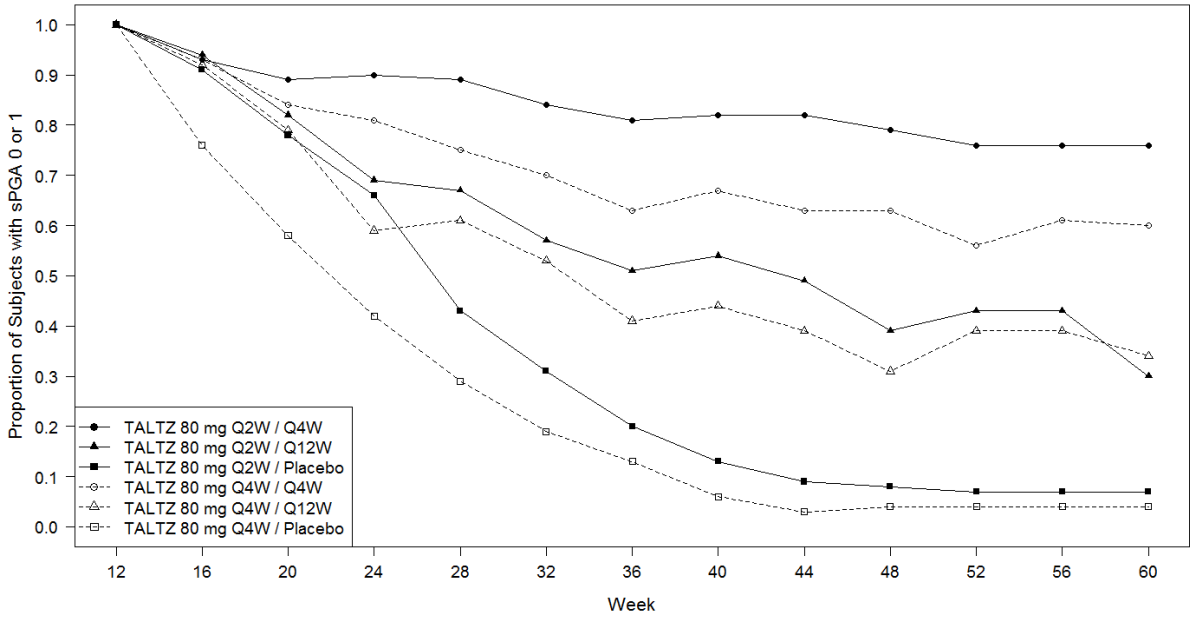
Figures 7 and 8 present the response rates (sPGA of 0 or 1) during the maintenance period.

Figure 7: sPGA of 0 or 1 Response for the Maintenance Period in Trial RHAZ (NRI)



Source: Reviewer's Analysis

Figure 8: sPGA of 0 or 1 Response for the Maintenance Period in Trial RHBA (NRI)



Source: Reviewer's Analysis

3.2.8 Comparison to Active Control (Etanercept)

Trials RHBA and RHBC included etanercept as an active comparator. In both trials, all subjects randomized to etanercept at US study sites received US-licensed Enbrel. Subjects randomized to etanercept at non-US study sites received EU-approved etanercept (except 30 subjects in Argentina, Chile, and Mexico in Trial RHBC received US-licensed Enbrel). The applicant has not provided an adequate bridge to scientifically justify the relevance of the comparative data generated using EU-approved etanercept.

Tables 21 and 22 present the efficacy results at Week 12 for the overall population and by country (US vs. Non-US) for Trials RHBA and RHBC, respectively. In both trials, 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 all of the efficacy endpoints listed in Tables 21 and 22.

Table 21: Efficacy Results at Week 12 by Country (US vs. Non-US) for Trial RHBA [ITT, NRI]

	TALTZ 80 mg			
Endpoint	**Q2W (N=351)**	**Q4W (N=347)**	**Etanercept (N=358)**	**Placebo (N=168)**
Co-Primary:				
sPGA of 0 or 1				
Overall	*292 (83%)*	*253 (73%)*	*129 (36%)*	*4 (2%)*
US(1)	73 (70%)	64 (61%)	24 (22%)	0 (0%)
Non-US(2)	219 (89%)	189 (78%)	105 (43%)	4 (3%)
PASI-75				
Overall	*315 (90%)*	*269 (78%)*	*149 (42%)*	*4 (2%)*
US(1)	89 (86%)	71 (68%)	36 (32%)	0 (0%)
Non-US(2)	226 (91%)	198 (82%)	113 (46%)	4 (3%)
Secondary:				
sPGA of 0				
Overall	*147 (42%)*	*112 (32%)*	*21 (6%)*	*1 (1%)*
US(1)	36 (35%)	24 (23%)	6 (5%)	0 (0%)
Non-US(2)	111 (45%)	88 (36%)	15 (6%)	1 (1%)
PASI-90				
Overall	*248 (71%)*	*207 (60%)*	*67 (19%)*	*1 (1%)*
US(1)	69 (66%)	51 (49%)	16 (14%)	0 (0%)
Non-US(2)	179 (72%)	156 (64%)	51 (21%)	1 (1%)
PASI-100				
Overall	*142 (40%)*	*107 (31%)*	*19 (5%)*	*1 (1%)*
US(1)	37 (36%)	24 (23%)	5 (5%)	0 (0%)
Non-US(2)	105 (43%)	83 (34%)	14 (6%)	1 (1%)

