

**CENTER FOR DRUG EVALUATION AND
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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: BLA 125504/0

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Indication(s): Moderate to severe plaque psoriasis

Applicant: Novartis

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Table of Contents

1. EXECUTIVE SUMMARY	3
2. INTRODUCTION	4
2.1 OVERVIEW	4
2.2 REGULATORY HISTORY	6
2.3 DATA SOURCES	6
3. STATISTICAL EVALUATION	6
3.1 DATA AND ANALYSIS QUALITY	6
3.2 EVALUATION OF EFFICACY	7
3.2.1 <i>Study Design and Endpoints</i>	7
3.2.2 <i>Patient Disposition, Demographic and Baseline Characteristics</i>	12
3.2.3 <i>Results and Conclusions</i>	15
3.3 OTHER PHASE 3 TRIALS	34
3.3.1 <i>Investigation of Prefilled Syringes (Trial 2308) and Autoinjectors (Trial 2309)</i>	34
3.3.2 <i>Investigation of two maintenance regimens: at the Start of Relapse (SoR) regimen vs. Fixed Interval (FI) regimen (Trial 2304)</i>	38
3.3.3 <i>Investigation of uptitration in partial responders (Trial 2307)</i>	42
3.4 EVALUATION OF SAFETY	45
3.5 BENEFIT-RISK ASSESSMENT	46
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	47
4.1 GENDER, RACE, AGE, AND WEIGHT	47
4.2 EFFICACY BY COUNTRY	49
5. SUMMARY AND CONCLUSIONS	50
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	50
5.2 CONCLUSIONS AND RECOMMENDATIONS	51

1. EXECUTIVE SUMMARY

Secukinumab (AIN457) 300 mg and 150 mg in lyophilisate in vial (LYO) were superior to placebo in the treatment of moderate to severe plaque psoriasis in two Phase 3 trials (2302 and 2303) with one trial that included an etanercept arm. The trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with Psoriasis Area and Severity Index (PASI) score ≥ 12 , Investigator's Global Assessment (IGA) score of at least 3, and body surface area (BSA) involvement $\geq 10\%$ at baseline. For secukinumab, subjects received a loading dose of weekly injections for the first 4 weeks followed by treatment every 4 weeks.

The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., $\geq 75\%$ reduction in PASI score) at Week 12 and scoring IGA 0 or 1 at Week 12, with a key secondary endpoint of PASI 90 response (i.e., $\geq 90\%$ reduction in PASI score) at Week 12. Table 1 summarizes the efficacy results for the co-primary endpoints and the key secondary endpoints for the two Phase 3 trials.

Table 1. Results of the Co-primary and Key Secondary Efficacy Endpoints at Week 12 for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
Co-primary endpoints							
IGA of clear or almost clear	160 (65%)	125 (51%)	6 (2%)	202 (62%)	167 (51%)	9 (3%)	88 (27%)
PASI 75 Response	200 (82%)	174 (71%)	11 (4%)	249 (76%)	219 (67%)	16 (5%)	142 (44%)
Key secondary endpoint							
PASI 90 response	145 (59%)	95 (39%)	3 (1%)	175 (54%)	137 (42%)	5 (2%)	67 (21%)

Source: reviewer table

Both secukinumab 300 mg and 150 mg were superior to placebo ($p < 0.0001$) for the co-primary endpoints of PASI 75 response and IGA of 0 or 1, as well as the key secondary endpoint of PASI 90 response in each of the pivotal trials. For Trial 2303, not only did each dose of secukinumab establish noninferiority to etanercept, but also established superiority as well ($p < 0.0001$). However, it should be noted that no replication of study findings for the comparisons against etanercept.

The patient reported outcomes (PRO) on itching, pain, and scaling were included as secondary endpoints in the testing strategy. However, it should be noted that not all centers had the Psoriasis Diary device available and furthermore, subjects could elect not to use the device at those sites where the device was available. As a result, approximately 40% of subjects from each trial participated in assessing the PRO responses on itching,

pain, and scaling, and it is not clear whether this subset is a random sample of the total population so that findings from these endpoints are generalizable to the overall population.

In addition to the two pivotal trials (2302 and 2303), the applicant’s development program for secukinumab also included a Phase 3 trial to support the safety and efficacy of secukinumab in liquid formulation in prefilled syringes (2308), and autoinjectors (2309). The same co-primary endpoints as those for the pivotal trials were used in Trials 2308 and 2309, and the results of the co-primary efficacy endpoints were statistically significant ($p < 0.0001$). While the trials showed that both secukinumab doses in prefilled syringes (PFS) and in autoinjectors (AI) were superior to placebo, the trials were not designed to address how the efficacies by using the PFS or the AI compare to those of the original LYO formulation of secukinumab. However, in comparing the efficacy results across trials, the response rates in Trials 2308 and 2309 were generally similar to those of the pivotal trials (2302 and 2303). Table 2 shows the results of the co-primary endpoints at Week 12 for Trials 2308 and 2309.

Table 2. Results of the Co-primary Efficacy Endpoints at Week 12 using the Prefilled Syringes (Trial 2308) and Autoinjectors (Trial 2309)

	Trial 2308 (PFS ⁽¹⁾)			Trial 2309 (AI ⁽²⁾)		
	AIN457 300 mg (N=59)	AIN457 150 mg (N=59)	Placebo (N=59)	AIN457 300 mg (N=60)	AIN457 150 mg (N=61)	Placebo (N=61)
IGA of clear or almost clear	40 (68%)	31 (53%)	0 (0%)	44 (73%)	32 (52%)	0 (0%)
PASI 75 response	44 (75%)	41 (69%)	0 (0%)	52 (87%)	43 (70%)	2 (3%)

(1) PFS: Prefilled syringes; (2) AI: Autoinjector
Source: reviewer table.

In the BLA submission, the applicant also included results from a Phase 3 trial (2304) that compared two maintenance regimens (i.e., retreatment at start of relapse (SoR) regimen versus the retreatment at fixed interval (FI) regimen), as well as results a Phase 3 trial (2307) that investigated uptitration in partial responders (i.e., PASI 50 but not PASI 75 responders). However, the primary objective of Trial 2304 was not met as the non-inferiority (NI) margin was not met, and the primary objective of Trial 2307 failed to show statistical significance mainly due to the small sample size.

2. INTRODUCTION

2.1 Overview

Secukinumab for subcutaneous injection is a recombinant human monoclonal antibody that selectively binds to human cytokine interleukin-17 (IL-17) intended for the treatment of moderate to severe plaque psoriasis. The safety and efficacy of secukinumab in lyophilisate in vial (LYO) are supported by two Phase 3 trials (2302 and 2303). These

two trials are the primary focus of this review along with a summary of the study design and analysis results of the other 4 Phase 3 trials (2308 that used PFS, 2309 that used AI, 2304 that compared the retreatment at SoR vs. the retreatment at FI maintenance regimens, and 2307 that studied uptitration in partial responders) .

Each of trials,2302, 2303, 2308, and 2309, evaluated two dose concentrations (150 mg and 300 mg) versus placebo, and Trial 2303 included an active biologic comparator arm (EU-sourced Enbrel) to which the Agency previously advised the sponsor that the trials utilizing comparator products should use the US approved product (Guidance Meeting, dated: 3/2/2011). Further, (b) (4)

The co-primary efficacy endpoints were the proportion of subjects with PASI 75 at Week 12, and the proportion of subjects with IGA of 0 or 1 at Week 12. The key secondary endpoint was PASI 90 at Week 12, and the applicant included the PROs of itching, scaling and pain as secondary endpoints to the statistical testing strategy in the amended protocol (amendment date: 8/12/2012).

The overview of the pivotal trials (2302 and 2303) is presented in Table 3 below.

Table 3. Clinical Study Overview for the Pivotal Trials (2302 and 2303)

Study	Study Sites	Study Population	Treatment Arms	N	Dates
A2302 (N=738)	86 ⁽²⁾ international centers	Age ≥18, diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization, PASI≥12, IGA ≥3, BSA≥10%	AIN457 300 mg	245	6/9/2011 - 3/7/2013
			AIN457 150 mg	245	
			Placebo	248	
A2303 (N=1306 ⁽¹⁾)	154 international centers	Age ≥18, diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization, PASI≥12, IGA ≥3, BSA≥10%	AIN457 300 mg	327	6/14/2011 - 7/7/2013
			AIN457 150 mg	327	
			Placebo	326	
			Etanercept	326	

(1) Randomized subjects.

(2) While subjects were screened at 88 centers; subjects from 86 centers were enrolled in the trial.

Source: Reviewer table.

As for safety, adverse events were comparable across both the 300 mg and 150 mg doses of secukinumab, and both doses were superior to placebo in achieving PASI 75, and IGA 0 or 1 at Week 12. However, the applicant is only seeking approval for the 300 mg dose, because the secukinumab 300 mg dose yielded about 10% higher responses for the co-primary as well as for the secondary endpoints compared to those for the 150 mg dose. See Table 1 (page 1 of this review) for the results of the co-primary and key secondary efficacy endpoints at Week 12 .

2.2 Regulatory History

The clinical development program for secukinumab started under IND 100418. However, as Protocol 2303 utilized an EU-sourced etanercept as an active comparator, the Agency stated (teleconference on 6/3/2011) that a new IND would be needed to utilize the EU-sourced Enbrel as an active comparator for Trial 2303. As such, the sponsor transferred their Protocol 2303 from IND 100418 to IND 113021, and IND 113021 was opened on 8/24/2011.

In response to the Agency's comments concerning the Protocol 2302 (Advice Letters dated: 7/12/2011 and 7/6/2012), Protocol 2302 was amended two times, in October 2011 and in August 2012. In response to the Agency's comments concerning the Protocol 2303 (Advice Letters, dated: 11/16/2011 and 11/27/2012), Protocol 2303 was amended in September 2011, and in September 2012. The first amendments included PRO on itching, pain, and scaling as secondary endpoints to the testing strategy, and the second amendments primarily included clarifications.

It should be noted that there had been no End of Phase 2 meetings nor a Phase 3 Special Protocol Assessment (SPA) on any of the applicant's Phase 3 protocols.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The datasets in this review are archived at: <\\cdsesub5\EVSPROD\BLA125504\0000\m5\datasets>

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review, and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The two LYO (powder formulation of secukinumab) Trials 2302 and 2303 were mostly identical in design except that Trial 2303 included an active biologic comparator arm (i.e., EU-sourced etanercept). The primary objective of Trials 2302 and 2303 was to demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response at Week 12 compared to placebo.

Table 4 presents the sponsor's IGA scale.

Table 4. Applicant's IGA Scale

Score	Short description	Detailed description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe/coarse scaling covering almost all or all lesions

Source: applicant's protocol

For Trial 2302, a total of 738 subjects from 86 global sites (88 sites screened) who were ≥ 18 of age with PASI score ≥ 12 , IGA score of at least 3, and BSA involvement $\geq 10\%$ at baseline were enrolled. For Trial 2303, a total of 1306 subjects from 154 global sites who were of ≥ 18 of age with PASI score ≥ 12 , IGA score of at least 3, and BSA involvement $\geq 10\%$ at baseline were enrolled in the trial. Using the Interactive Voice Response System (IVRS) or the Interactive Web Response System (IWRS), randomization was stratified by geographical region and by body weight (< 90 kg or ≥ 90 kg) at baseline. Subjects were equally allocated to the following treatment arms:

- Secukinumab 300 mg
- Secukinumab 150 mg
- Placebo
- EU-sourced etanercept (for 2303 only)

Although Protocol 2303 specified that every effort would be made so that each site recruit at least 8 subjects during the course of the study with a maximum of 32 subjects per site, there were many study centers that only enrolled 1 or 2 subjects per treatment arm. The large number of centers along with the relatively small sample size per treatment arm per center makes it difficult to assess the center-to-center variability in efficacy as the impact of any individual center on the efficacy results is limited.

The following Tables 5 and 6 list the geographical regions for Trials 2302 and 2303, respectively.

Table 5. Trial 2302 - Geographical Region for Stratified Randomization

Geographical Region ID	Geographical Region	Countries
1	Japan ⁽¹⁾	Japan
2	Eastern Europe	Latvia, Lithuania, Estonia
3	Middle and South America	Argentina, Colombia, Mexico
4	North America	US, Canada
5	Western Europe, Israel, And Taiwan	Iceland, Israel, Taiwan

Source: applicant's submission

- (1) According to the protocol, to support registration in Japan, study sites in Japan were selected for psoriatic arthritis assessments according to ACR criteria, and the randomization for subjects in Japan was stratified by body weight, as well as by history of psoriatic arthritis at screening

Table 6. Trial 2303 - Geographical Region for Stratified Randomization

Geographical Region ID	Geographical Region	Countries
1	Asia and Africa	India, South Korea, Singapore, Philippines, Egypt
2	Eastern Europe	Finland, Poland, Romania, Russia, Sweden
3	Middle and South America	Argentina, Brazil, Colombia, Guatemala, Peru, Venezuela
4	North America and Australia	US, Canada, Australia
5	Western Europe	Belgium, France, Germany, Hungary, Iceland, Italy, Spain, Turkey, United Kingdom

Source: applicant's submission.

Both trials consisted of 4 periods:

- Screening (up to 4 weeks)
- Induction (12 weeks)
- Maintenance (40 weeks)
- Follow-up (8 weeks)

During the induction period, subjects received a total of 12 weekly injections (2 injections of study treatment and/or placebo at baseline, Weeks 1, 2, 3, 4, and 8). During the Maintenance period (Week 12 to Week 48), subjects received a total of 26 injections (2 injections of study treatment and/or placebo at Week 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48). While subjects were scheduled to be dosed once every four weeks from Weeks 12 to 48 for maintenance, during Weeks 13, 14, 15, subjects received a weekly dose of placebo to maintain blinding because non-responders from the placebo group that were re-randomized at Week 12 to either secukinumab 150 mg or 300 mg received weekly injections at Week 12, 13, 14, 15 followed by injections once every four weeks from Week 16 to Week 48. For subjects in Trial 2303, in addition to the above, each subject received either etanercept or placebo etanercept twice per week in the induction period, and etanercept or placebo once a week in the maintenance period.

For the re-randomization of placebo subjects at Week 12 for the maintenance period in the pivotal trials, the protocol called for re-randomizing subjects based on PASI 75 response only where PASI 75 responders at Week 12 continued on placebo, and the PASI 75 nonresponders at Week 12 were re-randomized in a 1:1 to secukinumab 150 mg and 300 mg. However, it should be noted that the Agency previously recommended (Guidance Meeting, dated: 3/2/2011; Advice Letters, dated: 11/16/2011 and 7/12/2012) that the same efficacy endpoints be used for all comparisons throughout the trials and thus, the IGA should be considered as well.

At the end of maintenance period, qualifying subjects in the active treatment groups during the maintenance period entered an extension study designed to investigate long-term efficacy and safety of treatment with secukinumab.

3.2.2 Efficacy Assessment

The protocol-specified co-primary endpoints were:

- The proportion of subjects with PASI 75 at Week 12
- The proportion of subjects with IGA of 0 or 1 at Week 12 with at least a 2-grade improvement on the IGA.

The protocol specified the primary analysis method of the Cochran-Mantel-Haenszel test stratified by geographical region and body weight stratum. The following hypotheses at Week 12 were tested:

- H₁**: secukinumab 150 mg is not different to placebo with respect to PASI75 response
- H₂**: secukinumab 300 mg is not different to placebo with respect to PASI75 response
- H₃**: secukinumab 150 mg is not different to placebo with respect to IGA 0 or 1 response
- H₄**: secukinumab 300 mg is not different to placebo with respect to IGA 0 or 1 response

For the key secondary endpoints, the sponsor proposed the following:

- The proportion of subjects with PASI 90 response at Week 12
- maintenance of PASI 75 after 52 weeks of treatment,
- maintenance of IGA 0 or 1 response after 52 weeks of treatment.

As there was no placebo arm for the maintenance period and consequently no maintenance comparisons of secukinumab could be made against the placebo arm, and the sponsor stated that these endpoints were not included in the testing strategy. However, the PROs of itching, pain and scaling (assessed using an 11-point numeric rating scale) as secondary endpoints were included in the testing strategy as show below.