Source: Reviewer's Analysis
(1) Sample sizes for US subjects = (N_{Q2W}, N_{Q4W}, N_E, N_P) = (104, 105, 111, 49)
(2) Sample sizes for Non-US subjects = (N_{Q2W}, N_{Q4W}, N_E, N_P) = (247, 242, 247, 119)

Table 22: Efficacy Results at Week 12 by Country (US vs. Non-US) for Trial RHBC [ITT, NRI]

Endpoint	TALTZ 80 mg Q2W (N=385)	TALTZ 80 mg Q4W (N=386)	Etanercept (N=382) Country[3]	Etanercept (N=382) Source[3]	Placebo (N=193)
Co-Primary: sPGA of 0 or 1					
Overall	*310 (81%)*	*291 (75%)*	*159 (42%)*		*13 (7%)*
US[1]	105 (74%)	96 (65%)	46 (32%)	92 (45%)	4 (6%)
Non-US[2]	205 (84%)	195 (82%)	113 (48%)	67 (38%)	9 (7%)
PASI-75					
Overall	*336 (87%)*	*325 (84%)*	*204 (53%)*		*14 (7%)*
US[1]	124 (88%)	118 (80%)	68 (47%)	92 (52%)	6 (9%)
Non-US[2]	212 (87%)	207 (87%)	136 (58%)	112 (54%)	8 (6%)
Secondary: sPGA of 0					
Overall	*155 (40%)*	*139 (36%)*	*33 (9%)*		*0 (0%)*
US[1]	48 (34%)	48 (33%)	6 (4%)	12 (7%)	0 (0%)
Non-US[2]	107 (44%)	91 (38%)	27 (11%)	21 (10%)	0 (0%)
PASI-90					
Overall	*262 (68%)*	*252 (65%)*	*98 (26%)*		*6 (3%)*
US[1]	87 (62%)	85 (58%)	31 (21%)	45 (26%)	1 (1%)
Non-US[2]	175 (72%)	167 (70%)	67 (28%)	53 (26%)	5 (4%)
PASI-100					
Overall	*145 (38%)*	*135 (35%)*	*28 (7%)*		*0 (0%)*
US[1]	45 (32%)	47 (32%)	5 (3%)	11 (6%)	0 (0%)
Non-US[2]	100 (41%)	88 (37%)	23 (10%)	17 (8%)	0 (0%)

Source: Reviewer's Analysis

(1) Sample sizes for US subjects = (N_{Q2W}, N_{Q4W}, N_E, N_P) = (141, 147, 146, 69)

(2) Sample sizes for Non-US subjects = (N_{Q2W}, N_{Q4W}, N_E, N_P) = (244, 239, 236, 124)

(3) Subjects in Argentina, Chile and Mexico (total of 30 subjects) received US-licensed Enbrel. The left column "Country" separates based on country (US vs. Non-US) ignoring the fact that US-licensed Enbrel was used in Argentina, Chile and Mexico. The right column "Source" separates based on the source of etanercept (US-licensed Enbrel vs. EU-approved etanercept), and the sample size = (176, 206).

3.3 Evaluation of Safety

For this review, the evaluation of safety is limited to the induction period of the three pivotal Phase 3 trials (Trials RHAZ, RHBA, and RHBC).

3.3.1 Extent of Exposure

Tables 23, 24, and 25 present the extent of exposure during the induction period for Trials RHAZ, RHBA and RHBC, respectively. The duration of exposure during the induction period was similar between treatment arms within each trial and between each trial. The planned total study drug dose during the induction period was 560 mg for TALTZ Q2W (160 mg at Week 0 followed by 80 mg at Weeks 2, 4, 6, 8, and 10) and 320 mg for TALTZ Q4W (160 mg at Week 0 followed by 80 mg at Weeks 4 and 8).