- H₅**: secukinumab 150 mg is not different to placebo with respect to PASI 90 at Week 12
- H₆**: secukinumab 300 mg is not different to placebo with respect to PASI 90 at Week 12
- H₇**: secukinumab 150 mg is not different to placebo with respect to absolute changes from baseline for Psoriasis Diary item pain at Week 12
- H₈**: secukinumab 300 mg is not different to placebo with respect to absolute changes from baseline for Psoriasis Diary item pain at Week 12
- H₉**: secukinumab 150 mg is not different to placebo with respect to absolute changes

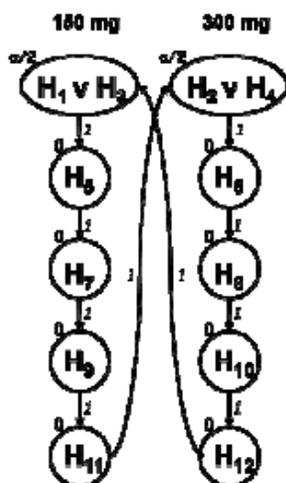
- from baseline for Psoriasis Diary item itch at Week 12
- H₁₀**: secukinumab 300 mg is not different to placebo with respect to absolute changes from baseline for Psoriasis Diary item itch at Week 12
- H₁₁**: secukinumab 150 mg is not different to placebo with respect to absolute changes from baseline for Psoriasis Diary item scaling at Week 12
- H₁₂**: secukinumab 300 mg is not different to placebo with respect to absolute changes from baseline for Psoriasis Diary item scaling at Week 12

The protocol-specified primary analysis method for the PRO endpoints of itch, pain, and scaling was the analysis of covariance (ANCOVA). Using the weekly average of the absolute change from baseline to Week 12, the ANCOVA model included treatment, geographical region and body weight stratum as explanatory variables and baseline value as a covariate.

To control the Type I error rate, the protocol specified the graphical approach of Bretz *et al.* (2009) where the family-wise error was set at 0.05. Using this method, within each pair of (H₁, H₃) and (H₂, H₄), the α was equally split at 0.025, and only if both hypotheses of a pair were rejected, the testing sequence could continue. If in the next sequence, H₅ or H₆ tested at 0.025 and rejected, the corresponding $\alpha/2$ could be passed to the next hypotheses in the sequence. If all hypotheses within a set referring to a secukinumab dose regimen were to be rejected (i.e., either (H₁, H₃, H₅, H₇, H₉, H₁₁) or (H₂, H₄, H₆, H₈, H₁₀, H₁₂)), then the approach allows that the corresponding Type I error rate to be passed onto the other group of hypotheses, and if needed, retested at a new significance level.

The applicant’s graphical approach for Trial 2302 is presented below.

Figure 1. Applicant’s Graphical Approach for Trial 2302



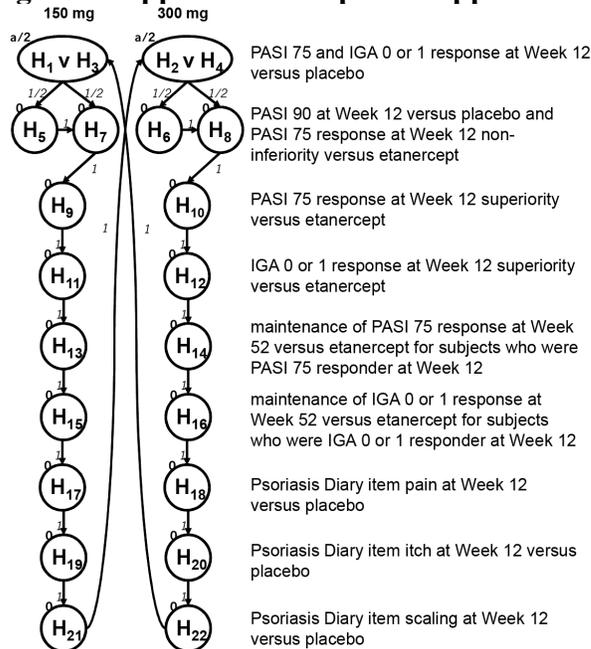
Source: applicant’s protocol

For Trial 2303, the sponsor included, in addition to the testing of the primary and secondary endpoints as in Trial 2302, the following: (i) a non-inferiority testing of comparing secukinumab against etanercept on PASI 75 endpoint (non-inferiority margin

of -10%), (ii) a superiority testing of secukinumab against etanercept on the co-primary endpoints, and (iii) testing PASI 75 and IGA responses against etanercept at Week 52.

The applicant's testing strategy for Trial 2303 is shown below.

Figure 2. Applicant's Graphical Approach for Trial 2303



Source: applicant's protocol

The following hypotheses pertain to Trial 2303 as they involve comparing the secukinumab to the etanercept:

- H₇**: secukinumab 150 mg is not non-inferior to etanercept with respect to PASI 75 at Week 12
- H₈**: secukinumab 300 mg is not non-inferior to etanercept with respect to PASI 75 at Week 12
- H₉**: secukinumab 150 mg is not superior to etanercept with respect to PASI 75 at Week 12
- H₁₀**: secukinumab 300 mg is not superior to etanercept with respect to PASI 75 at Week 12
- H₁₁**: secukinumab 150 mg is not superior to etanercept with respect to IGA 0 or 1 at Week 12
- H₁₂**: secukinumab 300 mg is not superior to etanercept with respect to IGA 0 or 1 at Week 12
- H₁₃**: secukinumab 150 mg is not superior to etanercept with respect to maintaining PASI75 response at Week 52 for subjects who were PASI 75 responder at Week 12
- H₁₄**: secukinumab 300 mg is not superior to etanercept with respect to maintaining PASI75 response at Week 52 for subjects who were PASI 75 responder at Week 12
- H₁₅**: secukinumab 150 mg is not superior to etanercept with respect to maintaining IGA 0 or 1 response at Week 52 for subjects who were IGA 0 or 1 responder at Week 12
- H₁₆**: secukinumab 300 mg is not superior to etanercept with respect to maintaining IGA 0 or 1 response at Week 52 for subjects who were IGA 0 or 1 responder at Week 12

The protocol specified the following analysis sets:

- Randomized Set: all subjects who were randomized at baseline visit.
- Full Analysis Set (FAS): all subjects to whom study treatment was assigned.
- Safety Set (SES): all subjects who took at least one dose of study treatment during the treatment period.

The sponsor used the FAS as the primary analysis set; however, the Agency recommended (Advice letters dated: 7/12/2011, 11/16/2011 and 7/6/2012) the Intent to Treat (ITT) analysis set defined as all randomized subjects, dispensed of medication, whether or not they have any post-baseline assessments.

For handling of missing data, the protocol-specified primary imputation method was to impute the missing PASI 75 and IGA responses as non-response, and as sensitivity analyses, the protocol specified the following:

- Subjects fulfilling at least one of the following criteria classified as non-responders with respect to PASI 75 and IGA 0 or 1 response at Week 12:
 - Subjects with missing injection(s) up to Week 12,
 - Dropouts due to AEs, unsatisfactory therapeutic effect up to Week 12,
 - Subjects with protocol deviations (PD) due inclusion/exclusion, and
 - Subjects with missing data at Week 12.
- PASI 75 and IGA 0 or 1 response at Week 12 evaluated using logistic regression model with treatment group, geographical region, body weight stratum, and baseline PASI as effects. Odds ratios were computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted.
- PASI 75 and IGA 0 or 1 response evaluated using the stratified CMH test with multiple imputation.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

In both trials, the applicant excluded a total of 2 placebo subjects from the FAS and the SES sets due to the following reason:

- For Trial 2302, subject AIN457A2302-5012014 was excluded because this subject did not sign the informed consent before starting study procedures. However, it should be noted that this subject completed the informed consent on 11/11/2011 and was then randomized on 11/16/2011. Therefore, this subject was included in the ITT set.
- For Trial 2303, subject AIN457A2303-3423011 was excluded because a lab test that occurred before the informed consent was provided; however, this reviewer considered this subject as an ITT subject for the analyses.

By including the above 2 subjects in his/her respective trial, the reviewer's ITT set was identical to the applicant's "randomized" set for each trial.

According to the applicant, a total of 9 subjects from Trials 2302 and 2303 were misrandomized (5 in Trial 2302, 4 in Trial 2303). In response to the Agency's information request, on 6/30/2014, the applicant stated that while the investigator or his/her delegate was asked to contact the Interactive Response Technology (IRT) after confirming that the subject fulfills all the inclusion/exclusion criteria, the investigator called the IRT before the eligibility had been fully assessed. Consequently, as these subjects did not meet the eligibility criteria, they were classified as screen failures and excluded from the analyses. The applicant stated that none of these subjects received study medication. As the Agency previously recommended (Advice Letters 7/12/2011;

11/16/2011; 7/6/2012) that the ITT set be used as the primary analysis set defined as all randomized subjects, dispensed of medication, whether or not one had any post-baseline assessments, this reviewer did not include these subjects for the analyses as these subjects were screen failures that did not receive any medications.

Approximately 6% of subjects had missing data at the Week 12 visit, and per the protocol-specified primary imputation method, these subjects were treated as non-response for the efficacy analyses. Note that with such low rates of missing data along with the large treatment effect, the impact of the imputation method on efficacy is minimal.

The two most common reasons for discontinuation for the placebo subjects as well as the secukinumab-treated subjects were adverse events and subject/guardian decision. Table 7 provides the induction period disposition for the pivotal trials.

Table 7. Induction Period Disposition for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300mg	AIN457 150mg	Placebo	AIN457 300mg	AIN457 150mg	Placebo	EU- Etanercept
Randomized⁽¹⁾	245	245	248	327	327	326	326
Applicant's FAS⁽²⁾	245	245	247	327	327	325	326
SES⁽³⁾	245	245	247	327	327	325	326
Completed Week 12	238 (97%)	230 (94%)	232 (95%)	312 (95%)	315 (96%)	301 (92%)	305 (94%)

Source: Applicant's table

- (1) Randomized Set: all subjects who were randomized at baseline visit.
- (2) Full Analysis Set (FAS): "all subjects to whom study treatment has been assigned.
- (3) Safety Set (SES): "all subjects who took at least one dose of study treatment during the treatment period."

Table 8 presents the baseline demographics for the pivotal trials (2302 and 2303). The baseline demographics were generally balanced across the treatment arms for the two pivotal trials (2302 and 2303). Approximately 70% of the subjects were male and 30% were female in both trials, and approximately 68% were Caucasians. The mean age was around 45 and the mean weight was about 88 kg in Trial 2302 and 83 kg in Trial 2303.

Table 8. Baseline Demographics for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300mg N=245	AIN457 150mg N=245	Placebo N=248	AIN457 300mg N=327	AIN457 150mg N=327	Placebo N=326	Etanercept N=326
Gender							
<i>Female</i>	76 (31%)	77 (31%)	76 (31%)	103 (32%)	91 (28%)	89 (27%)	94 (29%)
<i>Male</i>	169 (69%)	168 (69%)	172 (69%)	224 (69%)	236 (72%)	237 (73%)	232 (71%)
Age							
<i>Mean</i>	45	45	45	45	45	44	44
<i>SD</i>	14	13	13	13	13	13	13
<i>Range</i>	19-76	18-83	19-80	20-79	18-79	18-82	18-79
<i>Median</i>	45	45	45	45	45	44	44
<65	228 (93%)	223 (91%)	229 (92%)	305 (93%)	304 (93%)	311 (95%)	308 (94%)
≥65	17 (7%)	22 (9%)	19 (8%)	22 (7%)	23 (7%)	15 (5%)	18 (6%)
Race							
<i>Asian</i>	52 (21%)	54 (22%)	46 (19%)	73 (22%)	72 (22%)	72 (22%)	74 (23%)
<i>Black</i>	4 (2%)	5 (2%)	10 (4%)	2 (1%)	3 (1%)	3 (1%)	0 (0%)
<i>Caucasian</i>	171 (70%)	171 (70%)	176 (71%)	224 (69%)	219 (67%)	217 (67%)	219 (67%)
<i>Native American</i>	7 (3%)	5 (2%)	3 (1%)	22 (7%)	28 (9%)	25 (8%)	27 (8%)
<i>Pacific Islander</i>	3 (1%)	1 (0.4%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.3%)
<i>Other</i>	6 (2%)	9 (4%)	13 (5%)	5 (2%)	5 (2%)	5 (2%)	4 (1%)
<i>Unknown</i>	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	1 (0.3%)
Weight							
<i>Mean</i>	88.8	87.1	89.7	83.0	83.6	82.0	84.6
<i>SD</i>	24.0	22.3	25.0	21.6	20.8	20.4	20.5
<i>Range</i>	48-186	48-159	43-192	45-219	42-163	42-148	42-176
<i>Median</i>	84	85	85	81	82	80	82
<90 kg	142 (58%)	141 (58%)	143 (58%)	220 (67%)	215 (66%)	217 (67%)	219 (67%)
≥90 kg	103 (42%)	104 (42%)	105 (42%)	107 (33%)	112 (34%)	109 (33%)	108 (33%)

Source: applicant's table

Table 9 presents the baseline disease severity for the pivotal trials (2302 and 2303). The baseline disease characteristics of IGA, PASI and BSA were generally balanced across treatment groups in Trials 2302 and 2303. Approximately 62% of subjects had a baseline IGA of 3 (moderate), and the rest of the subjects had a baseline IGA of 4 (severe). The mean PASI score was about 23 (the minimum for inclusion was a PASI score of 12). Subjects were required to have a baseline BSA involvement of at least 10% and averaged about 33% involvement.

Table 9. Baseline Disease Severity for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300mg N=245	AIN457 150mg N=245	Placebo N=248	AIN457 300mg N=327	AIN457 150mg N=327	Placebo N=326	Etanercept N=326
IGA							
3	154 (63%)	161 (66%)	151 (61%)	203 (62%)	206 (63%)	202 (62%)	195 (60%)
4	91 (37%)	84 (34%)	97 (39%)	124 (38%)	121 (37%)	124 (38%)	131 (40%)
PASI							
<i>mean</i>	23	22	21	24	24	24	23
<i>SD</i>	9	10	9	10	11	11	10
<i>Range</i>	11-72	12-61	11-72	12-64	12-69	12-64	12-55
BSA							
<i>Mean</i>	32.8	33.3	29.7	34.3	34.5	35.2	33.6
<i>SD</i>	19.3	19.2	15.9	19.2	19.4	19.1	18.0
<i>range</i>	10-100	10-92	10-99	10-95	10-89	10-94	10-95

Source: applicant's table

3.2.3 Results and Conclusions

3.2.3.1 Week 12 Efficacy Results

Both secukinumab 300 mg and 150 mg were superior to placebo at Week 12 ($p < 0.0001$) for the co-primary endpoints of PASI 75 response and IGA of 0 or 1, as well as the key secondary endpoint of PASI 90 response at Week 12 in both Trials 2302 and 2303.

The results of the co-primary and the key secondary endpoints of Trials 2302 and 2303 are presented in Table 1 (page 1). As can be seen in Table 1, for the co-primary endpoints, secukinumab 300 mg showed a higher response (about 10%) than those of the 150 mg dose for the co-primary endpoints. Similarly, the key secondary endpoint of PASI 90 response at Week 12 was about 57%, 40%, 2% for the secukinumab 300 mg, 150 mg, and placebo group, respectively.

For Trial 2303, for the comparison of secukinumab against EU-sourced etanercept, using the protocol-specified NI margin of 10%, the lower limits of the confidence intervals were above -10% to conclude non-inferiority for both secukinumab doses, as shown in Table 10.

Table 10. Noninferiority Analysis of PASI 75 Response at Week 12 for Trial 2303

Dose	Secukinumab	Etanercept	Difference in response	CI ⁽¹⁾
300 mg	249/327 (76%)	142/326 (44%)	33	(14, 32)
150 mg	219/327 (67%)	142/326 (44%)	23	(24, 42)

Source: applicant's table. Missing was imputed as non-response.

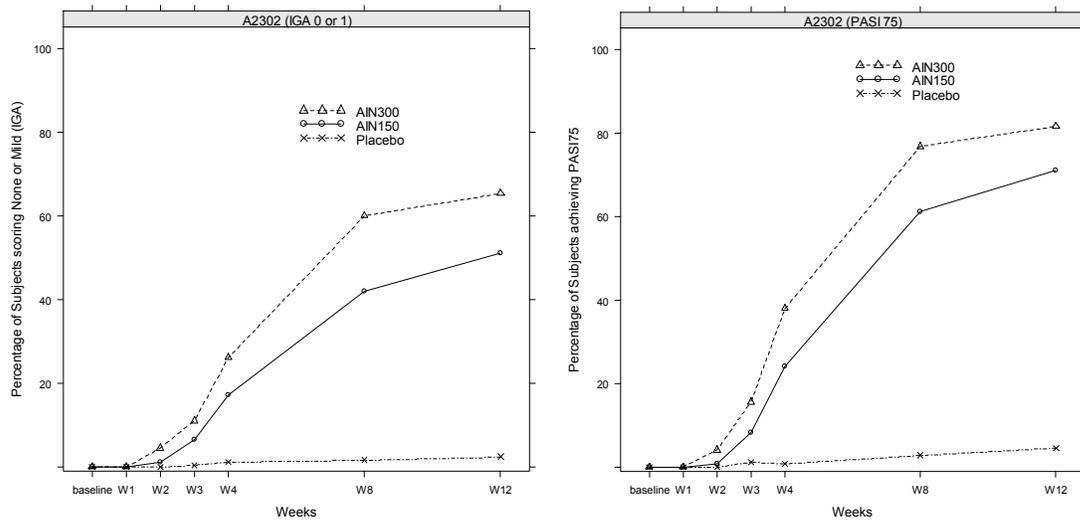
(1) NI margin of 10%

Furthermore, using the CMH test stratified by geographical region and weight strata at baseline, secukinumab was superior against etanercept at Week 12 ($p < 0.0001$) for the PASI 75 response (see Table 1).