Table 23: Extent of Exposure During the Induction Period for Trial RHAZ (Safety Population)

	TALTZ 80 mg		
	Q2W (N=433)	Q4W (N=432)	Placebo(N=431)
Days of Exposure			
> 0 to < 7 days	0	2 (<1%)	0
≥ 7 to < 14 days	1 (<1%)	1 (<1%)	7 (2%)
≥ 14 to < 30 days	6 (1%)	10 (2%)	8 (2%)
≥ 30 to < 60 days	5 (1%)	6 (1%)	6 (1%)
≥ 60 to < 90 days	398 (92%)	386 (89%)	394 (91%)
≥ 90 days	23 (5%)	27 (6%)	16 (4%)
Total Study Drug Dose (mg)			
Mean (SD)	545 (64)	312 (32)	-
Median	560	320	-
Range	160 – 560	160 – 320	-

Source: pg. 380-381 of Study Report for Trial RHAZ.

Table 24: Extent of Exposure During the Induction Period for Trial RHAZ (Safety Population)

	TALTZ 80 mg			
	Q2W (N=350)	Q4W (N=347)	Etanercept (N=357)	Placebo (N=167)
Days of Exposure				
> 0 to < 7 days	0	2 (<1%)	0	0
≥ 7 to < 14 days	0	2 (<1%)	5 (1%)	0
≥ 14 to < 30 days	4 (1%)	4 (1%)	9 (3%)	2 (1%)
≥ 30 to < 60 days	1 (<1%)	5 (1%)	4 (1%)	2 (1%)
≥ 60 to < 90 days	322 (92%)	311 (90%)	315 (88%)	150 (90%)
≥ 90 days	23 (7%)	23 (7%)	24 (7%)	13 (8%)
Study Drug Total Dose (mg)				
Mean (SD)	548 (51)	312 (32)	1124 (235)	-
Median	560	320	1200	-
Range	160 – 720	160 – 400	0 – 1200	-

Source: pg. 735-736 of Study Report for Trial RHBA.

Table 25: Extent of Exposure During the Induction Period for Trial RHBC (Safety Population)

	TALTZ 80 mg			
	Q2W (N=384)	Q4W (N=382)	Etanercept (N=382)	Placebo (N=193)
Days of Exposure				
> 0 to < 7 days	0	0	2 (<1%)	0
≥ 7 to < 14 days	2 (<1%)	2 (<1%)	0	1 (<1%)
≥ 14 to < 30 days	5 (1%)	5 (1%)	8 (2%)	2 (1%)
≥ 30 to < 60 days	7 (2%)	7 (2%)	1 (<1%)	5 (3%)
≥ 60 to < 90 days	356 (93%)	347 (91%)	354 (93%)	179 (93%)
≥ 90 days	14 (4%)	21 (5%)	17 (5%)	6 (3%)
Study Drug Total Dose (mg)				
Mean (SD)	541 (72)	312 (35)	1147 (183)	-
Median	560	320	1200	-
Range	160 – 800	0 – 400	50 – 1200	-

Source: pg. 265-266 of Study Report for Trial RHBC.

3.3.2 Adverse Events

Tables 26, 27, and 28 present an overview of the adverse events reported during the induction period in Trials RHAZ, RHBA and RHBC. The treatment-emergent adverse events occurring in at least 1% of subjects in the total TALTZ group (Q2W and Q4W) during the induction period for the three trials are displayed in Tables 29, 30, and 31.

Table 26: Overview of Adverse Events Reported During the Induction Period for Trial RHAZ (Safety Population)

	TALTZ 80 mg		
Subjects With:	**Q2W (N=433)**	**Q4W (N=432)**	**Placebo (N=431)**
Any Treatment-Emergent AEs	257 (59%)	264 (61%)	210 (49%)
Any Drug-related[(1)] AEs	127 (29%)	111 (26%)	49 (11.4%)
Any Severe AEs	14 (3%)	17 (4%)	18 (4%)
Any Serious AEs	6 (1%)	12 (3%)	5 (1%)
Any AEs Leading to Discontinuation	10 (2%)	10 (2%)	6 (1%)

Source: pg. 396 of Study Report for Trial RHAZ.
(1) Assessed by investigator as possibly drug-related.

Table 27: Overview of Adverse Events Reported During the Induction Period for Trial RHBA (Safety Population)

	TALTZ 80 mg			
Subjects With:	**Q2W (N=350)**	**Q4W (N=347)**	**Etanercept (N=357)**	**Placebo (N=167)**
Any Treatment-Emergent AEs	216 (62%)	204 (59%)	211 (59%)	89 (53%)
Any Drug-related[(1)] AEs	117 (33%)	92 (27%)	91 (26%)	30 (18%)
Any Severe AEs	11 (3%)	10 (3%)	18 (5%)	5 (3%)
Any Serious AEs	5 (1%)	8 (2%)	8 (2%)	2 (1%)
Any AEs Leading to Discontinuation	6 (2%)	5 (1%)	5 (1%)	1 (1%)

Source: pg. 751 of Study Report for Trial RHBA.
(1) Assessed by investigator as possibly drug-related.