3.2.3.2 Efficacy Over Time

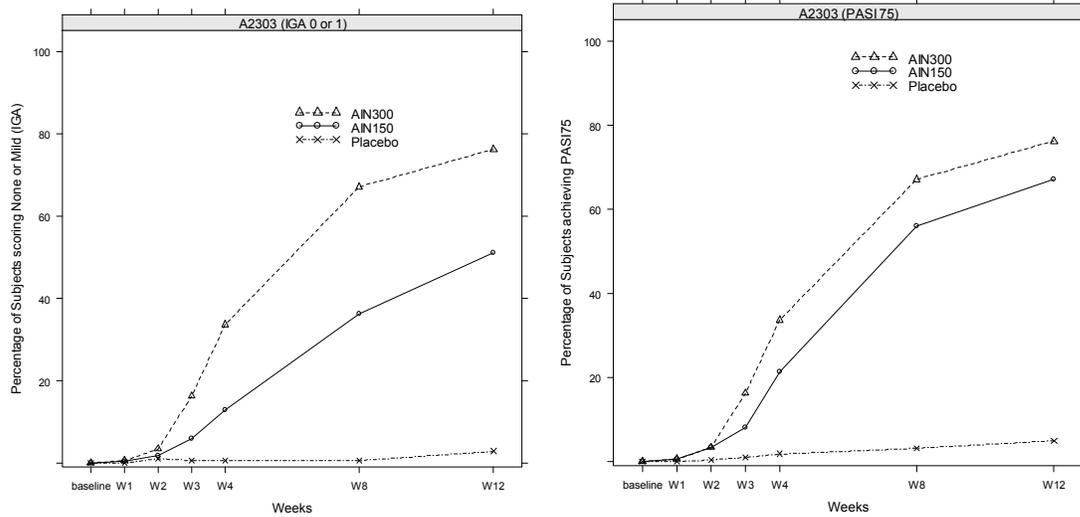
For the induction period, subjects were evaluated for IGA and PASI scores on Weeks 1, 2, 3, 4, 8, and 12. The following graphs Figures 3 and 4 show that the efficacy during the induction period is maximized at Week 12, and the differences between the two doses are more pronounced for the IGA responses compared to those of the PASI 75 responses.

Figure 3. IGA 0 or 1 and PASI 75 responses for the Induction Period of Trial 2302



Source: reviewer figures

Figure 4. IGA 0 or 1 and PASI 75 responses for the Induction Period of Trial 2303



Source: reviewer figures

The following Table 11 presents the efficacy response at Week 52 for those subjects who were successes at Week 12. With continued treatment in the maintenance period for the pivotal trials, 76% and 63% of the subjects maintained their IGA success status at Week 52 for those that received secukinumab 300 mg and 150 mg, respectively. Similarly for the PASI 75 responses, 82% and 75% of the PASI 75 responders at Week 12 maintained their PASI 75 responses at Week 52 for those that received the secukinumab 300 mg and 150 mg, respectively.

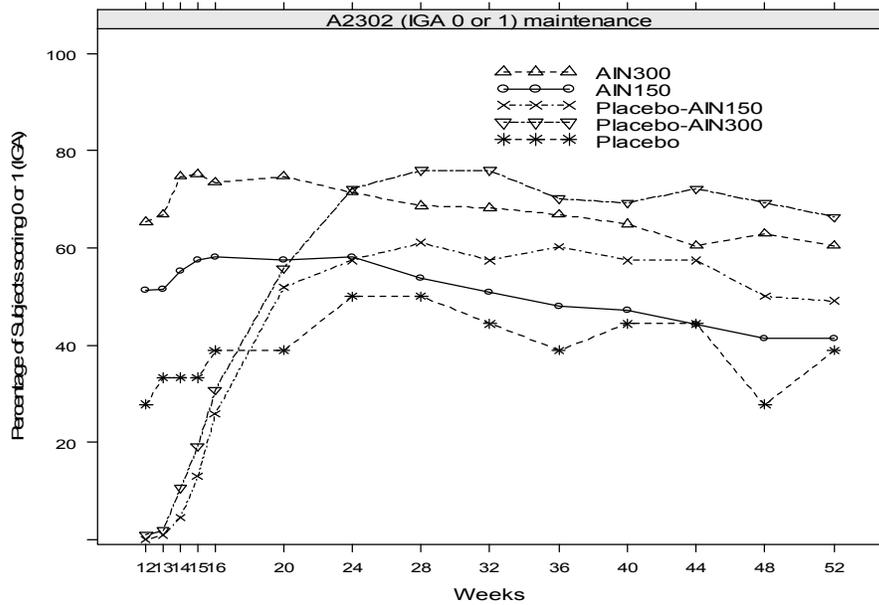
Table 11. Efficacy at Week 52 for the IGA and PASI Responders at Week 12 for the Pivotal Trials (2302 and 2303)

Trial	Endpoint	AIN457 300 mg	AIN457 150 mg
2302	IGA 0 or 1	119/160 (74%)	74/125 (59%)
	PASI 75	161/200 (81%)	126/174 (72%)
2303	IGA 0 or 1	161/202 (80%)	113/167 (68%)
	PASI 75	210/249 (84%)	180/219 (82%)

Source: Reviewer table

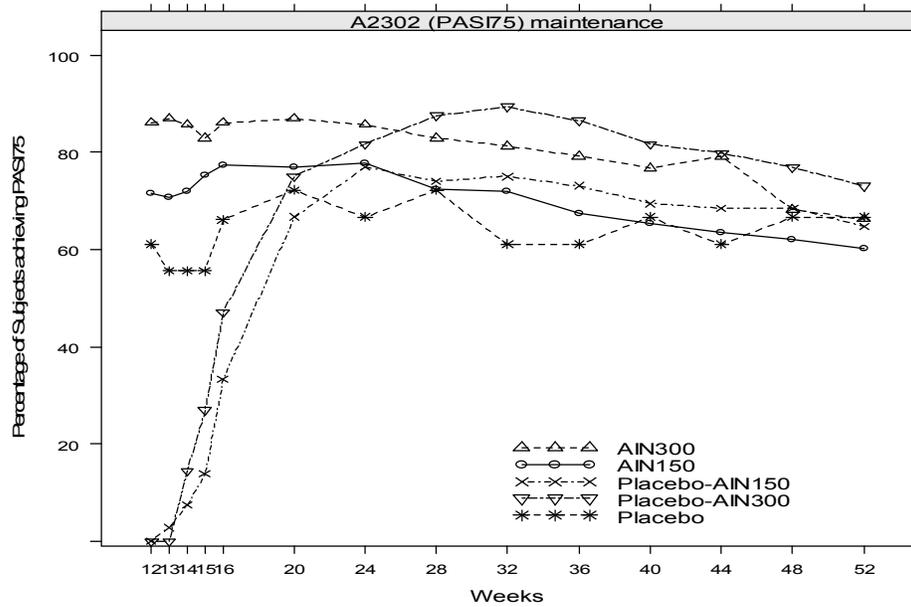
Figures 5-8 show the IGA 0 or 1 and PASI 75 responses in the maintenance period for the pivotal trials (2302 and 2303). The IGA and the PASI 75 responses were generally higher for the secukinumab 300 mg group compared to those of the secukinumab 150 mg group. Note that there is a slight declining trend over time which might be due to handling of the missing data as failures.

Figure 5. IGA 0 or 1 responses for the Maintenance Period in Trial 2302



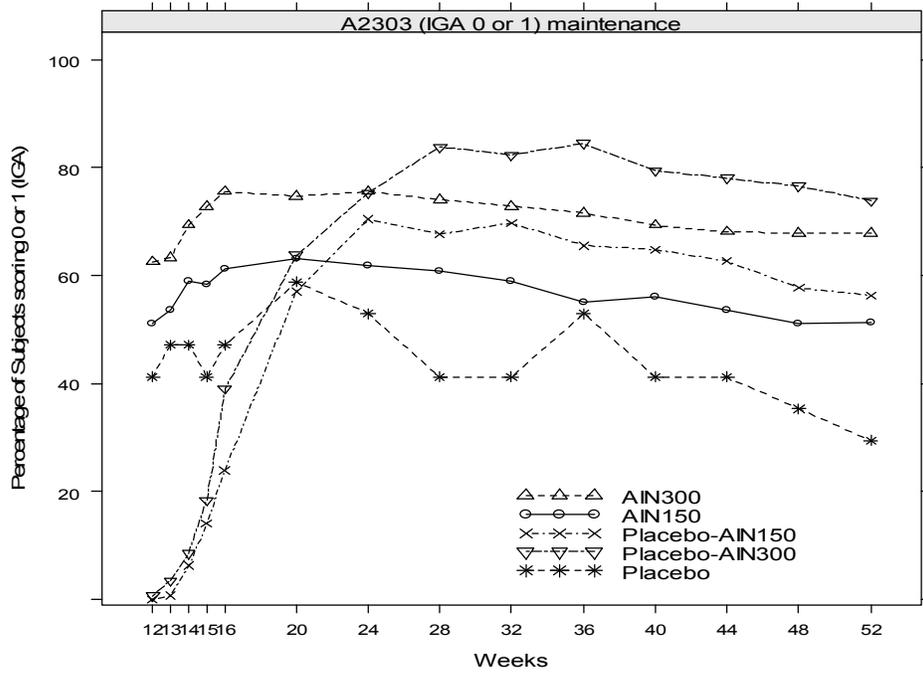
Source: reviewer's figure. Missing imputed as "non-responder".

Figure 6. PASI 75 responses for the Maintenance Period in Trial 2302



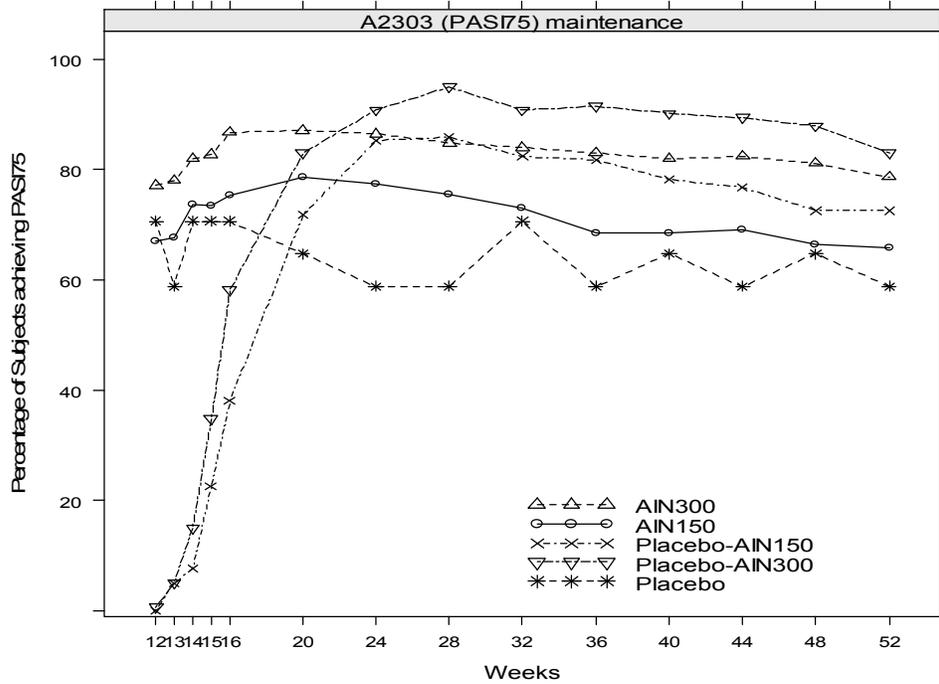
Source: reviewer's figure. Missing imputed as "non-responder".

Figure 7. IGA 0 or 1 responses for the Maintenance Period in Trial 2303



Source: reviewer's figure. Missing imputed as "non-responder".

Figure 8. PASI 75 responses for the Maintenance Period in Trial 2303



Source: reviewer's figure. Missing imputed as "non-responder".

3.2.3.3 Additional Analyses

Efficacy by Weight

Table 12 shows the IGA success at Week 12 classified by the subject baseline weight in 10 kg increment. The secukinumab 300 mg dose generally had higher IGA responses than the responses of the 150 mg dose group across most weight subgroups. As the number of subjects in the light weight (<60 kg) as well as in the heavy weight (≥ 120 kg) categories is small, it is difficult to draw conclusion regarding these weight subgroups.

Table 12. IGA success at Week 12 by Weight (in 10 kg increments) for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300mg N=245	AIN457 150mg N=245	Placebo N=248	AIN457 300mg N=327	AIN457 150mg N=327	Placebo N=326	EU- Etanercept N=326
Weight group							
<60	10/13 (77%)	16/25 (64%)	1/22 (5%)	21/35 (60%)	23/37 (62%)	1/40 (3%)	8/24 (33%)
60-70	29/42 (69%)	16/29 (55%)	1/27 (4%)	41/55 (75%)	25/49 (51%)	3/57 (5%)	16/51 (31%)
70-80	35/45 (78%)	23/51 (45%)	1/47 (2%)	40/69 (58%)	33/62 (53%)	1/63 (2%)	14/74 (14%)
80-90	29/42 (69%)	20/36 (56%)	0/47 (0%)	38/61 (62%)	38/67 (57%)	3/57 (5%)	28/70 (40%)
90-100	19/32 (59%)	22/39 (56%)	0/33 (0%)	33/49 (67%)	29/50 (58%)	1/54 (2%)	11/41 (27%)
100-110	17/29 (59%)	17/31 (55%)	1/28 (4%)	14/22 (64%)	7/24 (29%)	0/27 (0%)	6/31 (19%)
110-120	12/23 (52%)	7/15 (47%)	2/23 (9%)	9/17 (53%)	6/19 (32%)	0/8 (0%)	2/17 (12%)
≥ 120 kg	9/19 (47%)	4/19 (21%)	0/21 (0%)	6/19 (32%)	6/19 (32%)	0/19 (0%)	3/19 (16%)

Source: reviewer table

Table 13 shows the PASI 75 response at Week 12 classified by the subject baseline weight subgroups (in 10 kg increment).

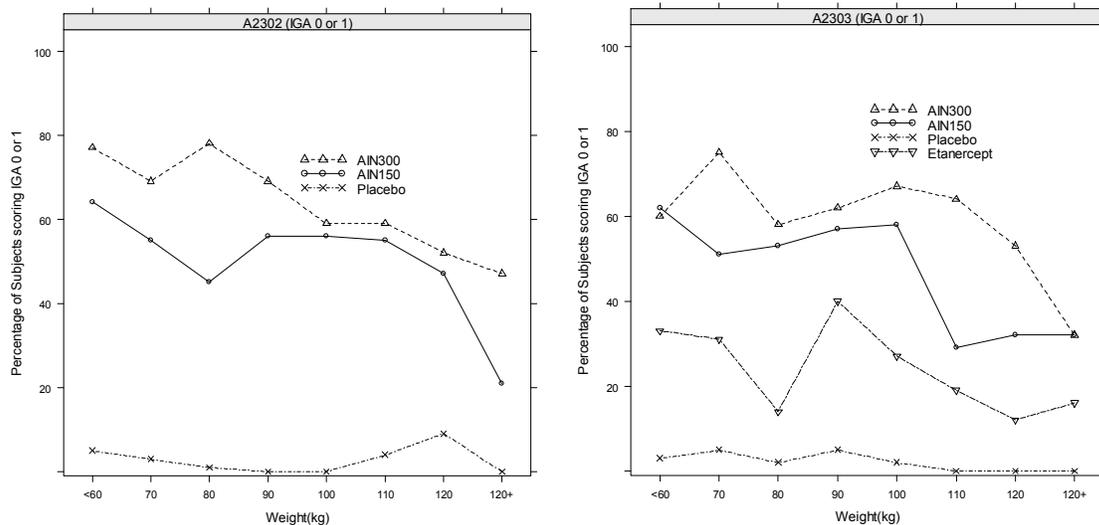
Table 13. PASI 75 success at Week 12 by Weight (in 10 kg increments) for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300mg N=245	AIN457 150mg N=245	Placebo N=248	AIN457 300mg N=327	AIN457 150mg N=327	Placebo N=326	EU- Etanercept N=326
Weight group							
<60	12/12 (100%)	21/24 (88%)	3/21 (14%)	24/31 (77%)	27/32 (84%)	1/35 (3%)	10/22 (45%)
60-70	37/40 (93%)	22/25 (88%)	1/22 (5%)	46/52 (88%)	31/46 (67%)	5/51 (10%)	23/45 (51%)
70-80	41/42 (98%)	34/46 (74%)	1/42 (2%)	54/66 (82%)	47/56 (84%)	3/59 (5%)	33/68 (49%)
80-90	36/40 (90%)	27/34 (79%)	1/44 (2%)	47/58 (81%)	52/64 (81%)	6/51 (12%)	34/65 (52%)
90-100	24/30 (80%)	28/35 (80%)	0/29 (0%)	38/46 (83%)	31/47 (66%)	1/51 (2%)	18/39 (46%)
100-110	23/28 (82%)	20/30 (67%)	1/27 (4%)	14/20 (70%)	12/23 (52%)	0/24 (0%)	11/27 (41%)
110-120	15/21 (71%)	12/13 (92%)	2/18 (11%)	12/17 (71%)	11/17 (65%)	0/8 (0%)	7/14 (50%)
≥120 kg	12/17 (71%)	10/18 (56%)	2/21 (10%)	14/18 (78%)	8/19 (42%)	0/18 (0%)	6/18 (33%)