Table 28: Overview of Adverse Events Reported During the Induction Period for Trial RHBC (Safety Population)

	TALTZ 80 mg			
Subjects With:	**Q2W (N=384)**	**Q4W (N=382)**	**Etanercept (N=382)**	**Placebo (N=193)**
Any Treatment-Emergent AEs	205 (53%)	215 (56%)	187 (49%)	70 (36%)
Any Drug-related[(1)] AEs	103 (27%)	83 (22%)	85 (22%)	24 (12%)
Any Severe AEs	11 (3%)	14 (4%)	17 (4%)	4 (2%)
Any Serious AEs	9 (2%)	6 (2%)	5 (1%)	5 (3%)
Any AEs Leading to Discontinuation	9 (2%)	8 (2%)	4 (1%)	2 (1%)

Source: pg. 272 of Study Report for Trial RHBC.
(1) Assessed by investigator as possibly drug-related.

Table 29: Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects in the Total TALTZ Group During the Induction Period in Trial RHAZ (Safety Population)

Subjects With:	TALTZ 80 mg Q2W (N=433)	TALTZ 80 mg Q4W (N=432)	Placebo (N=431)
Nasopharyngitis	50 (12%)	46 (10%)	41 (10%)
Injection site reaction	42 (10%)	26 (6%)	5 (1%)
Injection site erythema	27 (6%)	18 (4%)	0
Upper respiratory tract infection	24 (6%)	21 (5%)	16 (4%)
Headache	18 (4%)	16 (4%)	15 (3%)
Diarrhoea	8 (2%)	10 (2%)	5 (1%)
Pruritus	6 (1%)	10 (2%)	13 (3%)
Oropharyngeal pain	7 (2%)	8 (2%)	1 (<1%)
Nausea	8 (2%)	6 (1%)	3 (1%)
Injection site pain	7 (2%)	7 (2%)	9 (2%)
Arthralgia	9 (2%)	4 (1%)	9 (2%)
Fatigue	6 (1%)	7 (1%)	4 (1%)
Blood creatine phosphokinase increased	8 (2%)	4 (1%)	5 (1%)
Cough	7 (2%)	4 (1%)	6 (1%)
Bronchitis	6 (1%)	5 (1%)	4 (1%)
Sinusitis	5 (1%)	6 (1%)	4 (1%)
Back pain	4 (1%)	6 (1%)	4 (1%)
Dizziness	4 (1%)	6 (1%)	3 (1%)
Hypertension	4 (1%)	5 (1%)	2 (1%)

Source: pg. 412 of Study Report for Trial RHAZ.

Table 30: Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects in the Total TALTZ Group During the Induction Period in Trial RHBA (Safety Population)

Subjects With:	TALTZ 80 mg Q2W (N=350)	TALTZ 80 mg Q4W (N=347)	Etanercept (N=357)	Placebo (N=167)
Nasopharyngitis	35 (10%)	29 (8%)	36 (10%)	17 (10%)
Injection site reaction	39 (11%)	19 (5%)	39 (11%)	1 (1%)
Upper respiratory tract infection	19 (4%)	16 (5%)	26 (7%)	7 (4%)
Headache	17 (5%)	18 (5%)	20 (6%)	3 (2%)
Injection site erythema	12 (3%)	9 (3%)	18 (5%)	2 (1%)
Injection site pain	13 (4%)	6 (2%)	4 (1%)	2 (1%)
Fatigue	9 (3%)	6 (2%)	4 (1%)	2 (1%)
Arthralgia	7 (2%)	8 (2%)	10 (3%)	4 (2%)
Pruritus	7 (2%)	7 (2%)	4 (1%)	4 (2%)
Urinary tract infection	5 (1%)	8 (2%)	2 (1%)	2 (1%)
Nausea	7 (2%)	5 (1%)	1 (<1%)	2 (1%)
Diarrhoea	6 (2%)	5 (1%)	2 (1%)	1 (1%)
Oropharyngeal pain	5 (1%)	6 (2%)	5 (1%)	0
Psoriasis	4 (1%)	6 (2%)	7 (2%)	5 (3%)
Bronchitis	5 (1%)	4 (1%)	5 (1%)	3 (2%)
Blood creatine phosphokinase increased	5 (1%)	4 (1%)	4 (1%)	2 (1%)
Influenza	4 91%)	5 (1%)	5 (1%)	0
Pharyngitis	4 (1%)	4 (1%)	5 (1%)	0
Rhinitis	3 (1%)	4 (1%)	1 (<1%)	0
Sinusitis	2 (1%)	6 (2%)	3 (1%)	0
Toothache	1 (<1%)	7 (2%)	1 (<1%)	0
Injection site bruising	5 (1%)	2 (1%)	5 (1%)	1 (1%)
Nail psoriasis	4 (1%)	3 (1%)	4 (1%)	1 (1%)
Myalgia	4 (1%)	3 (1%)	2 (1%)	1 (1%)
Type 2 diabetes mellitus	0	7 (2%)	2 (1%)	0

Source: pg. 770 of Study Report for Trial RHBA.

Table 31: Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects in the Total TALTZ Group During the Induction Period in Trial RHBA (Safety Population)

Subjects With:	TALTZ 80 mg Q2W (N=384)	TALTZ 80 mg Q4W (N=382)	Etanercept (N=382)	Placebo (N=193)
Injection site reaction	37 (10%)	43 (11%)	41 (11%)	3 (2%)
Nasopharyngitis	26 (7%)	29 (8%)	19 (5%)	11 (6%)
Headache	16 (4%)	16 (4%)	11 (3%)	5 (3%)
Arthralgia	13 (3%)	10 (3%)	7 (2%)	4 (2%)
Injection site erythema	12 (3%)	5 (1%)	11 (3%)	0
Upper respiratory tract infection	8 (2%)	8 (2%)	8 (2%)	5 (3%)
Pruritus	7 (2%)	9 (2%)	4 (1%)	1 (1%)
Back pain	7 (2%)	8 (2%)	2 (1 %)	2 (1%)
Cough	6 (2%)	9 (2%)	4 (1 %)	0
Diarrhoea	11 (3%)	3 (1%)	6 (2%)	2 (1%)
Nausea	8 (2%)	4 (1%)	2 (1%)	0
Injection site pain	8 (2%)	3 (1%)	5 (1%)	3 (2%)
Blood creatine phosphokinase increased	6 (2%)	5 (1%)	3 (1%)	3 (2%)
Fatigue	4 (1%)	7 (2%)	7 (2%)	3 (2%)
Urinary tract infection	5 (1%)	5 (1%)	3 (1%)	0
Psoriasis	5 (1%)	5 (1%)	0	3 (2%)
Oropharyngeal pain	4 (1%)	6 (2%)	2 (1%)	3 (2%)
Pain in extremity	4 (1%)	6 (2%)	2 (1%)	0
Injection site bruising	2 (1%)	6 (2%)	0	1 (1%)

Source: pg. 282 and 284 of Study Report for Trial RHBC.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Weight and Baseline Disease Severity

Tables 32, 33, and 34 present the results for the co-primary efficacy endpoints at Week 12 by gender, race (white vs. non-white), age (< 65 vs. ≥ 65), and baseline disease severity subgroups for Trials RHAZ, RHBA, and RHBC. The majority of the subjects enrolled in the trials were white (approximately 93%) and of < 65 years of age (approximately 93%); therefore, it would be difficult to detect any differences in efficacy for the non-white and ≥ 65 subgroups. In all three trials, the efficacy results were generally consistent across gender and baseline disease severity. In trials RHBA and RHBC, the treatment effect was lower for subjects with a baseline sPGA score of 5 (very severe); however, a small proportion of subjects (approximately 6%) had a baseline sPGA score of 5. In all three trials, the treatment effect for the ≥ 100 kg weight subgroup was slightly smaller than the < 100 kg subgroup.

Table 32: Results for the Co-Primary Efficacy Endpoints at Week 12 by Gender, Race, Age, Weight, and Baseline Disease Severity for Trial RHAZ (ITT, NRI)

	sPGA of 0 or 1			PASI-75		
	TALTZ 80 mg			TALTZ 80 mg		
Subgroup (N_{Q2W}, N_{Q4W}, N_P)	Q2W (N=433)	Q4W (N=432)	Placebo (N=431)	Q2W (N=433)	Q4W (N=432)	Placebo (N=431)
Gender						
Female (142, 143, 128)	80%	78%	4%	89%	84%	3%
Male (291, 289, 303)	83%	76%	3%	89%	82%	4%
Race						
Non-White (32, 35, 30)	78%	80%	3%	84%	86%	7%
White (401, 397, 401)	82%	76%	3%	90%	82%	4%
Age						
< 65 (407, 401, 393)	82%	78%	3%	89%	84%	4%
≥ 65 (26, 31, 38)	85%	61%	8%	92%	68%	8%
Weight						
< 100 kg (288, 290, 289)	83%	79%	4%	91%	85%	4%
≥ 100 kg (145, 142, 142)	79%	70%	1%	86%	77%	3%
Baseline Disease Severity (sPGA)						
3 – Moderate (231, 197, 204)	82%	79%	4%	89%	81%	4%
4 – Severe (179, 205, 193)	81%	75%	3%	89%	83%	4%
5 - Very Severe (23, 30, 34)	87%	70%	0%	91%	87%	0%