Source: reviewer table

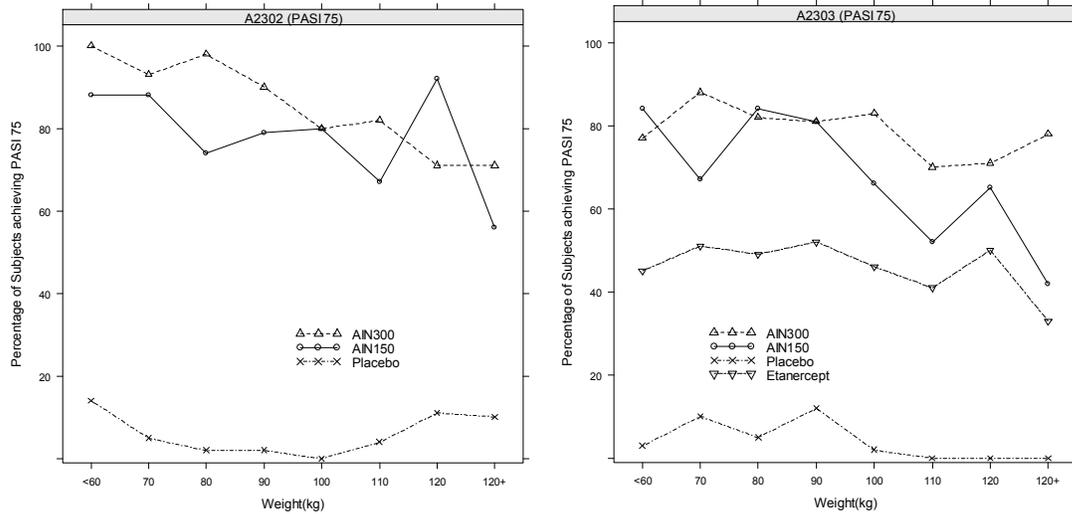
Figures 9 and 10 show the IGA 0 or 1 and PASI 75 response rates at Week 12 classified by the baseline weight group (in 10 kg increments).

Figure 9. IGA response rates at Week 12 by Weight (in 10 kg increments) for the Pivotal Trials (2302 and 2303)



Source: reviewer figures

Figure 10. PASI 75 response rates at Week 12 by Weight (in 10 kg increments) for the Pivotal Trials (2302 and 2303)



Source: reviewer figures

Efficacy by Weight and Gender

In general, as female subjects tend to be lighter than male subjects, the IGA responses by weight as well as by gender was investigated. Table 14 presents the IGA response by weight and by gender for the pivotal trials. For Trial 2303, the female subjects in the weight category of 70-90 kg showed higher IGA response for the lower secukinumab dose. However, when this was investigated in Trial 2304, the secukinumab 300 mg yielded higher IGA responses compared to those of the 150 mg dose irrespective of the weight and gender subgroups. These are discussed in further detail in Section 4.1 of this review.

Table 14. IGA responses by Weight (10 kg increment) and Gender for the Pivotal Trials (2302 and 2303)

Weight (kg)	Sex	Trial 2302			Trial 2303			
		AIN457 300mg N=245	AIN457 150mg N=245	Placebo N=248	AIN457 300mg N=327	AIN457 150mg N=327	Placebo N=326	Etanercept N=326
<70	F	19/26 (73%)	20/31 (65%)	2/27 (7%)	29/41 (71%)	27/39 (69%)	1/52 (2%)	12/34 (35%)
	M	20/29 (69%)	12/23 (52%)	0/22 (0%)	33/49 (67%)	21/47 (45%)	3/45 (7%)	12/41 (29%)
70-90	F	18/24 (75%)	13/23 (57%)	1/23 (4%)	21/41 (51%)	22/31 (71%)	1/18 (6%)	10/42 (24%)
	M	46/63 (73%)	30/64 (47%)	0/71 (0%)	57/89 (64%)	49/98 (50%)	3/102 (3%)	32/102 (31%)
≥90	F	14/26 (54%)	10/23 (43%)	2/26 (8%)	10/21 (48%)	9/21 (43%)	0/19 (0%)	3/19 (16%)
	M	43/77 (56%)	40/81 (49%)	1/79 (1%)	52/86 (60%)	39/91 (43%)	1/89 (1%)	19/89 (21%)

Source: reviewer table

3.2.3.4 Patient Reported Outcomes (PROs)

The mean PRO scores for itching, pain, and scaling at baseline, as well as the mean score for each PRO by baseline IGA severity, and by IGA response (i.e., success or failure) at Week 12 are summarized in this section.

Although the PRO endpoints were included in the testing strategy as secondary endpoints, according to the applicant, the electronic device (Psoriasis Diary) which was used to record the PROs was not available at all study centers, and furthermore, subjects could choose to opt out of using such device. As a result, approximately 40% of subjects reported the PROs in the pivotal trials (2302 and 2303), and as such, it is not clear whether this subset is a random sample of the total population so that the findings from these endpoints are generalizable to the overall population.

It should be noted that the protocols did not call for minimum baseline itch, pain, scaling severities as inclusion criteria. As such, the level of itching, pain and scaling at baseline varied widely from no symptoms (i.e., score of 0) to severe symptoms (i.e., score of 10). As a mere statistically significant change in PRO scores might not translate to clinically meaningful difference, a responder analysis that uses a pre-defined threshold for defining responders might provide useful information. For a clinically meaningful threshold, clinical judgment would be required.

Figures 11-16 present the mean scores for each symptoms by baseline IGA score (IGA of 3 vs. IGA of 4). For those subjects who reported the PROs, the figures show that at baseline:

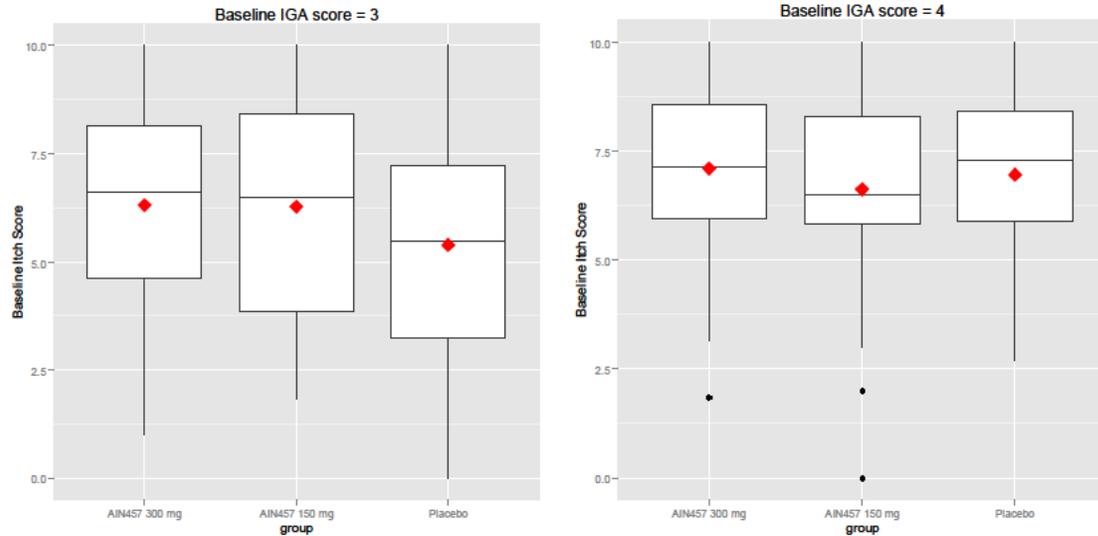
- (1) The mean scores were relatively balanced across the treatment arms.
- (2) Subjects of moderate psoriasis (i.e., IGA of 3) reported slightly lower mean scores for itching, pain, or scaling compared to those with severe psoriasis (i.e., IGA of 4).

The following boxplots show the mean (red dot), the median (solid black line), the interquartile range (box), the minimum and the maximum (whiskers) as well as the outliers (black dot) of the PRO scores.

Baseline Itch scores by Baseline IGA score

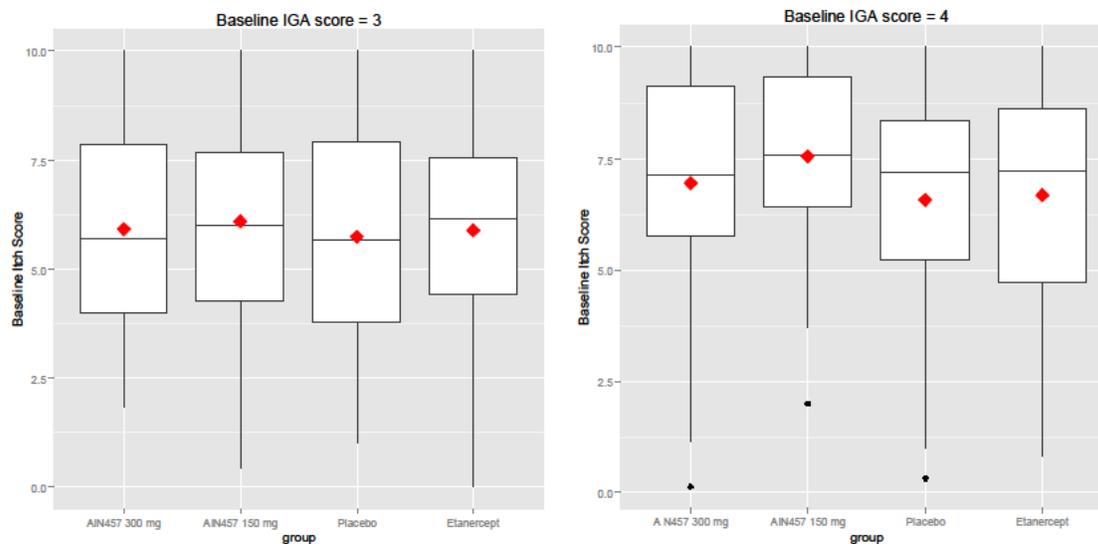
The baseline itch scores by the baseline IGA scores are presented in Figures 11 and 12. For those subjects who reported the PROs, the mean itch scores were relatively balanced across the treatment arms, and those subjects with moderate disease severity (IGA=3) had slightly lower mean itch scores compared to those with severe disease severity (IGA=4).

Figure 11. Mean Baseline Itch Scores by Baseline IGA Severity for Trial 2302



Source: reviewer figure

Figure 12. Mean Baseline Itch Scores by Baseline IGA Severity for Trial 2303

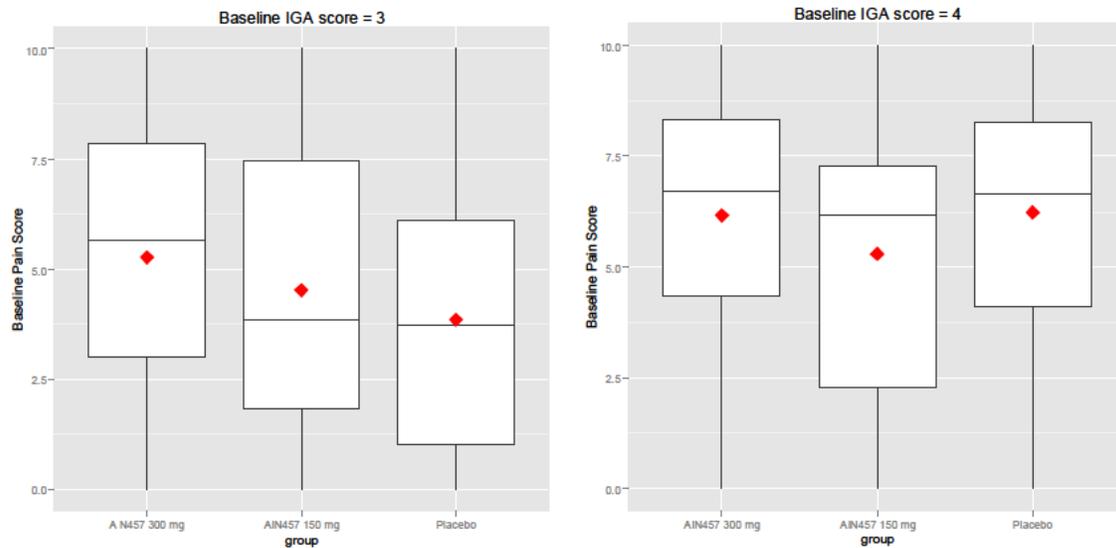


Source: reviewer figure

Baseline Pain scores by Baseline IGA score

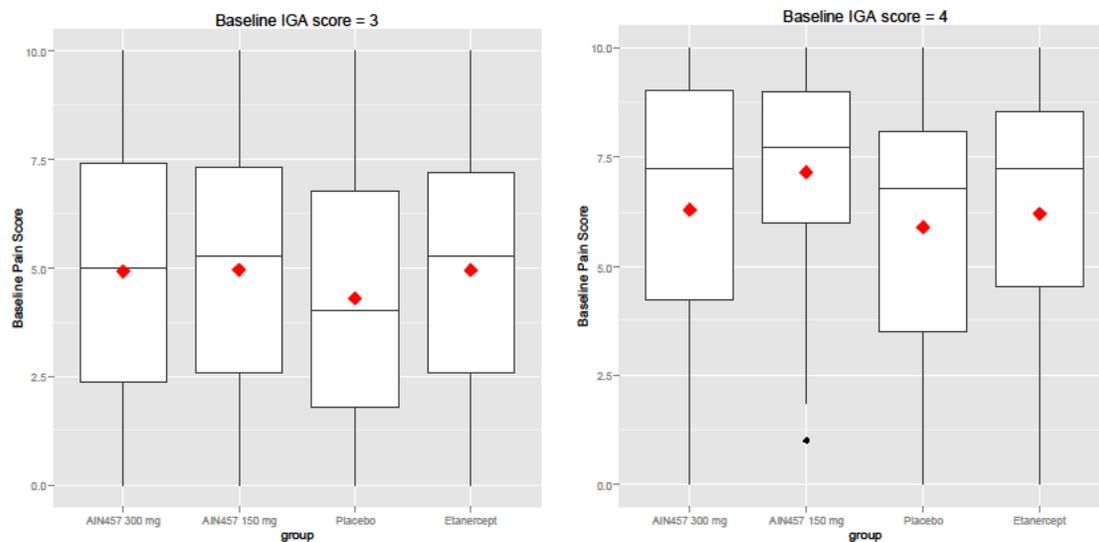
The mean pain scores by the baseline IGA scores at baseline are presented in Figures 13 and 14. For those subjects who reported the PROs, in comparison to the mean itching scores at baseline, the mean pain scores at baseline were generally lower across the treatment arms which might imply that pain might not have been as severe as itching for those that reported the outcome.