Source: Reviewer's Analysis

Table 33: Results for the Co-Primary Efficacy Endpoints at Week 12 by Gender, Race, Age, Weight, and Baseline Disease Severity for Trial RHBA (ITT, NRI)

	sPGA of 0 or 1			PASI-75		
	TALTZ 80 mg			TALTZ 80 mg		
Subgroup (N_{Q2W}, N_{Q4W}, N_P)	Q2W (N=351)	Q4W (N=347)	Placebo (N=168)	Q2W (N=351)	Q4W (N=347)	Placebo (N=168)
Gender						
Female (130, 103, 48)	82%	75%	4%	88%	78%	4%
Male (221, 244, 120)	84%	72%	2%	91%	77%	2%
Race[(1)]						
Non-White (21, 32, 19)	71%	53%	0%	86%	69%	0%
White (330, 315, 149)	84%	75%	3%	90%	78%	3%
Age						
< 65 (327, 324, 159)	83%	73%	3%	89%	78%	3%
≥ 65 (24, 23, 9)	88%	65%	0%	96%	70%	0%
Weight						
< 100 kg (256, 227, 111)	86%	73%	4%	90%	84%	4%
≥ 100 kg (95, 119, 55)	77%	61%	0%	89%	66%	0%
Baseline Disease Severity (sPGA)						
3 – Moderate (178, 166, 86)	84%	80%	3%	90%	80%	5%
4 – Severe (151, 164, 70)	84%	68%	1%	90%	76%	0%
5 - Very Severe (22, 17, 12)	68%	53%	0%	82%	71%	0%

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.

Table 34: Results for the Co-Primary Efficacy Endpoints at Week 12 by Gender, Race, Age, Weight, and Baseline Disease Severity for Trial RHBC (ITT, NRI)

	sPGA of 0 or 1			PASI-75		
	TALTZ 80 mg			TALTZ 80 mg		
Subgroup (N_{Q2W}, N_{Q4W}, N_P)	Q2W (N=385)	Q4W (N=386)	Placebo (N=193)	Q2W (N=385)	Q4W (N=386)	Placebo (N=193)
Gender						
Female (131, 128, 56)	80%	77%	7%	89%	86%	11%
Male (254, 258, 137)	81%	74%	7%	86%	83%	6%
Race						
Non-White (24, 26, 17)	67%	65%	0%	88%	81%	12%
White (361, 360, 176)	81%	76%	7%	87%	84%	7%
Age						
< 65 (351, 358, 180)	81%	76%	7%	87%	85%	8%
≥ 65 (34, 28, 13)	79%	64%	0%	94%	75%	0%
Weight						
< 100 kg (275, 274, 138)	85%	78%	7%	90%	88%	7%
≥ 100 kg (109, 107, 54)	71%	71%	6%	82%	79%	7%
Baseline Disease Severity (sPGA)						
3 – Moderate (207, 206, 92)	83%	79%	10%	87%	84%	10%
4 – Severe (157, 159, 91)	81%	75%	4%	88%	86%	4%
5 - Very Severe (21, 18, 10)	52%	56%	0%	81%	78%	10%