Figure 13. Mean Baseline Pain Scores by Baseline IGA Severity for Trial 2302



Source: reviewer figure

Figure 14. Mean Baseline Pain Scores by Baseline IGA Severity for Trial 2303

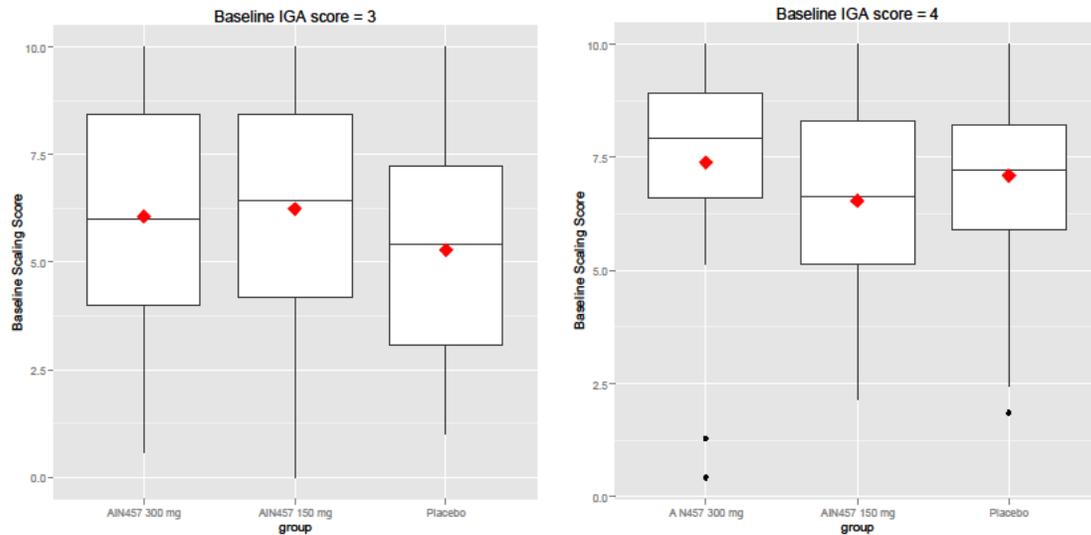


Source: reviewer figure

Baseline Scaling scores by Baseline IGA score

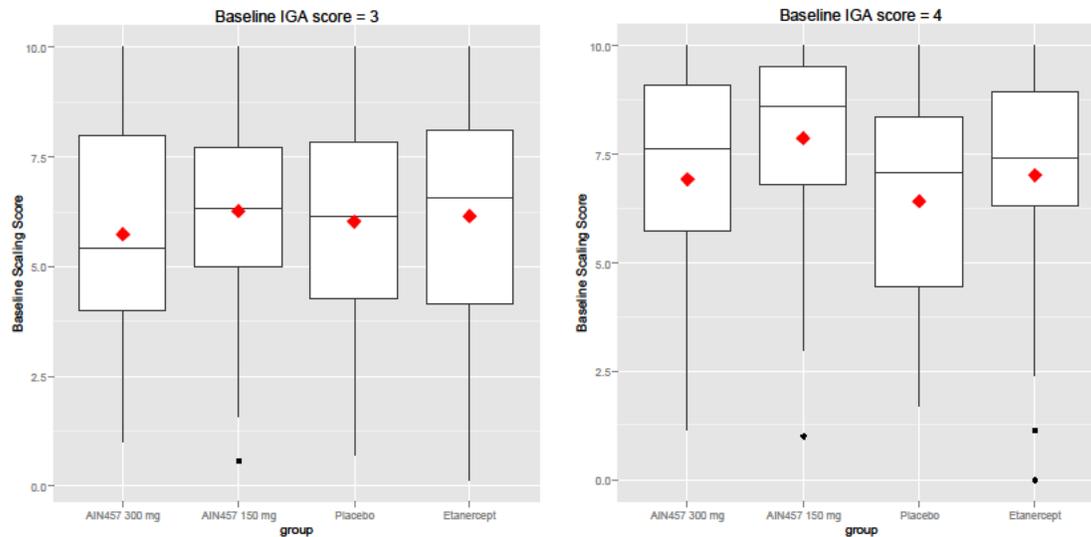
For those subjects who reported the PROs, the mean scaling scores at baseline were generally lower across the treatment arms, and those subjects with moderate disease severity (IGA=3) had slightly lower mean scaling scores compared to those with severe disease severity (IGA=4).

Figure 15. Mean Baseline Scaling Scores by Baseline IGA Severity for Trial 2302



Source: reviewer figure

Figure 16. Mean Baseline Scaling Scores by Baseline IGA Severity for Trial 2303



Source: reviewer figure

In conclusion, the mean baseline scores for the symptoms of itching, pain, and scaling were slightly higher for the subjects with the baseline IGA of 4 compared to those with the baseline IGA score of 3.

Itch by IGA success or failure at Week 12

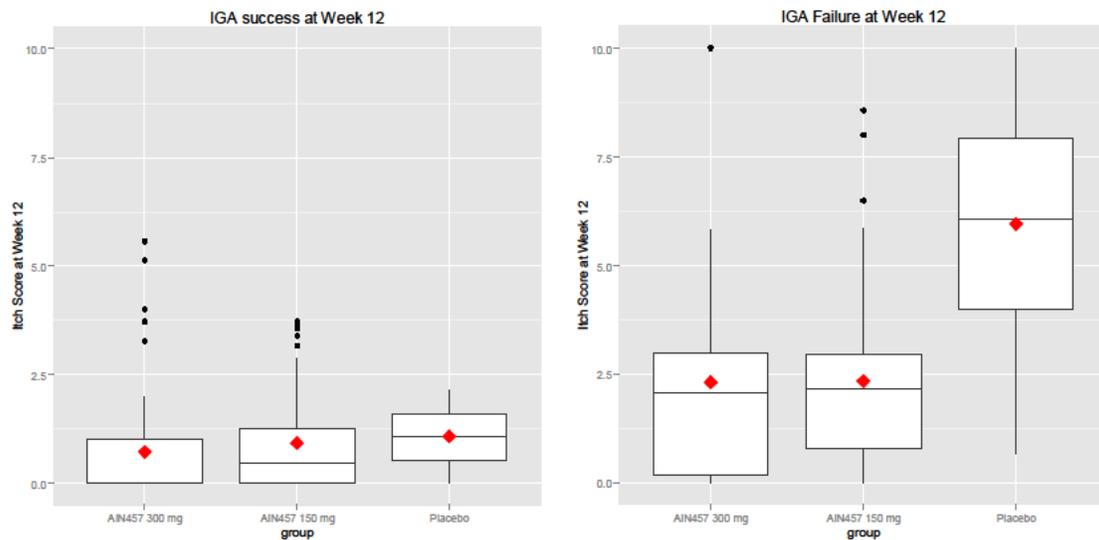
Among those subjects who reported their PROs on itching, pain, and scaling, the scores for each symptom were plotted by the IGA response status (i.e., IGA success vs. failure) at Week 12. Figures 17-22 show that the symptoms at Week 12 were improved for:

- (i) Those subjects who were IGA success at Week 12
- (ii) Those subjects who received secukinumab even among those that did not achieve IGA success.

The figures also show that the mean itching scores at Week 12 were generally lower for those subjects that received the secukinumab 300 mg dose compared to those that received the 150 mg dose, and this is consistent with the findings of the co-primary as well as the key secondary endpoints at Week 12 (Table 1, page 1).

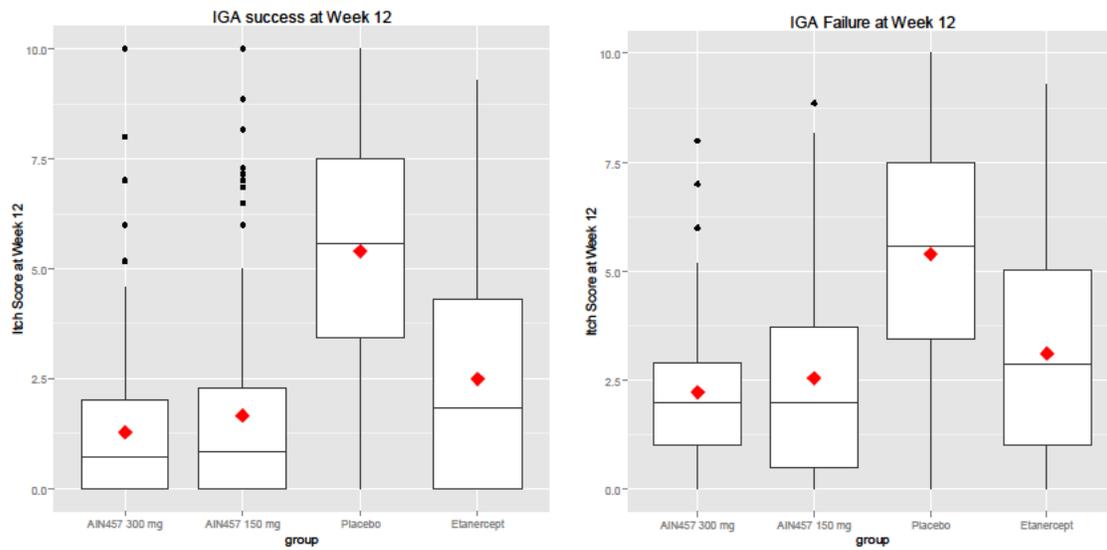
Figures 17 and 18 presents the mean itch scores by the IGA response status at Week 12.

Figure 17. Mean Itch Scores by IGA response at Week 12 for Trial 2302



Source: reviewer figures

Figure 18. Mean Itch Scores by IGA response at Week 12 for Trial 2303

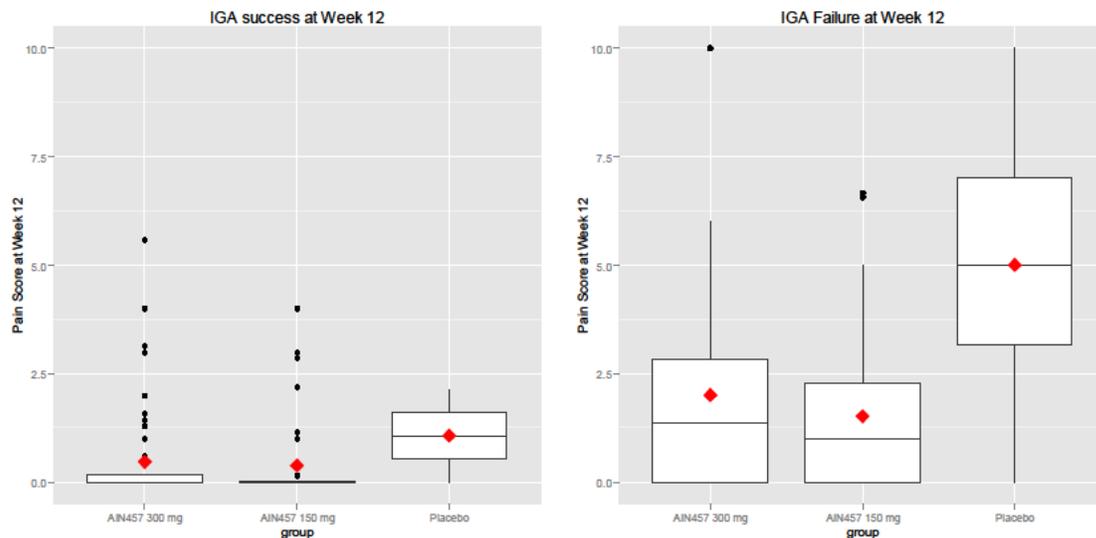


Source: reviewer figures

Pain score by IGA success or failure at Week 12

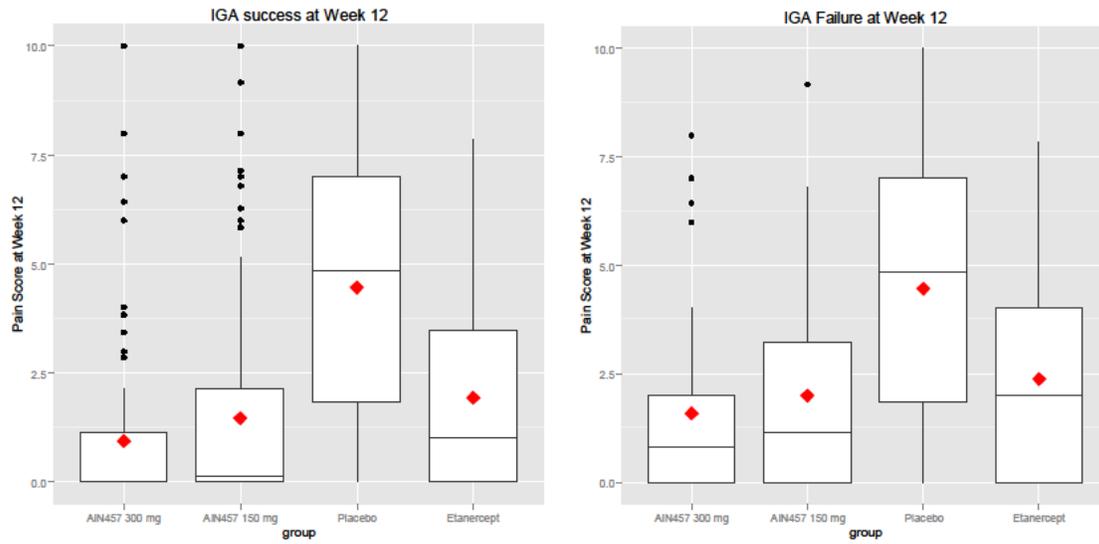
As with the itching, the pain severity at Week 12 showed that the severity generally improved for the IGA responders (i.e., IGA of 0 or 1), and also for the IGA non-responders that received secukinumab, although to a lesser extent.

Figure 19. Mean Pain Scores by IGA response at Week 12 for Trial 2302



Source: reviewer figures

Figure 20. Mean Itch Scores by IGA response at Week 12 for Trial 2303

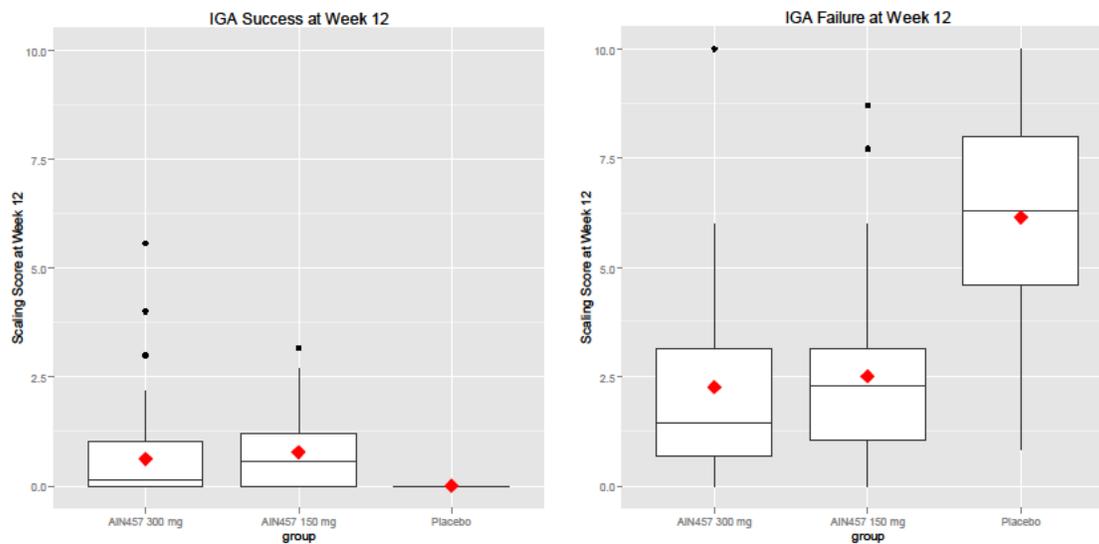


Source: reviewer figures

Scaling by IGA success or failure at Week 12

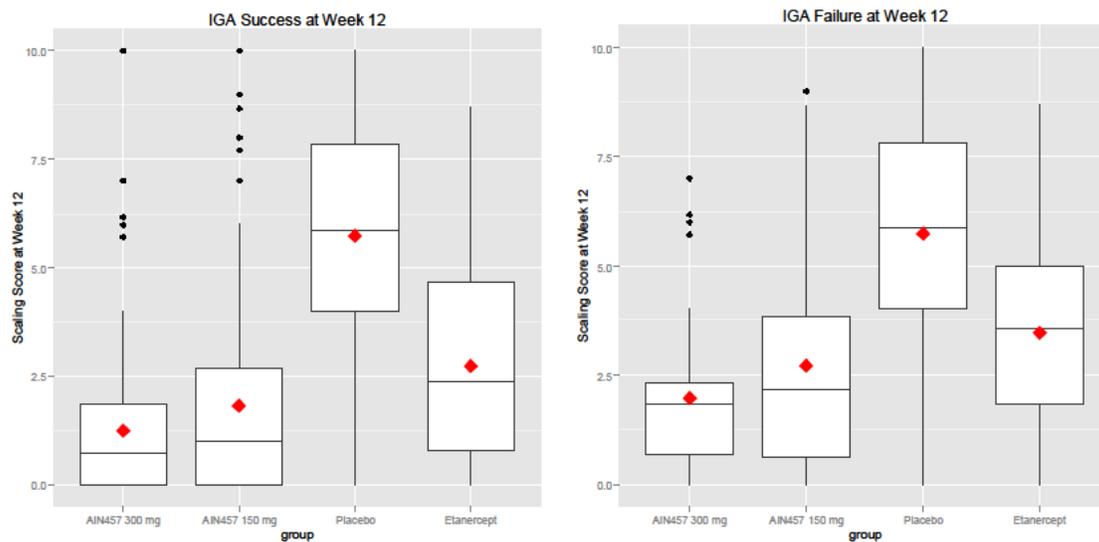
The scaling severity at Week 12 also showed that the severity generally improved for the IGA responders (i.e., IGA of 0 or 1), as well as for the IGA non-responders that received secukinumab, although to a lesser extent.

Figure 21. Mean Scaling Scores by IGA response at Week 12 for Trial 2302



Source: Reviewer figures

Figure 22. Mean Scaling Scores by IGA response at Week 12 for Trial 2303



Source: Reviewer figures

In conclusion, for those subjects that reported the PROs, the improvement in the severity of psoriasis disease severity also led to the improvement in itching, pain, and scaling. This was even the case for the subjects who were of IGA failures, although the improvements were smaller in magnitude compared to those of the IGA successes.

Responder Analysis

The applicant's primary analysis method for the PRO endpoints was ANCOVA; however, a statistically significant change from the ANCOVA model might not translate to clinically meaningful difference. The sponsor's sensitivity analyses included using a responder analysis with the responder thresholds of 2.2, 2.2, and 2.3, for itch, pain, and scaling, respectively. According to the applicant's Psoriasis Symptom Diary Evidence Dossier, these thresholds were selected based on an anchor-based method against the 5-point Patient Global Improvement of Change (PGIC) scale with categories of "moderately great deal worse, little worse, about the same, little better, moderately great deal better". The applicant's responder criteria of 2.2, 2.2, and 2.3 were for the "little better" category of the PGIC. However, these responder definitions were not previously agreed upon with the Agency. Furthermore, whether such improvement on an 11-point scale is clinically meaningful would require clinical judgment.

Using higher threshold values than those used by the applicant, the following results show that the secukinumab groups show higher responder rates for itching compared to those of placebo irrespective of the threshold value.

Table 15. Responders for Itching PRO at Week 12 for Trial 2302

Change from baseline to Week 12	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)
≥3	66 (27%)	59 (24%)	9 (4%)
≥4	55 (22%)	54 (22%)	5 (2%)
≥5	49 (18%)	43 (20%)	3 (1%)

Source: reviewer table

Trial 16. Responders for Itching PRO at Week 12 for Trial 2303

Change from baseline to Week 12	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
≥3	87 (27%)	86 (26%)	12 (4%)	71 (22%)
≥4	67 (20%)	75 (23%)	6 (2%)	49 (15%)
≥5	56 (17%)	56 (17%)	4 (1%)	40 (12%)

Source: reviewer table

Similarly, for pain, using higher threshold values, the following results show that the secukinumab groups show higher responder rates for pain compared to those of placebo irrespective of the threshold value.

Table 17. Responders for Pain PRO at Week 12 for Trial 2302

Change from baseline to Week 12	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)
≥3	60 (24%)	45 (18%)	6 (2%)
≥4	49 (20%)	40 (16%)	5 (2%)
≥5	35 (14%)	32 (13%)	3 (1%)

Source: reviewer table

Trial 18. Responders for Pain PRO at Week 12 for Trial 2303

Change from baseline to Week 12	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
≥3	74 (23%)	74 (23%)	12 (4%)	59 (18%)
≥4	65 (20%)	59 (18%)	8 (2%)	41 (13%)
≥5	50 (15%)	44 (14%)	3 (1%)	35 (11%)

Source: reviewer table

As with itching and pain, the following results show that the secukinumab groups show higher responder rates for scaling compared to those of placebo irrespective of the threshold value.

Table 19. Responders for Scaling PRO at Week 12 for Trial 2302

Change from baseline to Week 12	AIN457 300 mg (N=345)	AIN457 150 mg (N=345)	Placebo (N=348)
≥3	62 (25%)	64 (26%)	5 (2%)
≥4	57 (23%)	50 (20%)	3 (1%)
≥5	50 (20%)	40 (16%)	3 (1%)

Source: reviewer table

Trial 20. Responders for Scaling PRO at Week 12 for Trial 2303

Change from baseline to Week 12	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
≥3	86 (26%)	90 (28%)	12 (4%)	67 (21%)
≥4	48 (15%)	78 (24%)	7 (2%)	71 (22%)
≥5	55 (17%)	62 (19%)	4 (1%)	39 (12%)

Source: reviewer table

In conclusion, while the secukinumab 300 mg dose yielded higher IGA success rates compared to those of the 150 mg dose, the responses for itching, pain and scaling at Week 12 across the two secukinumab doses were similar. In addition, while the IGA as well as PASI 75 responses at Week 12 for the secukinumab doses were almost double the response as those for the etanercept, the itch responses at Week 12 for the secukinumab doses are only slightly higher in comparison to those for etanercept group.

3.2.3.5 Analysis Issues

There were two minor issues in using the applicant's data:

- (1) Protocol deviations of subjects outside the protocol-specified visit window
- (2) Common investigators across Trials 2302 and 2303.

However, because only a small number of subjects were outside the Week 12 visit window, a sensitivity analysis of excluding such subjects did not impact the study findings. Furthermore, a sensitivity analysis of excluding the largest site (Iceland) still showed that both secukinumab 300 mg and 150 mg were superior to placebo ($p < 0.0001$).

Details regarding analysis issues of the protocol deviations as well as the common investigator are provided below.

3.2.3.5.1 Protocol Deviations

The most common protocol deviation was the visit outside the windows. In Trial 2302, a total of 61 subjects either missed or were assessed outside the protocol-specified visit windows for Week 12. Table 21 shows the IGA success rates for the subjects that were assessed within the specified visit window (83-87) as well as those that were assessed outside the visit window. This analysis was done because the applicant used the visit window of 72-88 for the efficacy analyses although the protocol specified a visit window of Day 85 ± 2 for the Week 12 visit. As the number of subjects outside the protocol-specified visit window was small, and the impact on efficacy was minimal.

Table 21. IGA Success at Week 12 by Analysis Visit Days for Trial 2302

Visit Days	Number (Proportion) of subjects with IGA success n/N (%)		
	AIN457 300 mg N=235	AIN457 150 mg N=235	Placebo N=238
Missing ⁽¹⁾ or 72-82	2/10	1/16	0/22
83-87 (per protocol, protocol-specified window)	153/218 (72.7%)	121/216 (56.0%)	6/213 (2.8%)
88	6/7	2/3	0/3

Source: reviewer table. (1) subjects with missed visit were treated as failure.

Similarly, Table 22 shows the IGA success rates for the subjects that were assessed within the specified visit window (83-87) as well as the IGA successes among those that were outside the visit window, but included for the primary efficacy analysis. As the number of subjects outside the protocol-specified visit windows was small, the impact on efficacy was minimal.

Table 22. IGA Success at Week 12 by Analysis Visit Days for Trial 2303

Visit Days	Number (Proportion) of subjects with IGA success n/N (%)			
	AIN457 300 mg N=327	AIN457 300 mg N=327	Placebo N=326	Etanercept N=326
Missing ⁽¹⁾ or 72-82	7/30	5/34	0/39	3/15
83-87 (per protocol, protocol-specified window)	189/290 (65%)	156/287 (57%)	8/281 (3%)	83/279 (30%)
88	5/7	2/6	0/6	3/6

Source: reviewer table. (1) subjects with missed visit were treated as failure.

In conclusion, the applicant's approach for the primary analysis that included subjects with visits that occurred earlier between Days 72-82 may be reasonable for this disease as those subjects who became IGA successes prior to the scheduled visits (between Days 72-82) are most likely to maintain their disease status at the originally scheduled visit (between Days 83-87). Similarly, because the disease status at Day 88 is unlikely to have changed overnight, and because the number of subject is small, the impact of excluding these subjects on efficacy was minimal.

3.2.3.5.2 Common Investigators

The enrollment periods for the pivotal trials (2302 and 2303) overlapped. As a result, there were 10 common investigators across the two pivotal trials. On 2/6/2014, the Agency requested that the sponsor clarify how subjects were allocated to each of the pivotal trials, and the applicant responded on 2/6/2014 and stated that a total of 10 common Principal Investigators (PIs) from 5 countries randomized 116 subjects in Trial

2302, and 110 subjects in Trial 2303. The applicant stated that of the 10 common PIs, 5 PIs had a period during which both trials were recruiting. These 5 PIs together randomized 73 subjects in Trial 2302 (10% of all randomized subjects), and 89 subjects (about 7% of all randomized subjects) in Trial 2303. For those PIs that were enrolling subjects in both Trials 2302 and 2303, the applicant stated that the decision to enroll a subject to a specific trial was made exclusively by the investigators. Further, the applicant stated that each individual patient was only offered to participate in a single trial (i.e., the subject did not choose to participate in one trial over the other).

The details regarding the common PIs across the Trials 2302 and 2303 are in Table 23 below. However, the impact of common investigator was minimal as even after excluding the largest common site, Iceland, both secukinumab 300 mg and 150 mg were superior to placebo ($p < 0.0001$).

Table 23. Common Centers and the Number of Enrolled Subjects for the Pivotal Trials (2302 and 2303)

Country	Site# in 2302 (N)	Range of Reference Start Date ⁽¹⁾	Site# in 2303 (N)	Range of Reference Start Date
Argentina	1001 (4)	2012/1/20-2012/2/23	1101 (13)	2011/12/6-2012/4/20
	1003 (1)	2012/2/23	1104 (5)	2011/12/2-2012/1/6
	1005 (7)	2012/2/6-2012/2/29	1107 (5)	2012/2/23-2012/4/11
Canada	1023 (24)	2011/8/18-2012/2/16	2128 (11)	2011/12/21-2012/3/20
Colombia	1041 (5)	2011/11/3-2012/2/13	2160 (7)	2011/11/3-2012/4/17
Iceland	1080 (36)	2011/6/20-2012/2/26	3200 (52)	2011/6/28-2012/4/3
U.S.	5012 (11)	2011/7/28-2012/2/14	5139 (3)	2012/4/6-2012/4/23
	5013 (10)	2011/7/18-2012/2/15	5107 (9)	2011/12/13-2012/4/5
	5016 (5)	2011/11/15-2012/1/30	5137 (2)	2012/4/5-2012/4/19
	5032 (10)	2011/11/29-2012/2/7	5119 (2)	2012/4/10
	5039 (4)	2012/2/1-2012/2/16	5101 (6)	2012/1/10-2012/2/27

Source: reviewer table. (1) Randomized date

3.3 Other Phase 3 trials

3.3.1 Investigation of Prefilled Syringes (Trial 2308) and Autoinjectors (Trial 2309)

The applicant investigated the efficacy and safety of the liquid formulation of secukinumab in prefilled syringes (PFS) for Trial 2308, and in autoinjectors (AI) for Trial 2309. The

applicant intends to seek approval for both the liquid formulation of secukinumab in PFS and in AI, and consequently, seeking a labeling claim as well. Note that the induction periods of Trials 2308 and 2309 were identically designed to those of the pivotal trials (2302 and 2303).

The protocol-specified “co-primary” objective were to demonstrate the efficacy of secukinumab (150 mg and 300 mg) in subjects with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response at Week 12 compared to placebo. While the trials established efficacy against placebo, the trials were not designed to address how the efficacy compared against the original formulation within each trial. However, by comparing across the trials, the response rates for the PFS and the AI were generally comparable to those of the pivotal trials (2302 and 2303).

An overview of Trials 2308 and 2309 are presented below.

Table 24. Clinical Study Overview for Trials 2308 and 2309

Study	Study Sites	Study Population	Treatment Arms	N	Dates
A2308 (N=177)	32 international centers	Age ≥18, diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization, PASI≥12, IGA mod 2011≥3, BSA≥10%	AIN457 300 mg	59	5/8/2012 - 1/15/2013 ⁽¹⁾
			AIN457 150 mg	59	
			Placebo	59	
A2309 (N=182)	37 international centers	Age ≥18, diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization, PASI≥12, IGA mod 2011≥3, BSA≥10%	AIN457 300 mg	60	10/17/2012 - 4/10/2013 ⁽¹⁾
			AIN457 150 mg	61	
			Placebo	61	

Source: Reviewer table.

(1) Last patient last visit of the induction period (week 12).

For Trial 2308, a total of 177 subjects from 32 global sites who are ≥18 of age with PASI score ≥12, IGA score of at least 3, and BSA≥10% at baseline were enrolled, and for Trial 2309, a total of 182 subjects from 37 global sites who are ≥18 of age with PASI score ≥12, IGA score of at least 3, and BSA involvement ≥10% at baseline were enrolled.

The same co-primary endpoints as well as analysis methods as those for Trials 2302 and 2303 were used. Therefore, the following hypotheses at Week 12 were tested:

H₁: secukinumab 150 mg is not different to placebo with respect to PASI75 response

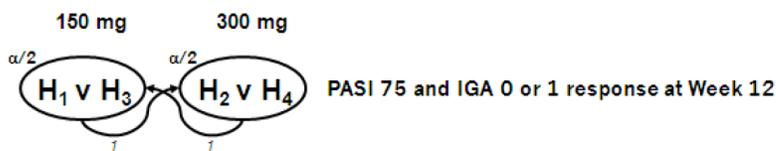
H₂: secukinumab 300 mg is not different to placebo with respect to PASI75 response

H₃: secukinumab 150 mg is not different to placebo with respect to IGA 0 or 1 response

H₄: secukinumab 300 mg is not different to placebo with respect to IGA 0 or 1 response

The applicant’s testing strategy for Trials 2308 and 2309 were as below.

Figure 23. Testing strategy for Trials 2308 and 2309



Approximately 4% of subjects had missing data at the Week 12 visit, and per the protocol-specified primary imputation method, these subjects were treated as “failures” for the efficacy analyses. The most common reason for discontinuation was adverse events. The following is a table of subject disposition for Trials 2308 and 2309.

Table 26. Subject Disposition for Trials 2308 and 2309

	A2308			A2309		
	AIN457 300mg	AIN457 150mg	Placebo	AIN457 300mg	AIN457 150mg	Placebo
Randomized	59	59	59	60	61	61
Applicant’s FAS	59	59	59	60	61	61
SES	59	59	59	60	61	61
Completed Week 12	56 (95%)	58 (98%)	56 (95%)	60 (100%)	58 (95%)	59 (97%)

Source: applicant’s table

The baseline demographics characteristics were generally balanced across the PFS and the AI trials. Approximately, 68% and 32% were male and female, respectively, and approximately 93% were Caucasians. The mean age was around 45 and the mean weight was about 91kg in Trial 2308 and 94 kg in Trial 2309.

While the gender, age, and weight distributions in these trials were similar to those of the pivotal trials (2302 and 2303), the racial distribution was more skewed in these trials with about 93% Caucasians compared to the 70% in the pivotal trials (2302 and 2303). However, it should be noted that Trials 2308 and 2309 were relatively small in size compared to the pivotal trials (2302 and 2303).

See the baseline demographics table for Trials 2308 and 2309 below.

Table 27. Baseline Demographics for Trials 2308 and 2309

	A2308			A2309		
	AIN457 300mg N=59	AIN457 150mg N=59	Placebo N=59	AIN457 300mg N=60	AIN457 150mg N=61	Placebo N=61
Gender						
<i>Female</i>	21 (36%)	19 (32%)	20 (34%)	14 (23%)	20 (33%)	23 (38%)
<i>Male</i>	38 (64%)	40 (68%)	39 (66%)	46 (77%)	41 (67%)	38 (62%)
Age						
<i>Mean</i>	45	46	47	47	44	44
<i>SD</i>	13	15	14	14	14	13
<i>Range</i>	18-72	18-75	19-77	18-83	19-76	19-69
<i>Median</i>	46	46	44	44	43	45
<65	58 (98%)	51 (86%)	53 (90%)	52 (87%)	56 (92%)	58 (95%)
≥65	1 (2%)	8 (14%)	6 (10%)	8 (13%)	5 (8%)	3 (5%)
Race						
<i>Asian</i>	1 (2%)	2 (3%)	1 (2%)	3 (5%)	1 (2%)	2 (3%)
<i>Black</i>	3 (5%)	3 (5%)	1 (2%)	0 (0%)	2 (3.3%)	0 (0%)
<i>Caucasian</i>	54 (92%)	51 (87%)	57 (97%)	56 (93%)	58 (95%)	59 (97%)
<i>Other</i>	1 (2%)	2 (3%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
<i>Unknown</i>	0 (0%)	1 (2%)	0 (0%)	-	-	-
Weight						
<i>Mean</i>	93	94	88	91	94	90
<i>SD</i>	26	26	22	23	32	21
<i>Range</i>	57-150	53-204	52-140	54-162	46-215	53-148
<i>Median</i>	89	89	85	88	89	88

Source: applicant's table

The baseline IGA, PASI and BSA disease severities were generally balanced across treatment groups in Trials 2308 and 2309. Approximately 62% of subjects had a baseline IGA of 3 (moderate), and the rest of the subjects had a baseline IGA score of 4 (severe). The mean PASI score was about 21 (the minimum for inclusion was a PASI score of 12). Subjects were required to have a baseline body surface area (BSA) involvement of at least 10% and averaged about 32% involvement in Trial 2308 and 27% involvement in Trial 2309. The baseline disease severities for Trials 2308 and 2309 were similar to those of the pivotal trials (2302 and 2303). See the baseline disease severity table for Trials 2308 and 2309 below.