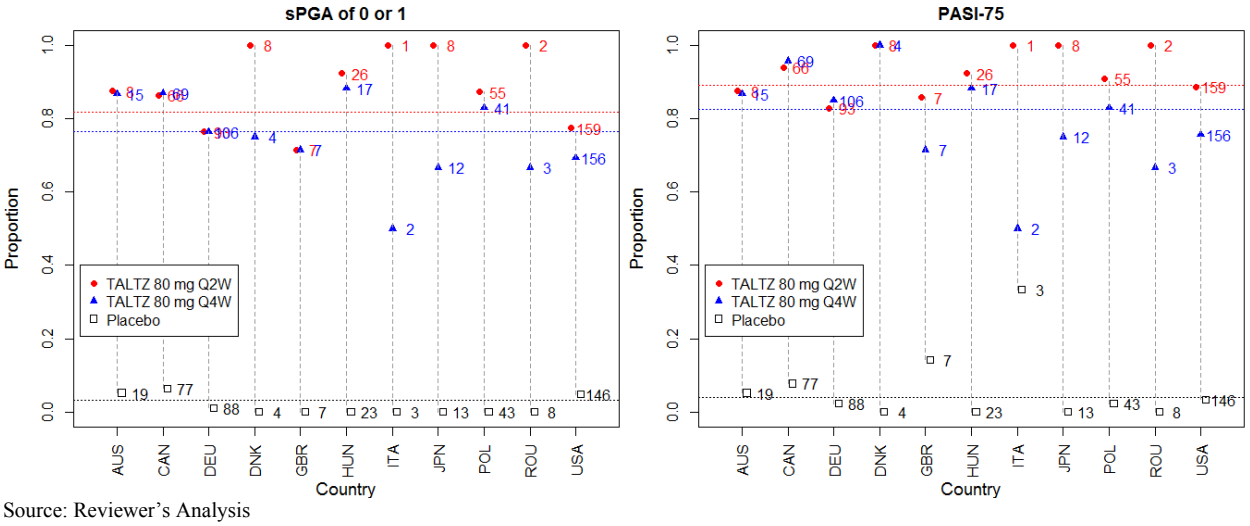
Source: Reviewer's Analysis

4.2 Country

Trial RHAZ was conducted in 11 countries (i.e., Australia, Canada, Denmark, Germany, Hungary, Italy, Japan, Poland, Romania, UK, and US). Trial RHBA was conducted in 12 countries (i.e., Australia, Austria, Canada, Czech Republic, France, Germany, Poland, Romania, Spain, UK, and US). Trial RHBC was conducted in 10 countries (i.e., Argentina, Bulgaria, Canada, Chile, Germany, Hungary, Mexico, Poland, Russia, and US). The country that enrolled the most subjects was the US with 458 subjects (35%) in Trial RHAZ, 369 subjects (30%) in Trial RHBA, and 503 subjects (37%) in Trial RHBC.

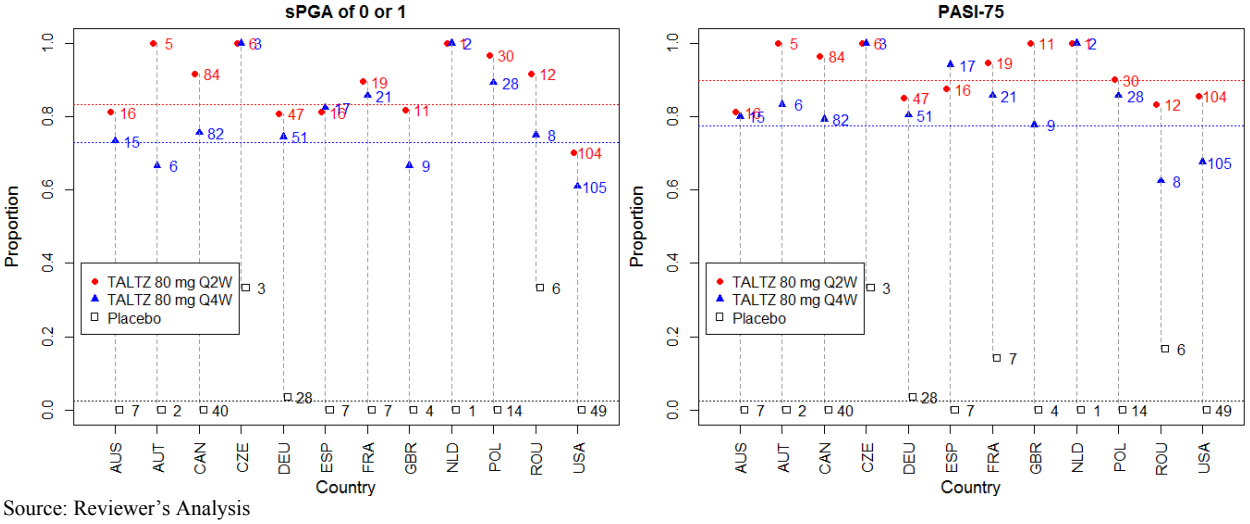
Figures 9, 10, and 11 present the results for the co-primary efficacy endpoints at Week 12 by country for Trials RHAZ, RHBA, and RHBC, respectively. While the treatment effect for PASI-75 was generally consistent across the countries in all three trials, the treatment effect for sPGA response was lower for the US compared to the other countries. This reviewer conducted a sensitivity analysis where the co-primary efficacy endpoints at Week 12 were analyzed using only US subjects, and the results were still statistically significant (p-values < 0.001).

Figure 9: Results for the Co-Primary Efficacy Endpoints at Week 12 by Country for Trial RHAZ (ITT, NRI)