Table 28. Baseline Disease Severity for Trials 2308 and 2309

	Trial 2308			Trial 2309		
	AIN457 300mg N=59	AIN457 150mg N=59	Placebo N=59	AIN457 300mg N=60	AIN457 150mg N=61	Placebo N=61
IGA						
3	40 (68%)	37 (63%)	34 (58%)	39 (65%)	35 (57%)	38 (62%)
4	19 (32%)	22 (37%)	25 (42%)	21 (35%)	26 (43%)	23 (38%)
PASI						
<i>Mean</i>	21	21	21	19	22	19
<i>SD</i>	8	8	8	6	9	8
<i>Range</i>	12-43	12-53	12-49	12-45	12-55	12-43
<i>Median</i>	18	18	19			
BSA						
<i>Mean</i>	33	31	32	26	30	26
<i>SD</i>	18	17	17	13	17	15
<i>Median</i>	28	29	28	25	26	23
<i>Range</i>	10-78	10-88	10-88	10-78	10-87	11-81

Source: applicant's table

Both secukinumab 300 mg and 150 mg were superior to placebo ($p < 0.0001$) at Week 12 for the co-primary endpoints of PASI 75 response and IGA of 0 or 1 in both trials. The PASI 75 and the IGA 0 or 1 response rates of the secukinumab 300 mg using the AI (2309) were slightly higher than those of Trials 2302, 2303, 2308; however, it should be noted that Trials 2308 and 2309 were relatively small in size compared to the pivotal trials (2302 and 2303). The results of Trials 2308 and 2309 are presented in Table 2 on page 4 of this review.

3.3.2 Investigation of two maintenance regimens: retreatment at the Start of Relapse (SoR) regimen vs. retreatment at Fixed Interval (FI) regimen (Trial 2304)

The primary objective of Trial 2304 was to demonstrate the non-inferiority of 150 mg and 300 mg of secukinumab administered at the start of relapse (SoR) versus the fixed interval (FI) regimens of 150 mg and 300 mg of secukinumab respectively with respect to PASI 75 response. The applicant is not proposing any labeling claims based on this trial because the primary objective was not met. However, the study design and the study findings are summarized in this section.

In this multicenter, randomized, double-blind trial, a total of 843 subjects with moderate to severe chronic plaque-type psoriasis from about 133 global study sites were enrolled. For enrollment, men or women who are ≥ 18 of age, PASI score ≥ 12 , IGA score of at least 3, and BSA involvement $\geq 10\%$ at baseline were enrolled. Enrolled subjects were randomized in a 1:1 ratio to either secukinumab 300 mg or 150 mg. The sponsor stated that the placebo arm was not included in this trial because the sponsor's intent was to assess the maintenance of therapy in each of the two dosing regimens.

The randomization were stratified by geographical region and body weight collected at baseline (<90 kg or ≥90 kg). Subjects received treatment at randomization, Weeks 1, 2, 3, 4 and 8 with assessment at Week 12.

Based on the Week 12 PASI 75 responses, these subjects were then re-randomized to one of the two maintenance treatment arms in a 1:1 ratio:

- Fixed Interval (FI) – the same dose as in the induction period every 4 weeks from Weeks 12 to 48
- Retreatment at Start at Relapse (SoR) where SoR was defined as “a loss of ≥20% of the maximum PASI gain achieved during the study compared to baseline, and a loss of PASI 75 response”. Whenever a subject fulfilled the start of relapse criteria, active secukinumab were administered at their scheduled visits until the subject was back to PASI 75 response.

As a result, at the re-randomization at Week 12, 217 subjects were randomized to secukinumab 300 mg FI, 203 subjects to secukinumab 150 mg FI, 217 subjects to 300 mg SoR and 206 subjects to 150 mg SoR dosing regimen. It should be noted that the Agency previously commented that this trial would be considered as an exploratory trial (Guidance meeting, dated: 3/2/2011).

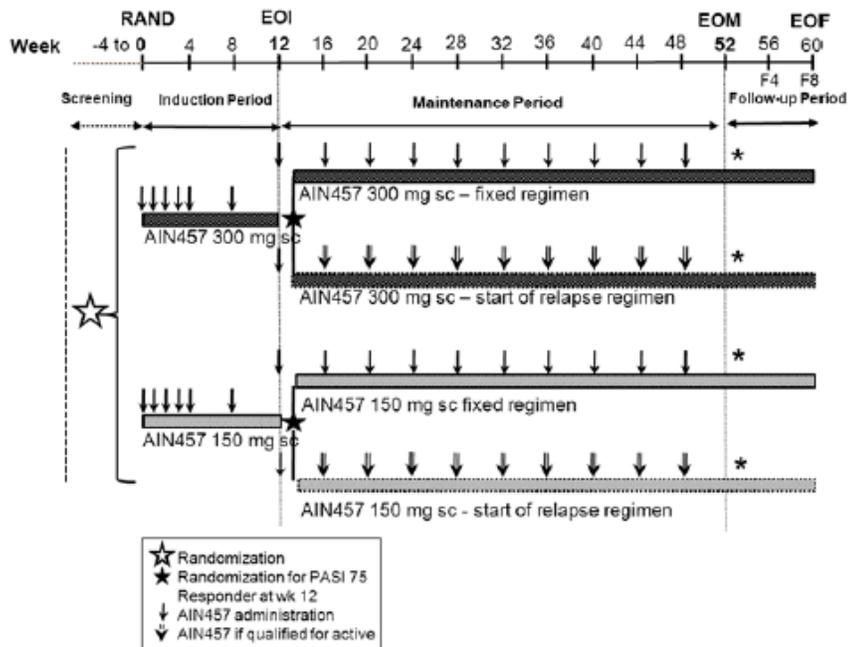
Subjects who finished the maintenance period entered the treatment-free follow-up period with visits on Weeks 56 and 60.

Table 30. Clinical Study Overview for Trial 2304

Study	Study Sites	Study Population	Treatment Arms	N	Dates
A2304 (N=843)	133 international centers	Age ≥18, diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization, PASI ≥12, IGA mod 2011 ≥3, BSA ≥10%	AIN457 300 mg Fixed Interval (FI)	217	8/4/2011 - 3/7/2013
			AIN457 150 mg Fixed Interval (FI)	203	
			AIN457 300mg Start of Relapse (SoR)	217	
			AIN457 150 mg Start of Relapse (SoR)	206	

The following is the study design diagram for Trial 2304.

Figure 24. Study Design for Trial 2304



Source: applicant's study report (p.67)

For the primary endpoint for Trial 2304, the “maintenance of response” for each regimen was defined as below:

- FI regimens - PASI75 response at Week 52
- SoR regimens – PASI 75 response at:
 - Week 52 for subjects who qualified for active treatment at Week 40 and
 - Week 40 for subjects who did not qualify for active treatment at Week 40

The sponsor's choice of timepoint for those who did not qualify for active treatment at Week 40 is reasonable under the assumption that the subjects maintain their disease status at Week 40 to Week 52.

The sponsor conducted non-inferiority testing of the retreatment at SoR regimen vs. the FI regimen with respect to the maintenance of response, separately for the 150 mg and 300 mg dose groups. That is, the hypotheses were:

- **H₁**: secukinumab retreatment at SoR regimen with 150 mg is not non-inferior to FI regimen with 150 mg with respect to maintenance response
- **H₂**: secukinumab retreatment at SoR regimen with 300 mg is not non-inferior to FI regimen with 300 mg with respect to maintenance response

The sponsor used a non-inferiority margin (Δ) of 15%, and stated that the margin was based on clinical judgment.

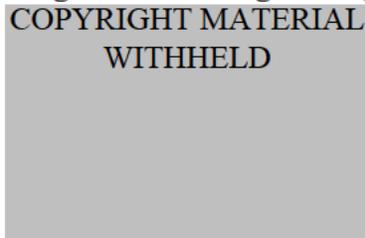
The one-sided Cochran-Mantel-Haenszel test stratified by geographical region and body weight stratum was used, and for the non-inferiority comparison of each of the two doses,

the one-sided 98.75% confidence interval was derived (i.e., H_1 and H_2 tested at the level of 1.25%). The non-inferiority would be concluded in case $-\Delta$ is smaller than the lower bound of the confidence interval for the difference in maintenance responder rates “retreatment at SoR regimen” minus “FI regimen”.

The sponsor did not include the secondary endpoints in the testing strategy, and the following is the diagram for the applicant’s testing strategy for Trial 2304.

Figure 25. Testing Strategy for Trial 2304 (Bretz et al., 2009)

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For handling missing data, the same primary imputation of imputing missing as failure was used.

Table 32 shows the subject disposition for the first 12 weeks as well as for the maintenance period that compared retreatment at SoR vs. FI regimens. Note that the applicant removed one secukinumab 300 mg subject (AIN457A2304-4044007) from the FAS and SES sets as this subject did not have any post-baseline efficacy nor safety data. However, per the ITT definition, this subject should be considered as ITT and included in the efficacy analyses.

Of the 928 subjects who completed the induction period, a total of 843 (91%) of subjects were re-randomized to the maintenance period to either FI dosing or start of SoR dosing at their respective dose level. As a result, 217 subjects were re-randomized to secukinumab 300 mg FI, 203 to secukinumab 150 mg FI, 217 to secukinumab 300 mg SoR, and 206 to secukinumab 150 mg SoR arms. See Table 32.

Table 32. Disposition for the Induction and Maintenance Period of Trial 2304

Trial 2304				
First 12 weeks	AIN457 300mg		AIN457 150mg	
Randomized	484		482	
Applicant's FAS	483		482	
SES	483		482	
Completed Week 12	464 (96%)		464 (96%)	
MAINTENANCE	AIN457 300mg FI	AIN457 300mg SoR	AIN457 150mg FI	AIN457 150mg SoR
Randomized	217	217	203	206
Applicant's FAS	216	217	203	206
SES	216	217	203	205
Completed Week 52	199 (92%)	201 (93%)	186 (92%)	181 (88%)

Source: applicant's table

Approximately 91% of subjects completed the 52-week maintenance period, and the discontinuation rate was highest for the 150 mg SoR arm (12%) compared to the other treatment arms (about 8%). The most common reason for discontinuation was subject/guardian decision (4%), and the rates were similar for 150 mg SoR and 150 mg FI, and also for 300 mg SoR and 300 mg FI arms. The discontinuation rate due to adverse events was highest for the 300 mg FI arm compared to the rest of the arms.

Using the prespecified non-inferiority (NI) margin of 15%, the applicant compared the PASI 75 response rates of the retreatment at SoR regimen to the retreatment at FI regimen using the NI testing. While the point estimates were about -10% different between the SoR and the FI regimens; however, the lower limit of the confidence interval was -20% which exceeded the prespecified -15% margin. Thus, the non-inferiority of the SoR regimen to the FI regimen was not achieved.

Table 33. Comparison of PASI 75 Response at Week 52⁽¹⁾ for Trial 2304

AIN457	SoR	FI	Difference in responses	CI ⁽²⁾
150 mg	108/206 (52%)	126/203 (62%)	-10	(-20, 1)
300 mg	147/217 (68%)	169/217 (78%)	-10	(-19, -1)

Source: applicant's table. (1) Week 40 for those subjects that did not qualify for active treatment at Week 40; Week 52 for those that qualified for active treatment at Week 40 and for those that received FI. (2) One-sided confidence interval.

3.3.3 Investigation of uptitration for partial responders (Trial 2307)

The primary objective of Trial 2307 was to demonstrate the efficacy of intravenous (*i.v.*) versus subcutaneous (*s.c.*) administration of secukinumab in moderate to severe plaque-type psoriasis subjects who achieved a partial response after 12 weeks of treatment in Study CAIN457A2304 with respect to both PASI75 and IGA 0 or 1 response at Week 8.

In this multicenter, randomized, double-blind, parallel-group trial, while the sponsor expected that approximately 140 partial responders (PASI 50 but not PASI 75) from Trial

2304 would enroll into this trial, due to an “unexpected high PASI 75 response in Trial 2304”, only 43 subjects enrolled in this trial. The non-responders (i.e., those who do not achieve at least PASI 50) were not eligible to participate in this trial.

Table 34. Trial 2307 - Clinical Study Overview for Trial 2307

Study	Study Sites	Study Population	Treatment Arms	N	Dates
2307 (N=43)	23 international centers	Age ≥18, Subjects who participated in Trial 2304 and had achieved a partial response (i.e., PASI 50 but not PASI 75) after 12 weeks of treatment with no major protocol deviations.	AIN457 300 mg - AIN457 300 mg (s.c.)	6	12/2/2011 - 2/28/2013
			AIN457 300 mg - AIN457 10mg/kg (i.v.)	8	
			AIN457 150 mg - AIN457 300 mg (s.c.)	15	
			AIN457 150mg - AIN457 10mg/kg (i.v.)	14	

Source: reviewer table

Trial 2307 had 3 periods:

- I.V. period (8 weeks)
- Maintenance (Weeks 8-40)
- Follow-up (8 weeks)

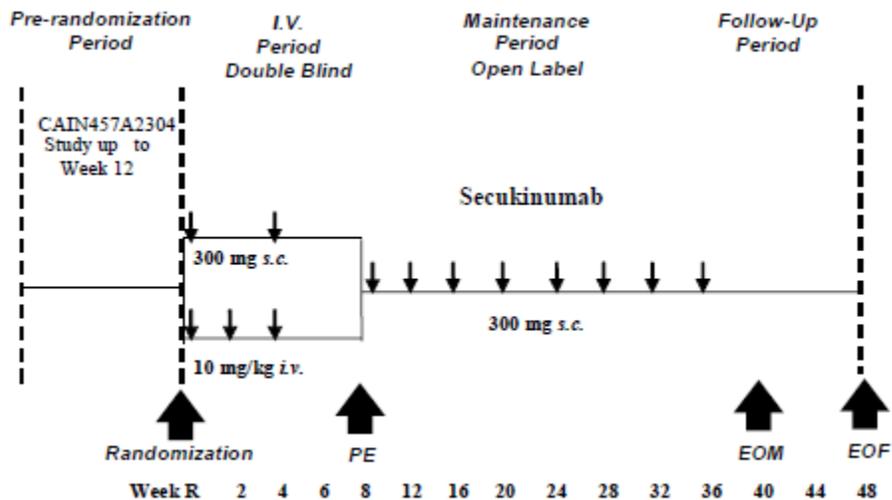
In the “I.V. period”, the sponsor randomized subjects in 1:1 ratio to the following treatment arms:

- Secukinumab *i.v.*: secukinumab 10 mg/kg administered via *i.v.* at baseline, Weeks 2, 4 + secukinumab placebo administered via *s.c.* at baseline and Week 4 (22 subjects: 8 from secukinumab 300 mg; 14 from secukinumab 150 mg)
- Secukinumab *s.c.*: secukinumab 300 mg administered via *s.c.* at baseline, Week 4 + secukinumab placebo administered via *i.v.* at baseline, Weeks 2, 4 (21 subjects: 6 from secukinumab 300 mg; 15 from secukinumab 150 mg)

No placebo arm was included, as the sponsor’s intent was to compare the effect of the *i.v.* route with the *s.c.* dosing in partial responders to *s.c.* secukinumab.

Randomization was stratified by previous treatment in Trial 2304.

Figure 26. Applicant's Trial Design for Trial 2307



Source: applicant's protocol

In the maintenance period, all subjects received 300 mg of secukinumab open-label, administered *s.c.* at Week 8, and subsequently every 4 weeks with the last dose given at Week 36. In the follow-up period, visits occurred on Weeks 44 and 48.

The co-primary endpoints were PASI 75 at Week 8 and IGA 0 or 1 (with 2-grade improvement) at Week 8.

The protocol specified the two-sided Cochran-Mantel-Haenszel test stratified by previous treatment group as the primary analysis method in Trial 2304. The sponsor tested the following hypotheses:

- H_1 : secukinumab *i.v.* administration is not different to secukinumab *s.c.* administration with respect to PASI 75 response at Week 8 vs. H_{A1} : secukinumab *i.v.* administration is different to secukinumab *s.c.* administration with respect to PASI 75 response at Week 8
- H_2 : secukinumab *i.v.* administration is not different to secukinumab *s.c.* administration with respect to IGA 0 or 1 response at Week 8 vs. H_{A2} : secukinumab *i.v.* administration is different to secukinumab *s.c.* administration with respect to IGA 0 or 1 response at Week 8

The Type I error rate was set to 0.05, and the hypotheses were tested at the level of 0.05. The sponsor stated that significant results were only be achieved if both tests were rejected (i.e., if only one hypothesis is rejected and the other is not rejected, efficacy of the *i.v.* administration has not been demonstrated).

The following is a subject disposition table for Trial 2307.

Table 35. Trial 2307 – Subject Disposition for Trial 2307

	AIN457 300mg - AIN457 300 mg s.c.	AIN457 150mg - AIN457 300 mg s.c.	AIN457 300mg - AIN457 10 mg/kg i.v.	AIN457 150mg - AIN457 10 mg/kg i.v.
Randomized	6	15	8	14
Applicant's FAS	6	15	8	14
SES	6	15	8	14
Completed treatment	5 (83%)	14 (93%)	6 (75%)	11 (79%)

Source: applicant's table

The utility of the study findings is limited due to the small sample size. The applicant attributed this due to the higher than predicted PASI 75 responses in Trial 2304. Consequently, the trial did not meet the required statistical significance for the co-primary endpoints, although the applicant stated that there were trends in favor of the i.v. dose. The applicant stated that there were no new safety signals identified during this trial. The following table shows the results of the protocol-specified co-primary endpoints at Week 8.

Table 36. Results of the Co-primary Efficacy Endpoints at Week 8 for Trial 2307

Endpoint	AIN457 10 mg/kg i.v. (N=21)	AIN457 300 mg s.c. (N=21)	p-value
IGA 0 or 1	14/21 (67%)	7/21 (33%)	0.033
PASI 75	19/21 (91%)	14/21 (67%)	0.065

Source: applicant's table.

3.4 Evaluation of Safety

This review only discusses the adverse events observed during the placebo-controlled induction period (first 12 weeks) of the pivotal trials (2302 and 2303). The incidence of the top 10 most frequently reported adverse events in each trial are presented in the table below. The incidences of the most common events were similar across all treatment arms (300 mg, 150mg, and placebo).

Table 37. Most common Treatment-Emergent Adverse Events during the Induction Period for Trial 2302 (SES)

Adverse Events (preferred term)	AIN457 300mg N=245	AIN457 150 mg N=245	Placebo N=247
Any	135 (55%)	148 (60%)	116 (47%)
Nasopharyngitis	22 (9%)	23 (9%)	19 (8%)
Headache	12 (5%)	13 (5%)	7 (3%)
Upper respiratory tract infection	9 (4%)	10 (4%)	0 (0%)
Pruritus	9 (4%)	8 (3%)	5 (2%)
Oropharyngeal pain	4 (2%)	10 (4%)	3 (1%)
Fatigue	2 (1%)	8 (3%)	2 (1%)
Diarrhea	5 (2%)	4 (2%)	3 (1%)
Hypertension	0 (0%)	9 (4%)	3 (1%)
Arthralgia	2 (1%)	6 (2%)	7 (3%)
Influenza like illness	5 (2%)	3 (1%)	3 (1%)

Source: an excerpt from the applicant's table

Table 38. Most common Treatment-Emergent Adverse Events during the Induction Period for Trial 2303 (SES)

Adverse Events (preferred term)	AIN457 300mg N=326	AIN457 150 mg N=327	Placebo N=326	Etanercept N=323
Any	181 (58%)	191 (58%)	163 (50%)	186 (57%)
Nasopharyngitis	35 (11%)	45 (14%)	26 (8%)	36 (11%)
Headache	30 (9%)	16 (5%)	23 (7%)	23 (7%)
Diarrhea	17 (5%)	12 (4%)	6 (2%)	11 (3%)
Pruritus	8 (3%)	12 (4%)	11 (3%)	8 (3%)
Arthralgia	5 (2%)	14 (4%)	10 (3%)	12 (4%)
Upper respiratory tract infection	7 (2%)	10 (3%)	3 (1%)	7 (2%)
Back pain	8 (3%)	8 (2%)	6 (2%)	9 (3%)
Cough	11 (3%)	5 (2%)	4 (1%)	4 (1%)
Hypertension	5 (2%)	10 (3%)	4 (1%)	5 (2%)
Nausea	8 (3%)	6 (2%)	7 (2%)	4 (1%)

Source: an excerpt from the applicant's table

3.5 Benefit-Risk Assessment

All the Phase 3 trials evaluated two doses (150 mg and 300 mg) of secukinumab, and both 300 mg and 150 mg of secukinumab doses were superior to placebo in achieving PASI 75, and IGA 0 or 1 at Week 12. However, the applicant is only seeking approval for the 300 mg dose for the reasons that:

- although infections were more frequent with secukinumab, the incidence of serious infections was low and comparable across both secukinumab dose groups and placebo,
- because the dose of 300 mg had higher IGA as well as PASI 75 responses (about 10%) in comparison to the 150 mg dose
- the response rates for the key secondary endpoint of PASI 90 at Week 12 was higher for the secukinumab 300 mg dose compared to those of the 150 mg group.

Whether exposing all plaque psoriasis patients to the higher dose (secukinumab 300 mg) irrespective of weight so as to achieve a 10% more treatment success, at the cost of possibly increasing the risk of adverse events, would require clinical judgment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the efficacy by gender, age, race, weight as well as by country for the pivotal trials (2302 and 2303) were considered.

4.1 Efficacy by Gender, Race, Age, and Weight

Table 39 presents the IGA 0 or 1 success by gender, race, age, and weight strata at baseline for the pivotal trials. The majority of the subjects enrolled in the trials were Caucasians (approximately 70%), and of <65 of age (approximately 93%). Therefore, any differences in efficacy for the non-Caucasians and the older age (≥ 65) subgroups would be difficult to detect.

The IGA success by gender presented inconsistent findings across the pivotal trials for the female subjects (i.e., secukinumab 150 mg dose yielded higher IGA success rates compared to those of the 300 mg group for the female subjects); however, this is likely due to chance, as the secukinumab 300 mg dose yielded higher IGA responses for both men and women across all weight subgroups in Trial 2304. Note that Trials 2308 and 2309 had relatively small sample sizes compared to those of the pivotal trials, thus, any differences in efficacy across subgroups would be difficult to detect. Table 40 presents the IGA success by weight and gender subgroups for Trial 2304.

Table 39. IGA Success by Gender, Age, Race, and Weight for the Pivotal Trials (2302 and 2303)

	Trial 2302			Trial 2303			
	AIN457 300mg N=245	AIN457 150mg N=245	Placebo N=248	AIN457 300mg N=327	AIN457 150mg N=327	Placebo N=326	Etanercept N=326
Gender							
<i>Female</i>	51/76 (67%)	43/77 (56%)	5/76 (7%)	60/103 (58%)	58/91 (64%)	2/89 (2%)	25/94 (26%)
<i>Male</i>	109/169 (65%)	82/168 (49%)	1/172 (0.6%)	142/224 (63%)	109/236 (46%)	7/237 (3%)	63/232 (27%)
Age							
<65	149/228 (65%)	112/225 (59%)	6/229 (3%)	194/311 (62%)	161/310 (52%)	9/311 (3%)	85/313 (27%)
≥65	11/17 (65%)	13/20 (65%)	0/19 (0%)	8/16 (50%)	6/17 (35%)	0/15 (0%)	3/13 (23%)
Race							
<i>Asian</i>	33/52 (63%)	31/54 (57%)	1/47 (2%)	33/73 (45%)	27/72 (38%)	2/72 (3%)	13/74 (17%)
<i>Black</i>	2/4	3/5	0/9	2/2	3/3	0/3	-
<i>Caucasian</i>	110/171 (64%)	82/171 (48%)	3/176 (2%)	143/224 (64%)	118/219 (54%)	5/217 (2%)	60/219 (27%)
<i>Native American</i>	5/7	2/5	0/3	18/22 (81%)	18/28 (64%)	2/25 (8%)	12/27 (44%)
<i>Pacific Islander</i>	2/3	1/1	-	1/1	-	0/1	0/1
<i>Other</i>	6/6	6/9	2/13	5/5	1/5	0/5	3/4
<i>Unknown</i>	2/2	-	-	-	-	0/2	0/1
Weight group							
<90 kg	103/142 (73%)	75/141 (53%)	3/143 (2%)	140/220 (64%)	119/215 (55%)	8/217 (4%)	66/219 (30%)
≥90 kg	57/103 (55%)	50/104 (48%)	3/105 (3%)	62/107 (58%)	48/112 (43%)	1/109 (1%)	22/108 (20%)

Source: reviewer table

As a supportive analysis, IGA success rates by gender and weight group for Trial 2304 are presented in Table 40. Three weight categories (<70, 70-90, and ≥ 90 kg) were used to investigate whether the lighter female subjects benefited from the lower dose (i.e., 150 mg), and the results show that the secukinumab 300 mg dose group showed higher IGA success rates across all subgroups irrespective of the gender. Note that Trial 2304 did not include a placebo arm, because subjects were randomized in a 1:1 ratio to either secukinumab 300 mg or 150 mg dose.

Table 40. IGA Success by Weight and Gender for Trial 2304

Weight (kg)	Gender	Trial 2304	
		AIN457 300 mg N=484	AIN457 150 mg N=482
<70	F	53/61 (87%)	56/70 (80%)
	M	60/76 (79%)	37/60 (62%)
70-90	F	32/43 (74%)	32/55 (58%)
	M	95/113 (84%)	67/102 (66%)
≥90	F	30/47 (64%)	24/52 (46%)
	M	97/144 (67%)	86/143 (60%)

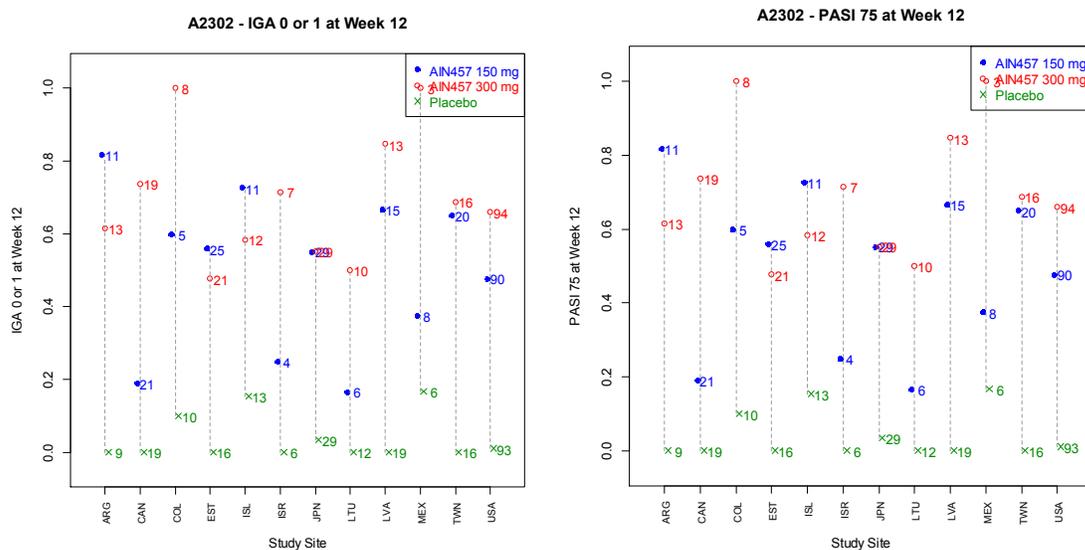
Source: reviewer table

4.2 Efficacy by Country for the two pivotal trials (2302 and 2303)

The efficacy by country plots for the pivotal trials are presented below (see Figures 27 and 28). The country that enrolled the most numbers of subjects was USA with 278 subjects in Trial 2302, and Germany with 319 subjects in Trial 2303, and about 3-4 countries in each trial showed that secukinumab 150 mg had higher IGA response rates than 300 mg (Argentina, Estonia, Iceland in Trial 2302, and Iceland, Italy, South Korea, Poland in Trial 2303).

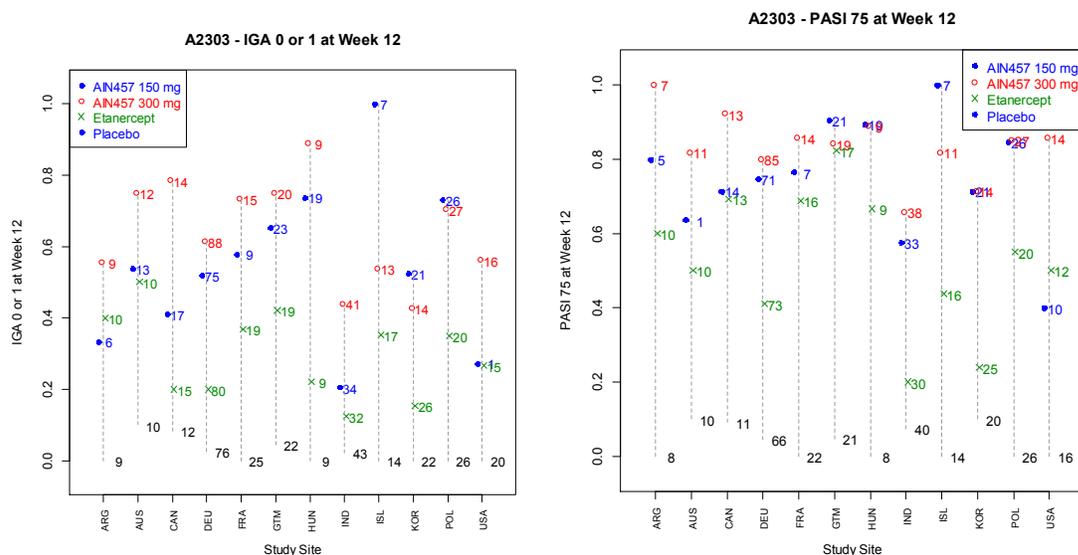
A total of 23 countries enrolled subjects for Trial 2303, and many of the countries enrolled a small number of subjects per treatment arm. As such, the top 12 countries with the most enrolled number of subjects are included in Figure 28.

Figure 27. Efficacy by Country for Trial 2302 (all countries)



Source: reviewer figures.

Figure 28. Efficacy by Country for the Top 12 Countries with the Most Number of Enrolled Subjects



Source: reviewer figures.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant has evaluated the efficacy of secukinumab 300 mg and 150 mg in two Phase 3 trials (2302 and 2303). Both trials were statistically significant for the co-primary endpoints of PASI 75 response at Week 12 and IGA 0 or 1 at Week 12 ($p < 0.0001$). Treatment effects were generally consistent across subgroups with consistent conclusions across the trials.

The comparisons of the PRO endpoints were added to the testing strategy as secondary endpoints in the amended protocol, and only a subset (approximately 40%) of subjects reported the PRO response on itching, pain, and scaling. As such, it is difficult to conclude whether these subjects who reported the PROs are a random sample of the total population so that the findings are generalizable to the overall population.

For the efficacy assessment, some subjects were outside the protocol-specified visit windows, and there were some common investigators across the two pivotal trials; however, these did not impact the overall conclusions of the trials.

5.2 Conclusions and Recommendations

For establishing an efficacy claim, the applicant conducted two pivotal trials (2302 and 2303), and compared each dose of secukinumab (300 mg and 150 mg) to placebo.

The trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with PASI score ≥ 12 , IGA score of at least 3, and BSA involvement $\geq 10\%$ at baseline. The co-primary endpoints were the proportion of subjects achieving PASI 75 response at Week 12 and IGA 0 or 1 at Week 12, with a key secondary endpoint of PASI 90 response at Week 12. Both secukinumab 300 mg and 150 mg were superior to placebo ($p < 0.0001$) for the co-primary endpoints of PASI 75 response and IGA of 0 or 1, as well as the key secondary endpoint of PASI 90 response in each of the pivotal trials. For Trial 2303, not only did each dose of secukinumab establish noninferiority to etanercept, but also established superiority as well ($p < 0.0001$). However, it should be noted that no replication of study findings for the comparisons against etanercept.

Further, for those subjects who continued treatment in the maintenance period of the pivotal trials, 76% and 63% of those subjects maintained their IGA success status at Week 52 for those subjects treated with secukinumab 300 mg and 150 mg, respectively. Similarly, 82% and 75% of the PASI 75 responders at Week 12 maintained their PASI 75 status at Week 52 for those treated with secukinumab 300 mg and 150 mg, respectively.

For the subjects who reported their PRO (about 40% of the total study subjects):

- (1) At baseline, subjects of moderate psoriasis on the IGA scale (i.e., IGA=3) reported slightly less itching, pain, or scaling compared to those with severe psoriasis (i.e., IGA of 4).
- (2) At Week 12, improvement in the disease severity based on the IGA score led to an improvement in symptoms of itching, pain and scaling as well. Subjects who did not achieve success status also showed improvement, although to a lower extent.

For Trials 2308 and 2309 that used the liquid formulation of secukinumab in PFS and in AI, respectively, both secukinumab doses were superior to placebo ($p < 0.0001$). Note that the trials were not designed to address whether the efficacies from using the PFS or the AI compared to those of the original LYO secukinumab formation within each trial. However, in comparing the efficacy results across the trials, the IGA as well as the PASI 75 response rates for the PFS and the AI were similar to those of the pivotal trials that used the LYO formulation.

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/s/

CARIN J KIM
09/08/2014

MOHAMED A ALOSH
09/08/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 122504

Applicant: Novartis

Stamp Date: 10/24/2013

Drug Name: Cosentyx

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		Analyses on the pooled data (included in the ISE and ISS) was done, but not on the study level.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New BLA_BLA 122504

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Information Requests to be forwarded to the Applicant for the 60-day letter:

- For Studies A2302 and A2303, there were 10 common investigators, and the trials were conducted simultaneously. It's not clear how patient allocation to each trial was determined. For each common investigator, provide detailed information on how such patient allocation to each trial was made.
- Although the applicant provided the overall efficacy and safety analysis results by gender, race, and age subgroups on the pooled data as part of the ISE and ISS, it would be useful for the applicant to provide study-level subgroup analysis results, as this would enable assessing the consistency (or lack thereof) in any subgroup analysis findings across trials.

Carin Kim

12/04/2013

Statistical Reviewer

Date

Supervisor/Team Leader

Date

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/s/

CARIN J KIM
12/06/2013

MOHAMED A ALOSH
12/06/2013