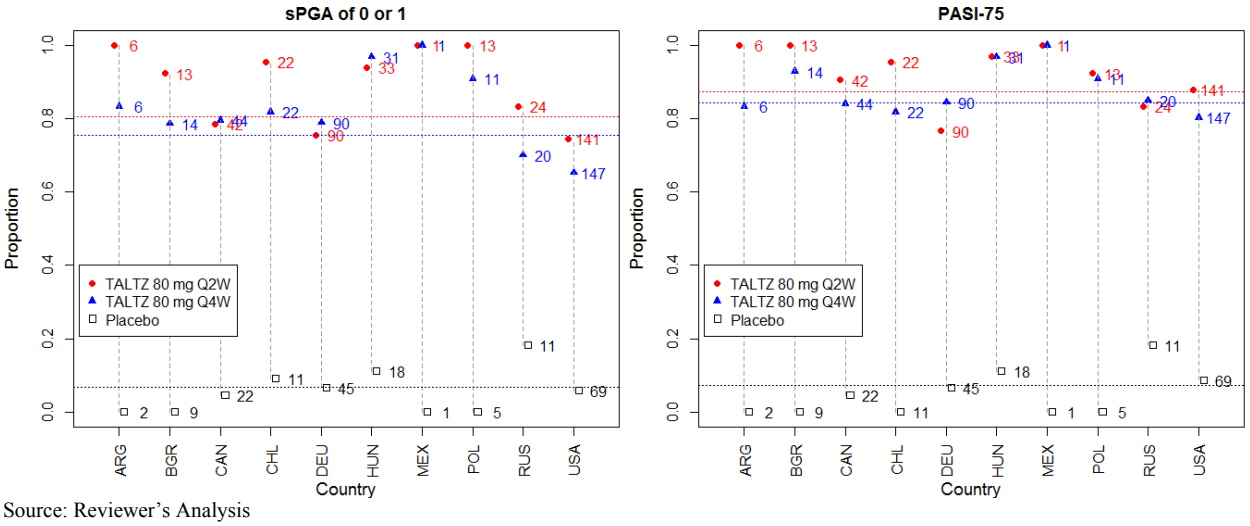
Source: Reviewer's Analysis

Figure 10: Results for the Co-Primary Efficacy Endpoints at Week 12 by Country for Trial RHBA (ITT, NRI)



Source: Reviewer's Analysis

Figure 11: Results for the Co-Primary Efficacy Endpoints at Week 12 by Country for Trial RHBC (ITT, NRI)



Source: Reviewer's Analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

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. For the handling of missing data, this reviewer conducted an additional sensitivity analyses under the worst case scenario (i.e., missing data for TALTZ is imputed as non-responders and missing data for placebo is imputed as responders). In this extreme case, both dose regimens of TALTZ 80 mg were still statistically superior (p-values < 0.001) to placebo for both co-primary efficacy endpoints in all three trials.

Treatment effects were generally consistent across subgroups. While the treatment effect for PASI-75 was generally consistent across the countries in all three trials, the treatment effect for sPGA response was lower for the US compared to the other countries. This reviewer conducted a sensitivity analysis where the co-primary efficacy endpoints at Week 12 were analyzed using only US subjects, and the results were still statistically significant (p-values < 0.001).

5.2 Collective Evidence

The applicant submitted data from three randomized, multicenter, placebo-controlled, parallel-group, pivotal Phase 3 trials (Trials RHAZ, RHBA, and RHBC). The trials enrolled subjects 18 years of age and older who had plaque psoriasis with PASI score ≥ 12, sPGA score of at least 3 (moderate) and BSA involvement ≥ 10%. All three trials evaluated two dose regimens of TALTZ during a 12-week induction period (Weeks 0-12). TALTZ subjects received a loading dose of 160 mg at baseline (Week 0) followed by 80 mg Q2W or Q4W.

The co-primary efficacy endpoints were the proportion of subjects achieving a 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 PASI-75 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 ≥4-point improvement of itch severity as measured by an itch NRS. Table 35 summarizes the efficacy results for the co-primary and secondary efficacy endpoints at Week 12. For all three trials, both dose regimens of TALTZ were statistically superior (p-values < 0.001) to placebo for all of the efficacy endpoints listed in Table 35.

Table 35: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (ITT, NRI)

	Trial RHAZ			Trial RHBA			Trial RHBC		
	TALTZ 80 mg			TALTZ 80 mg			TALTZ 80 mg		
Endpoints	Q2W N=433	Q4W N=432	Placebo N=431	Q2W N=351	Q4W N=347	Placebo N=168	Q2W N=385	Q4W N=386	Placebo N=193
Co-Primary:									
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%
Secondary:									
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%)	258/303 (85%)	225/293 (77%)	19/135 (14%)	264/320 (83%)	250/313 (80%)	33/158 (21%)

Source: Reviewer's Analysis

Trials RHBA and RHBC included etanercept as an active comparator. In both trials, all subjects randomized to etanercept at US study sites received US-licensed Enbrel. Subjects randomized to etanercept at non-US study sites received EU-approved etanercept (except 30 subjects in Argentina, Chile, and Mexico in Trial RHBC received US-licensed Enbrel). The results for both the overall population and the US only subgroup are presented in Section 3.2.8. In both trials, 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.

5.3 Conclusions and Recommendations

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.

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